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[Authors]. [Abstract Title]. Program No. XXX.XX. 2022 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2022. Online.

Poster

685. Hippocampal Neurogenesis and Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 685.01

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Ro1 NS093009
UTHSC Neuroscience Institute

Title: Cellular and electrophysiological abnormalities in hippocampal dentate gyrus in dreher (Lmx1a-/-) mutant mice

Authors: *I. ISKUSNYKH, N. FATTAKHOV, M. KIRCHNER, A. ZAKHAROVA, L. MUKHAMETZYANOVA, V. CHIZHIKOV;
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Abstract: The dentate gyrus (DG) of the hippocampus is one of the very few brain regions capable of adult neurogenesis in most mammal species. The DG is pivotal for learning and memory. Disruptions of the DG function contribute to numerous neurological and psychiatric disorders, such as amnesia and depression. The LIM homeodomain transcription factor 1 alpha (Lmx1a) is an essential determinant of dopaminergic neurons. It also regulates neurogenesis in the spinal cord and cerebellum. *Lmx1a* is believed to participate in hippocampus development; it is yet to be uncovered how *Lmx1a* regulates hippocampal formation. To unveil the role of Lmx1a in hippocampal development and study its function in the establishment of electrophysiological properties of DG cells, we performed immunohistochemical studies and electrophysiological recordings on homozygous *dreher* mice, in which *Lmx1a* is inactivated by a point mutation. We found that loss of *Lmx1a* function affected electrophysiological properties of hippocampal neurons in adult mice, particularly input resistance of DG granule cells. In addition, the number of Prox1+ DG granule cells was reduced in *Lmx1a-/-* mutants. During embryonic development, loss of *Lmx1a* was associated with a disrupted migration of Cajal-Retzius cells from the cortical hem, abnormal development of the transhilar radial glial scaffold, and disrupted hippocampal fissure formation. Therefore, *Lmx1a* is a novel regulator of electrophysiological properties of DG granule cells and migration of neuronal and glial cells during hippocampal development.

Disclosures: I. Iskusnykh: None. **N. Fattakhov:** None. **M. Kirchner:** None. **A. Zakharova:** None. **L. Mukhametzyanova:** None. **V. Chizhikov:** None.

Poster

685. Hippocampal Neurogenesis and Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 685.02

Topic: A.01. Neurogenesis and Gliogenesis

Support: MOST grants 106-2410-H-006-029-MY3

Title: The role of oxytocin- and conspecifics-associated buffering effects against stress-induced decreases in dorsal dentate neurogenesis

Authors: *L.-H. SUN[1], L. YU[1,2,3];
[1]Inst. of Basic Med. Sci., [2]Dept. of Physiol., [3]Inst. of Behavioral Med., Col. of Medicine, Natl. Cheng Kung Univ., Tainan, Taiwan

Abstract: Social support is critical for maintaining individual's psychological and physiological well-being. Lacking of social interaction may associate with poor quality of life and the development of psychosomatic disorders. In previous studies, we have demonstrated that tandem robust stressors may stimulate animals' rapid corticosterone (CORT) secretion and acutely decrease early neurogenesis in dorsal dentate gyrus (dDG). While presence of conspecifics and airborne oxytocin (OT) does not affect the stress-induced CORT secretion, these may prevent the stress-caused decreases in the number of newly proliferated cells and proliferative neuroblasts. However, the underlying mechanism in this regard was still unclear. This study was undertaken to investigate what local transcription factors may be involved in these conspecifics- and airborne OT-associated buffering effects against CORT-produced neurogenesis-suppressing effect in dDG. We observed that stressed mice had greater protein level of p-GR, STAT3 and NFκB-p65 in dorsal hippocampus, while lower protein level of STAT5 and c-Jun as compared to non-stressed controls. The presence of three conspecifics and airborne OT during the stressor regimen may prevent stress-induced decreases in STAT5 protein level. We further assessed the downstream target genes of STAT5 and observed that stressed mice had lower IGF-1 protein level as compared with non-stressed controls 6 hours following the stressors. To extend these findings, mice' visual, auditory, and olfactory pathways were assessed respectively for their determining roles in conspecifics- and airborne OT-associated stress-buffering effects in this regard. Our data showed that olfactory tract transection did not affect dDG cell proliferation or early neurogenesis, while such surgery prevented these buffering effects. Moreover, we demonstrated nasal epithelial *Oxtr* KO mice failed to exhibit OT buffering effect after airborne OT exposure. Mice receiving bilateral medial and lateral intra-main olfactory bulb (MOB) AAV(2/9)-ChAT-Cre and AAV5-hM4Di infusions and intraperitoneal C21 administration also failed to exhibit these buffering effects, suggesting cholinergic neurons originated from main olfactory epithelium (MOE) to MOB plays a critical role in relaying odor-related buffering effects. Taken together, the results prompt us to conclude that STAT5 warrants further study as a candidate of switching hub between stress and buffering effects on dDG neurogenesis. Cholinergic neurons from MOE-MOB appear to be a mandatory olfactory pathway to relay conspecifics- and airborne OT-associated stress-buffering effects on neurogenesis in dDG.

Disclosures: L. Sun: None. **L. Yu:** None.

Poster

685. Hippocampal Neurogenesis and Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 685.03

Topic: A.01. Neurogenesis and Gliogenesis

Support: FONDECYT 1190461 (LV-N)
FONDECYT 11180540 (FJB)
ANID 21210618 (DV-B)

Title: Role of RSPO/LGR signaling in adult neural progenitor cells

Authors: *D. VALENZUELA-BEZANILLA, S. B. ARREDONDO, N. MERINO-VÉLIZ, F. J. BUSTOS, L. VARELA-NALLAR;
Fac. of Med. and Fac. of Life Sci., Univ. Andrés Bello, Santiago, Chile

Abstract: In the dentate gyrus (DG) of the adult hippocampus, new neurons are generated from neural stem/progenitor cells (NSPCs). This process is regulated by signaling factors secreted by local astrocytes. Among these, Wnt signals control the proliferation and differentiation of NSPCs. During development, the Wnt signaling pathway is regulated by R-spondin (RSPO) proteins, which bind to LGR receptors and potentiate Wnt signaling activity. Here we explored the potential role of RSPO/LGR signaling on adult NSPCs. We determined that RSPOs and LGRs are expressed in the adult DG and in primary cultures of adult hippocampal progenitors (AHP), which was assessed by RT-qPCR, immunofluorescence and western blot. Treatment of AHP with recombinant RSPO (rRSPO) induced a significant increase in proliferation as assessed by incorporation of the nucleotide analog BrdU. Moreover, treatment with the soluble ectodomain of LGR receptors (Fc-chimeras), which act as RSPO neutralizers, prevented the increase in AHP proliferation induced by co-culture with hippocampal astrocytes. A similar effect was observed when the expression of an LGR receptor was knocked down in AHP. These results demonstrate that RSPOs secreted by astrocytes regulate the proliferation of NSPCs through LGRs. Altogether, our data suggest that RSPO/LGR signaling regulates adult hippocampal neurogenesis.

Disclosures: D. Valenzuela-Bezanilla: None. **S.B. Arredondo:** None. **N. Merino-Véliz:** None. **F.J. Bustos:** None. **L. Varela-Nallar:** None.

Poster

685. Hippocampal Neurogenesis and Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 685.04

Topic: A.01. Neurogenesis and Gliogenesis

Support: Grant 21K15272
Grant 19K16375
Grant 21H02673
Grant 18H02580

Title: L-DOPA and its receptor GPR143 are involved in hippocampal neurogenesis and mood regulation.

Authors: *Y. KASAHARA[1,2], D. MASUKAWA[2], K. KOBAYASHI[3], Y. GOSHIMA[2];
[1]Kyushu Univ., Fukuoka, Japan; [2]Yokohama City Univ., Kanagawa, Japan; [3]Natl. Inst. For Physiological Sci., Okazaki, Japan

Abstract: Neurogenesis occurs in the hippocampus throughout life and is implicated in various physiological brain functions such as memory encoding and mood regulation. L-3,4-dihydroxyphenylalanine (L-DOPA) has long been believed to be an inert precursor of dopamine. Here, we show that L-DOPA and its receptor, GPR143, the gene product of ocular albinism 1, regulate neurogenesis in the dentate gyrus (DG) in a dopamine-independent manner. L-DOPA at concentrations far lower than that of dopamine promoted proliferation of neural stem and progenitor cells in wild-type mice under the inhibition of its conversion to dopamine; this effect was abolished in GPR143 gene-deficient (*Gpr143*$^{-/y}$) mice. Hippocampal neurogenesis decreased during development and adulthood, and exacerbated depression-like behavior was observed in adult Gpr143$^{-/y}$ mice. Replenishment of GPR143 in the DG attenuated the impaired neurogenesis and depression-like behavior. Our findings suggest that L-DOPA through GPR143 modulates hippocampal neurogenesis, thereby playing a role in mood regulation in the hippocampus.

Disclosures: Y. Kasahara: None. **D. Masukawa:** None. **K. Kobayashi:** None. **Y. Goshima:** None.

Poster

685. Hippocampal Neurogenesis and Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 685.05

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH RO1 A6054649

Title: Isolation and culture of hippocampal progenitor cells in a free-floating neurosphere culture from adult and aged mice

Authors: *O. VAFAEVA[1], K. D. MURRAY[2], H.-J. CHENG[3], E. DIAZ[4];
[1]Ctr. for Neurosci., Univ. of California,Davis, Davis, CA; [2]Dept. of Psychiatry and Behavioral Neurosci., Univ. of California, Davis, CA; [3]Inst. of Mol. Biol., Academia Sinica, Nankang, Taiwan; [4]Dept Med. Pharmacol, Univ. Of California Davis, Davis, CA

Abstract: Adult neurogenesis in the dentate gyrus (DG) of the hippocampus is involved in physiological functions such as learning and memory while disruption in this process is implicated in many disorders including schizophrenia and depression. While several *in vitro* assays have been developed to model the process of adult neurogenesis, they are predominantly applied to the growth of embryonic and early postnatal DG-derived progenitor cells. Such approach however does not provide much insight to population of cells that continuously generates neurons contributing to hippocampal function and diseases later in life. The neurosphere assay is the gold standard for determining the proliferative and differentiation potential of neural progenitor cells (NPCs). Culturing adult NPCs provides an important *in vitro* model to investigate cellular and molecular properties of this unique cell population and to expand the understanding of plasticity in the adult and aging brain.Here, we show a free-floating neurosphere culture system that was developed to isolate NPCs from the subgranular zone of DG of mice ranging from young adult to aged. We were able to isolate and establish multiple stable neurosphere cell lines from mixed sex C57bl/6J mice from 1-3 months old (adult) to ≥12 months old (aged). In this assay, the DG is microdissected and dissociated into single-cell suspension that is cultured in a chemically defined medium. Isolated proliferating NPCs form free-floating primary neurospheres. Upon dissociation neurospheres from adult and aged brain generated secondary neurospheres. We demonstrated that this process can be repeated over ten passages which indicates the capacity of these cells for self-renewal. Additionally, neurospheres isolated across different ages are expressing progenitor cell markers Nestin and Sox2. We found that culturing time between plating and neurosphere formation is positively correlated with the age of the animal. Interestingly, the likelihood of establishing stable neurosphere cells lines drastically decreases with increasing age. Additionally, cells from neurospheres from different age groups are multipotent. Cultured in monolayer assay for 8 days NPCs differentiate to astrocytes and neurons as demonstrated by immunocytochemical staining for βIII-tubulin (Tuj1) and glial fibrillary acidic protein (GFAP). Overall, this approach for isolating and propagating NPCs from DG of adult and aged brain offers novel *in vitro* model of neurogenesis in the adulthood and can serve as a platform for investigating important biological questions regarding the development and differentiation of hippocampal neurons generated throughout adult life.

Disclosures: **O. Vafaeva:** None. **K.D. Murray:** None. **H. Cheng:** None. **E. Diaz:** None.

Poster

685. Hippocampal Neurogenesis and Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 685.06

Topic: A.01. Neurogenesis and Gliogenesis

Support: King's College London Faculty Graduate School International Research Studentship 2015-16

Title: In vitro characterisation on the role of APOE polymorphism in human hippocampal neurogenesis

Authors: *H. LEE[1], D. P. SRIVASTAVA[1], J. PRICE[1], S. THURET[2];
[1]Dept. of Basic & Clin. Neuroscience, Inst. of Psychiatry, Psychology, and Neurosci., King's Col. London, London, United Kingdom; [2]Dept. of Basic & Clin. Neuroscience, Inst. of Psychiatry, Psychology, and Neurosci., King's Col. London, London, United Kingdom

Abstract: Hippocampal neurogenesis (HN) is considered an important mechanism underlying lifelong brain plasticity, and alterations of this process has been implicated in early Alzheimer's disease progression. *APOE* polymorphism is the most common genetic risk factor for late-onset Alzheimer's disease where ε4 genotype is associated with a significantly earlier disease onset compared to the neutral ε3 allele. Recently, *APOE* has been shown to play an important role in the regulation of HN. However, the impact of its polymorphism at the cellular level is not well understood, particularly in humans, due to the difficulties of studying this process *in vivo*. To bridge this gap of knowledge, we used an *in vitro* cellular model of human HN and performed a time-course characterisation on isogenic induced pluripotent stem cells with different genotypes of *APOE*. We found that *APOE* itself was differentially expressed at the stem cell stage, while the phenotypic divergence between ε4 and ε3 became more prominent at the neuronal stage of differentiation. However, this divergence was not associated with the differential capacity to generate dentate gyrus granule cell-like neurons, as its level was comparable between ε4 and ε3. Transcriptomic profiling across different stages of neurogenesis revealed that genes associated with 'maturation of functional neurons' did not clearly emerge in ε4 neurons as it did in ε3 neurons. The data further suggested that mitochondrial dysfunction could be an underlying defect in ε4 neural progenitor cells and neurons, as *CHCHD2* expression was significantly decreased at both stages of differentiation in ε4 compared to ε3. Taken together, our *in vitro* investigation suggests that APOE ε4 allele can exert a transcriptome-wide effect at the later stages of HN, without altering the overall level of neurogenesis *per se*. Differential expression of *CHCHD2* could be an indication of mitochondrial vulnerability in APOE ε4, which justifies future investigations into the link between altered mitochondrial and hippocampal function in ε4 carriers.

Disclosures: H. Lee: None. **D.P. Srivastava:** None. **J. Price:** None. **S. Thuret:** None.

Poster

685. Hippocampal Neurogenesis and Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 685.07

Topic: A.01. Neurogenesis and Gliogenesis

Support: MRC: MR/N014863/1
MRC: MR/N030087/1
National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre
Guy's and St Thomas' Charity
Rayne Foundation

Title: The psychiatric disorder drug lithium affects human hippocampal neurogenesis

Authors: A. B. PALMOS[1], R. R. DUARTE[1], D. SMEETH[1], E. C. HEDGES[1], D. F. NIXON[2], S. THURET[1], ***T. R. POWELL**[1];
[1]King's Col. London, London, United Kingdom; [2]Weill Cornell Med., New York, NY

Abstract: Background: Lithium is a first-line treatment for bipolar disorder, where it acts as a mood-stabilizing agent. Although its precise mechanism remains unclear, neuroimaging studies have shown that lithium accumulates in the hippocampus and that chronic use amongst bipolar disorder patients is associated with larger hippocampal volumes. **Methods:** Here, we tested the chronic effects of low (0.75 mM) and high (2.25 mM) doses of lithium on human hippocampal progenitor cells. We used immunocytochemistry to investigate the effects of lithium on cell parameters implicated in neurogenesis, such as cell proliferation and differentiation. Corresponding RNA-sequencing and gene-set enrichment analyses were used to evaluate whether genes affected by lithium in our model overlap with those regulating the volume of specific layers of the dentate gyrus. **Results:** We observed that high-dose lithium treatment in human hippocampal progenitors increased the generation of neuroblasts ($P \leq 0.01$), neurons ($P \leq 0.01$), and glia ($P \leq 0.001$), alongside the expression of genes, which regulate the volume of the molecular layer of the dentate gyrus. **Discussion:** This study provides empirical support that adult hippocampal neurogenesis and gliogenesis are mechanisms that could contribute to the effects of lithium on human hippocampal volume. Future research should continue to bridge the gap between in vitro and in vivo observations, and to explore whether neurogenesis is also a critical mechanism explaining lithium's therapeutic effects.

Disclosures: A.B. Palmos: None. **R.R. Duarte:** None. **D. Smeeth:** None. **E.C. Hedges:** None. **D.F. Nixon:** None. **S. Thuret:** None. **T.R. Powell:** None.

Poster

685. Hippocampal Neurogenesis and Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 685.08

Topic: A.01. Neurogenesis and Gliogenesis

Support: T32 AA007471
R01 AA016959

Title: Blunted arborization of immature neurons in adult male and female rat hippocampus during reactive neurogenesis after alcohol dependence

Authors: *K. R. THOMPSON, K. NIXON;
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Abstract: Excessive alcohol (ethanol) drinking is central to alcohol use disorder and may result in neurodegeneration. However, with abstinence, recovery of cognition and brain structure may

occur in regions such as the hippocampus. A mechanism that may contribute to hippocampal recovery is adult neurogenesis in the dentate gyrus subgranular zone. In rodent models of ethanol dependence, there is a reactive increase in the number of newborn neurons in protracted abstinence. It is not known if these cells mature or function normally, however. To begin to study this, we used the neuroblast marker doublecortin (DCX) to quantify arborization of immature neurons in adult male (M) and female (F) rats two weeks (T14) following ethanol dependence. Ethanol (25% w/v in vanilla Ensure Plus®) was given intragastically to rats (65-70 PND; M&F) every 8 hours for 4 days. Control animals received either an isocaloric diet or *ad libitum* access to food. Rats received 10.9 ± 0.4 (F) and 9.8 ± 0.4 for (M) g/kg/day resulting in a blood ethanol concentration of 320.2 ± 45.3 (F) and 371.6 ± 23.1 (M) after the sixth dose. Withdrawal behavior was scored 10-28 hours following the last dose of ethanol, which averaged 0.5 ± 0.2 (F) and 0.7 ± 0.2 (M) on a 0-4 scale (hyperactivity) and peaked at 2.6 ± 0.5 (F) and 2.6 ± 0.4 (M; generalized tremors). No sex differences were found in intoxication or withdrawal parameters. Brains were harvested after transcardial perfusion with phosphate buffered saline then 4% paraformaldehyde at T14, during increased reactive neurogenesis. Brains were postfixed, brains sectioned on a vibrating microtome at 40µm, and tissue was processed for DCX immunofluorescence. DCX+ cells were imaged using confocal microscopy and arbors skeletonized using the SNT plugin on ImageJ. Arbor complexity was determined by Sholl analysis, as well as measuring cable length, average branch length, and number of tips. For the Sholl analysis, main effects were found for radii and for diet condition as well as an interaction between radius and diet (all $p<0.05$). Similarly, the area under the curve (AUC) showed a main effect for diet condition. Ethanol rats had fewer intersections and a 20% smaller AUC than controls. Ethanol rats were also found to have 20% lower cable length and 10% lower average branch length than controls ($p<0.05$), though no differences for average number of tips. These results indicate that though reactive neurogenesis occurs in number, the arbors of newborn cells in ethanol treated animals are less complex than neurons born normally. Future work will explore if these reactive-born cell arbors normalize as cells mature and if this morphological difference hinders hippocampal recovery.

Disclosures: K.R. Thompson: None. **K. Nixon:** None.

Poster

685. Hippocampal Neurogenesis and Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 685.09

Topic: A.01. Neurogenesis and Gliogenesis

Support: AG033570
AG061628
AG062251
AG060238

Title: Presence of hippocampal neurogenesis in aging and Alzheimer’s disease

Authors: *A. DISOUKY[1], M. TOBIN[1], A. SHETTI[1], W. G. HONER[2], N. KIM[3], R. DAWE[3], K. ARFANAKIS[3], D. BENNETT[3], O. LAZAROV[1];
[1]Univ. of Illinois at Chicago, Chicago, IL; [2]Ctr. For Complex Disorders, BCMHARI, Vancouver, BC, Canada; [3]Rush Univ. Med. Ctr., Chicago, IL

Abstract: The continuous generation of new neurons in the hippocampus of rodents during adulthood is well established. These neurons play important roles in hippocampal function. Therefore, the existence of adult hippocampal neurogenesis in the aging and Alzheimer's disease (AD) human hippocampus has critical translational and therapeutic implications. Thus, we investigated the extent of neurogenesis in the hippocampus of patients from the Rush Memory and Aging project (MAP), a large, comprehensive longitudinal epidemiological study. Examination of postmortem brain sampled from Individuals with mild cognitive impairments (MCI), or Alzheimer's dementia (AD) were compared to age- matched samples of individuals with no cognitive impairments (NCI). Immunohistochemical analysis revealed that neurogenesis persists in the hippocampus of NCI, MCI and AD up to the tenth decade of their life. Neural progenitor cells, neuroblasts and immature neurons were distributed throughout the ventral-dorsal axis of the hippocampus. In addition, we observed significantly fewer number of neuroblast and new neurons in individuals with MCI, suggesting that neurogenesis is compromised in an early stage of cognitive deterioration. Interestingly, higher numbers of neuroblasts (DCX+PCNA+) was significantly correlated with better cognition and was less likely to be associated with cognitive decline diagnosis. Furthermore, we show that the number of new neurons correlated with the expression of key presynaptic proteins, previously shown to be associated with cognitive reserve. Taken together these data suggest that hippocampal neurogenesis persists in the human brain throughout life and that enhancing neurogenesis may support cognitive function in AD.

Disclosures: A. Disouky: None. **M. Tobin:** None. **A. Shetti:** None. **W.G. Honer:** None. **N. Kim:** None. **R. Dawe:** None. **K. Arfanakis:** None. **D. Bennett:** None. **O. Lazarov:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.01

Topic: A.01. Neurogenesis and Gliogenesis

Support: NS100839
CSRA Parkinson's Disease Support Group

Title: Ganglioside microdomains on cellular and intracellular membranes regulate neural stem cells and neuronal differentiation in health and disease

Authors: *Y. ITOKAZU;
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Abstract: Gangliosides are sialylated glycosphingolipids with essential but enigmatic functions in healthy and disease's brains. We reported the importance of gangliosides for growth factor receptor signaling and epigenetic regulation of neural stem cell (NSC) activity and differentiation. The primary localization of gangliosides is on cell-surface microdomains and the drastic dose and composition changes during neural differentiation and in disease progression strongly suggest that they are not only important as biomarkers, but also are involved in modulating NSC fate determination. Ganglioside GD3 is the predominant species in NSCs and GD3-synthase knockout (GD3S-KO) revealed reduction of postnatal NSC pools with severe behavioral deficits. Exogenous administration of GD3 significantly restored the NSC pools and enhanced the stemness of NSCs with multipotency and self-renewal. Since morphological changes during neurogenesis require a huge amount of energy, mitochondrial functions are vital for neurogenesis. We discovered that a mitochondrial fission protein, the dynamin-related protein-1 (Drp1), as a novel GD3-binding protein, and GD3 regulates mitochondrial dynamics. Furthermore, we discovered that nuclear GM1 promotes neuronal differentiation by an epigenetic regulatory mechanism. GM1 binds with acetylated histones on the promoters of N-*acetylgalactosaminyltransferase (GalNAcT; GM2 synthase; GM2S)* as well as on the *NeuroD1* genes in differentiated neurons. In addition, epigenetic activation of the *GM2S* gene was detected as accompanied by an apparent induction of neuronal differentiation in NSCs responding to an exogenous supplement of GM1. Interestingly, GM1 induced epigenetic activation of the tyrosine hydroxylase (TH) gene, with recruitment of nuclear receptor related 1 (Nurr1, also known as NR4A2), a dopaminergic neuron-associated transcription factor, to the TH promoter region. In this way, GM1 epigenetically regulates dopaminergic neuron specific gene expression and it would modify Parkinson's disease. Multifunctional gangliosides significantly modulate lipid microdomains to regulate functions of important molecules on multiple sites: the plasma membrane, mitochondrial membrane, and nuclear membrane. Versatile gangliosides regulate functional neurons as well as sustain NSC functions via modulating protein and gene activities on ganglioside microdomains. Maintaining proper ganglioside microdomains benefits to healthy neuronal development and to millions of senior citizens with neurodegenerative diseases.

Disclosures: Y. Itokazu: None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.02

Topic: A.01. Neurogenesis and Gliogenesis

Support: National Science Centre (NCN) Grant, UMO-2017/25/B/NZ3/01665

Title: Tcf7l2 isoform-specific regulation of thalamic development in mice

Authors: *M. O. GABRIEL, M. A. LIPIEC, J. M. BEM, M. B. WISNIEWSKA;
Lab. of Mol. Neurobiology, Ctr. of New Technologies, Univ. of Warsaw, Warsaw, Poland

Abstract: The thalamus is a brain structure that relays sensory signals to the cortex and regulates behavioural responses. Its abnormal development has been linked to neurodevelopmental disorders like autism spectrum disorder (ASD). Transcription factor 7-like 2 (TCF7L2), an effector of the Wnt/β-catenin signalling pathway and ASD-associated gene, regulates cell migration & clustering, axon guidance and terminal differentiation of thalamic neurons by regulating gene expression in the thalamus. This protein exists as a full-length isoform (fl-TCF7L2) that contains the β-catenin-binding domain and a truncated (dn-TCF7L2) isoform lacking this domain. In the embryonic mouse thalamus, the dn-TCF7L2 is more abundant when compared to the fl-TCF7L2 whereas, in the adult, the fl-TCF7L2 is more abundant. However, the purpose for the switch in their expression and the individual roles of the isoforms on thalamic development remains to be explored. In this study, we monitored the relative expression of TCF7L2 isoforms across different developmental stages of the mouse thalamus by probing the protein levels in thalamic lysates. The result suggests that the switch in the expression of TCF7L2 isoforms correlates with the functional maturation of thalamic neurons. Furthermore, we generated a CRISPR-Cas-mediated fl-TCF7L2 knockout mouse model with a single nucleotide deletion in exon 2 of the TCF7L2 gene. We used this mouse model together with mice with a total knockout of TCF7L2 to show the isoform-specific effects of TCF7L2 on the growth of thalamocortical axons, formation of thalamic anatomical boundaries and expression of genes conferring thalamic identity during prenatal development. Overall, our study provides a clear and robust understanding of the in vivo regulatory activities of TCF7L2 isoforms on thalamic development.

Disclosures: M.O. Gabriel: None. **M.A. Lipiec:** None. **J.M. Bem:** None. **M.B. Wisniewska:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.03

Topic: A.01. Neurogenesis and Gliogenesis

Support: KNRF Grant 2019R1C1C1010482
KNRF Grant 2018R1D1A1B07043238
KAIST Grant N11180123

Title: Metabolic changes of human neurogenesis are linked to microRNA-124 function

Authors: *G. SON[1], Y. KIM[2], Y. NA[3], J.-H. SON[1], H. DO[1], D. KIM[1], G. D. CLEMENSON JR[2], S. T. SCHAFER[2], J.-S. KIM[3], F. H. GAGE[2], J. HAN[1];
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Abstract: Metabolic reprogramming takes place during neurogenesis, but much about how noncoding elements affect the metabolic aspect of neurogenesis still needs exploration. microRNAs are one of the major constituents of noncoding elements and their expression pattern varies by the cell type. Interestingly, the metabolic power of mitochondria is also dependent on cell state. To survey the relationship between microRNAs and metabolism in neurogenesis, we used a microRNA sponge system to inhibit key functions of a neuron-specific microRNA: microRNA-124 (miR-124), at the initiating stages of neurogenesis. Surprisingly, miR-124 depleted neurogenesis resulted in the impairment of neurogenesis both *in vivo* and *in vitro*. From the phenotype observed, we were curious to examine intracellular changes at a systemic level. We utilized human embryonic stem cell-derived neural progenitor cells (NPCs) to study changes in the proteome of one-week differentiated neurons with or without miR-124 during neurogenesis. Proteomic analysis was performed to identify the differentially expressed proteins (DEPs) of miR-124 knockdown (KD) neurons versus control. The KEGG pathway analysis was carried out with the list of DEPs and has revealed that the term oxidative phosphorylation (OXPHOS) was annotated with the highest significance. OXPHOS as the major change following the sequestration of miR-124 in the initiation of neurogenesis led us to investigate further onto the functional and morphological changes of mitochondria. For miR-124 KD neurons, the analyses of oxygen consumption rate (OCR) and mitochondrial membrane potential (MMP) resulted in a reduction of both OCR and MMP levels, denoting mitochondrial dysfunctions. In line with preceding findings, examining mitochondrial structures depicted immature and globular mitochondrial morphologies. We then compared the list of DEPs with online mitochondrial protein databases to sort for the candidates of unexplored mitochondrial proteins participating in neuronal differentiation. From the selection, an exemplary gene, GSTK1 – upregulated in miR-124 KD neurons, was overexpressed with CRISPRa system to validate how reliable the list is to be associated in metabolism during neurogenesis. An OCR analysis after overexpressing GSTK1 in both NPCs and neurons confirmed a reduction of mitochondrial cell respiration. In conclusion, we propose an association of miR-124 to metabolic changes in neurogenesis and also provide a putative list of mitochondrial proteins vital to the start of neuronal differentiation.

Disclosures: G. Son: None. **Y. Kim:** None. **Y. Na:** None. **J. Son:** None. **H. Do:** None. **D. Kim:** None. **G.D. Clemenson Jr:** None. **S.T. Schafer:** None. **J. Kim:** None. **F.H. Gage:** None. **J. Han:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.04

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH/NIAAA intramural grant

Title: The role of GPR110 in neurodevelopment in human stem cell and mouse models

Authors: *Y. JOO, E. AFLAKI, B. X. HUANG, H.-Y. KIM;
NIAAA, NIH, Rockville, MD

Abstract: G-protein coupled receptor 110 (ADGRF1, GPR110) is an adhesion GPCR involved in the development of neurons and cognitive function. Synaptamide, an endogenous ligand for GPR110, binds to the *N*-terminal G-protein autoproteolysis-inducing (GAIN) domain of GPR110 and activates GPR110/cAMP signaling, promoting neurogenic differentiation of neural stem cells, neurite growth and synaptogenesis of developing neurons in mouse primary cells in culture. To further understand the role of GPR110 in neurodevelopment, we investigated the developmental phenotype and related molecular pathways using GPR110 knockout (KO) mouse model and human neural progenitor cells (hNPCs) where we found a high level of GPR110 expression. In hNPCs, GPR110 ligands dose-dependently increased cAMP production which was blocked by the pretreatment with *N*-terminal targeting GPR110 antibody. Deleting GPR110 *in vivo* or introducing inactive mutation to hNPCs that was identified in a schizophrenic patient population caused abnormal developmental phenotypes according to the RNA sequencing and imaging analysis. In addition to the downregulated neurogenesis and neurite growth, the expression of glutamate receptors and synaptic molecules associated with postsynaptic density were significantly reduced in GPR110 KO mouse brain or differentiating hNPCs with inactivating mutation. Our results indicate a significant role of GPR110 and its downstream signaling in neuronal differentiation and neuromaturation during development. The lack of GPR110 signaling leading to aberrant neuronal development may contribute to the psychiatric abnormality in adult stage.

Disclosures: Y. Joo: None. **E. Aflaki:** None. **B.X. Huang:** None. **H. Kim:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.05

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01MH097236-10

Title: Neuronal excitatory VGLUT1 and VGLUT2 distribution is nuclei-specific in the non-human primate amygdaloid complex.

Authors: *A. SHAH[1,2], E. L. CARLSON[1,2], K. L. HANSON[1,2], C. M. SCHUMANN[1,2];
[1]Psychiatry and Behavioral Sci., Univ. of California, Davis, Sch. of Med., Sacramento, CA; [2]UC Davis MIND Inst., Sacramento, CA

Abstract: The amygdaloid complex, comprised of individual subnuclei, is implicated in multiple neurodevelopmental and psychiatric disorders given the structure's role in modulating social behavior and anxiety. A common hypothesis of neurodevelopmental disorders, such as autism spectrum disorder (ASD) and schizophrenia, is an imbalance in neuronal excitatory to inhibitory

signaling, likely due to an altered distribution of excitatory and inhibitory cells. This study aimed to identify reliable excitatory and inhibitory neuronal markers in the primate brain, specifically focusing on the amygdaloid complex. Vesicular glutamate transporters (VGLUTs) 1 and 2, proteins responsible for transporting glutamate into synaptic vesicles, are widely used as markers of excitatory neurons. However, literature on the distribution of these markers in the nonhuman primate (NHP) amygdaloid complex remains sparse, which limits the region-specific reliability of VGLUT1 and VGLUT2 as a categorical marker of excitation. In this preliminary study, we mapped the distribution and localization of SLC17A7 (VGLUT1) and SLC17A6 (VGLUT2) mRNA across the rostrocaudal extent of the amygdala in two NHP animals utilizing duplexed RNAscope, an optimized *in situ* hybridization assay to detect VGLUT transcripts. The amygdaloid complex was anatomically delineated into lateral, basal, accessory basal, medial, central, and paralaminar nuclei using reference nissl sections. Quantitative measures were based on the ratio of mRNA transcripts among the individual nuclei. We observed 4 staining types: VGLUT1 dominant/VGLUT2+, VGLUT1+/VGLUT2 dominant, VGLUT1+/VGLUT2-, and VGLUT1-/VGLUT2+. VGLUT1 dominant/VGLUT2+ was the most common staining type, however the ratio of subtypes varied by amygdala subregion. Specifically, a subset of cells in the medial and paralaminar nuclei were highly VGLUT1-/VGLUT2+ or VGLUT1+/VGLUT2 dominant. Therefore, utilizing only the VGLUT1 marker would fail to detect some excitatory neuron subtypes. By using a multiplex approach to detect both VGLUT1 and VGLUT2 mRNA on the same section of tissue, we can develop a more comprehensive picture of neuronal excitation. Additionally, these results underscore the cytoarchitectural heterogeneity of amygdaloid nuclei, emphasizing the importance of region-specific sampling to accurately detect differences in excitatory neuron distribution and localization.

Disclosures: A. Shah: None. **E.L. Carlson:** None. **K.L. Hanson:** None. **C.M. Schumann:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.06

Topic: A.01. Neurogenesis and Gliogenesis

Support: MOST 110-2628-B-A49-001
Systems biology for therapeutic development

Title: An atypical localization of the proton pump V-ATPase subunit ATP6V1B2 is associated with human microcephaly

Authors: *T. KUO[1], M.-H. TSAI[2,3], E. HWANG[1];
[1]Dept. of Biol. Sci. and Technol., Natl. Yang Ming Chiao Tung Univ., Hsinchu, Taiwan; [2]Dept. of Neurol., Kaohsiung Chang Gung Mem. Hosp., Kaohsiung City, Taiwan; [3]Sch. of Med., Chang Gung Univ., Taoyuan City, Taiwan

Abstract: A Taiwanese patient born with autosomal dominant microcephaly has de novo mutation in ATP6V1B2 (V1B2) gene, which encodes a subunit of V1 subcomplex of the vacuolar-type ATPase (V-ATPase). It has been shown that mutations of V1B2 can lead to a variety of dominant disorders such as dominant deafness-onychodystrophy (DDOD), Zimmermann-Laband syndrome-2 (ZLS2), epilepsy, and/or microcephaly. How mutations in a single gene can lead to drastically different phenotypes remains elusive. Using the in vitro neuronal differentiation model, we found that the expression of microcephalic V1B2 mutations compromises neuronal differentiation while those causing ZLS2 do not. In addition, the microcephalic V1B2 mutations do not affect the acidification of organelles. Interestingly, ATP6V1B2 localizes to Golgi apparatus in embryonal carcinoma cells and the microcephalic mutations disrupts this localization. Our data suggest that V1B2 plays a role in the function of Golgi apparatus which in turn regulates neuronal differentiation and brain development.

Disclosures: T. Kuo: None. **M. Tsai:** None. **E. Hwang:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.07

Topic: A.01. Neurogenesis and Gliogenesis

Support: 3R01GM134358-03S1

Title: Characterization of SIX3 in Human Neural Differentiation

Authors: *C. TORRES ROJAS, X. YANG, J. C. PENG;
Developmental Neurobio., St Jude Children's Res. Hosp., Memphis, TN

Abstract: SIX3 is a transcription factor that controls gene expression in a spatiotemporal specific manner. SIX3 functions in *Shh* signaling, Wnt signaling, postnatal ependymal cell maturation, and in post-proliferative neurons of the hypothalamus and pituitary. However, we still do not know what regulates *SIX3* expression during development in human brain. Also, it is unclear how SIX3 controls its targets in different developmental stages. More than 60 mutations in SIX3 have been causally associated with Holoprosencephaly (HPE), which occurs during the first few weeks of pregnancy in one in 5,000 live births. HPE is characterized by many signs including brain malformation, seizures, and developmental delay. Our lab previously obtained experimental findings suggesting that *SIX3* gene is epigenetically regulated by the UTX-53BP1 axis during human neural differentiation. UTX is a lysine-27-specific demethylase of histone 3, and 53BP1 is a factor that binds to specific histones at double-strand break sites and contributes to the maintenance of heterochromatin and genome stability. Interestingly, there is strong evidence that supports the interaction between SIX3 and NR4A3. NR4A3 is a transcription factor linked to neurogenesis and memory formation in the forebrain. However, little is known about the synchronicity of the expression patterns of SIX3 and NR4A3 in human forebrain

development. We are characterizing the status of SIX3 and NR4A3 in UTX-KO human forebrain stem cells and cortical organoids by RNA-seq and immunofluorescence. We will compare SIX3, NR4A3, and markers of neural stem cells, forebrain stem cells, intermediate progenitors, and cortical neurons. To characterize the effects of SIX3 depletion by CRISPRi in human embryonic stem cells and neural differentiation, we are performing chromatin fractionation, western blot, and immunofluorescence to analyze SIX3 and NR4A3 proteins along stem cell and neural markers. Next, we will compare chromatin fractionation of UTX-KO and wild-type control cells to examine the expression of SIX3 and NR4A3 in cytoplasmic and nucleoplasmic fractions under different experimental conditions. The successful completion of these experiments will illuminate the relationship between the UTX-53BP1 axis and SIX3-NR4A3.

Disclosures: C. Torres Rojas: None. **X. Yang:** None. **J.C. Peng:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.08

Topic: A.01. Neurogenesis and Gliogenesis

Support: HCMI
NIH
SPARK

Title: Therapy-induced changes by BRAF and MEK inhibitors in BRAF V600E-mutated glioma models provide potential novel therapeutic opportunities

Authors: J. PARK[1], ***H. LANCERO**[1], E. NASAJPOUR[1], C. GARCIA[1], C. TRAN[1], G. PEREZ[1], L. PROLO[1], G. GRANT[2], C. K. PETRITSCH[1];
[1]Neurosurg., Stanford Univ., Stanford, CA; [2]Neurosurg., Duke Univ. Sch. of Med., Durham, NC

Abstract: BRAF V600E-mutated murine and patient-derived glioma cell lines (STN-10049, SU-aGBM5) were generated and together with established BRAF V600E-mutated cell lines (DBTRG, AM38) were analyzed for changes in gene expression in response to 48 hrs treatment with BRAFi dabrafenib and MEKi trametinib. Cells were analyzed by RNA-seq and gene enrichment analyses while cell culture supernatant was analyzed for cytokine production using an ELISA. Syngeneic, orthotopic BRAF V600E-mutated tumor allograft-bearing mice were treated with BRAFi+MEKi, with therapeutic antibodies against immune checkpoint molecules (anti-PD-L1 and anti-CTLA-4) and with combination of all four agents, and tumors were analyzed by mass cytometry and immunofluorescence for stem and T cell markers. BRAFi+MEKi treatment induced an interferon gamma (IFNg) response gene signature in BRAF V600E-mutated glioma cells and increased HLA gene expression. The frequency of tumor-infiltrating CD4+ CD8+ T cells in syngeneic BRAF V600E-mutated tumor allografts increased with BRAFi+MEKi treatment. Combining BRAFi+MEKi with anti-PD-L1 and anti-CTLA-4

treatment decreased CD133+ cells more effectively than either therapy alone, and resulted in a T cell-dependent survival benefit of mice with orthotopic BRAF V600E-mutated high-grade glioma. Combination of BRAFi+MEKi with immune checkpoint inhibition should be further explored as a viable option to prevent tumor rebound and therapy resistance in patients with BRAF V600E-mutated glioma.

Disclosures: J. Park: None. **H. Lancero:** None. **E. Nasajpour:** None. **C. Garcia:** None. **C. Tran:** None. **G. Perez:** None. **L. Prolo:** None. **G. Grant:** None. **C.K. Petritsch:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.09

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF IOS 1845673

Title: Persistence of courtship behavior neurons from larval to adult life in Drosophila

Authors: *M. C. WEINSTOCK, J. C. DUCKHORN, J. DIAMANDI, S. LEONE, T. SHIRANGI;
Villanova Univ., Villanova, PA

Abstract: The Tlx/tailless-like nuclear receptor encoded by the dissatisfaction (dsf) gene influences the development of female and male courtship behaviors in Drosophila. Our previous work identified a small sexually dimorphic population of dsf-expressing interneurons in the abdominal ganglion of adult flies, collectively called the DDAG neurons, that regulates most courtship behaviors altered in dsf mutants. Here, we show that the DDAG neurons are anatomically diverse, and a subset of local DDAG interneurons contributes to the opening of the vaginal plates in virgin females during courtship. We provide evidence that the DDAG neurons are born during embryogenesis, exist in the larval CNS of both sexes as mature monomorphic neurons, and sexually differentiate during metamorphosis for functions in the courtship behaviors of adults. This work provides new insights into the development of neural circuits that mediate courtship behavior in Drosophila.

Disclosures: M.C. Weinstock: None. **J.C. Duckhorn:** None. **J. Diamandi:** None. **S. Leone:** None. **T. Shirangi:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.10

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIMH 5R01MH119156
NINDS R01NS102228

Title: A role for septal eminence-derived lateral septum neurons in novelty exploration behavior.

Authors: *M. TURRERO GARCIA[1], C. M. REID[2], D. N. TRAN[2], R. E. PETERSON[2], C. C. HARWELL[1];
[1]Neurol., Univ. of California San Francisco, San Francisco, CA; [2]Harvard Med. Sch., Boston, MA

Abstract: The septum is a ventral forebrain structure that functions as a relay between the limbic system and higher cognition areas. Through their long-range connections with other brain areas, GABAergic neurons in the lateral septum (LS) are involved in circuits that control innate behaviors such as anxiety and aggression. To understand the function of distinct LS neuronal subpopulations, it is necessary to investigate the full extent of their cell type diversity, connectivity patterns, and involvement in defined behaviors. In this study, we generated a mouse model where the deletion of the transcriptional regulator *Prdm16* in neural progenitors expressing *Nkx2.1* and their progeny leads to the loss of an abundant population of LS neurons. We found that this population is largely composed of *Crhr2*-expressing GABAergic neurons, known to drive persistent anxiety through their connections with the anterior hypothalamus. Loss of septal eminence derived neurons led to significant reductions in enkephalinergic innervation into the LS. We performed a series of anxiety-related assays to understand the behavioral relevance of this neuronal population and subsequent altered circuitry, and found increased preference for novelty in mutant *vs*. control mice. Our results show that the developmental loss of *Crhr2*-expressing LS GABAergic neurons leads to altered connectivity patterns, resulting in increased novelty exploration behaviors.

Disclosures: M. Turrero Garcia: None. **C.M. Reid:** None. **D.N. Tran:** None. **R.E. Peterson:** None. **C.C. Harwell:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.11

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH T32HG000045
NIH RF1MH117070

Title: Genome wide profiling of Brd4 enhancer usage across brain masculinization and neurodevelopment using Calling Cards

Authors: *A. YEN, R. D. MITRA, J. D. DOUGHERTY;
Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Behavioral dimorphisms arise from gonadal steroid hormones which play a central role in the development and activation of neural circuits. In males, a perinatal testosterone surge is thought to masculinize the brain and specify sex differences in different cell populations and circuitry across brain regions through hormone-dependent gene regulation. Brd4 is an epigenomic reader that is enriched at active enhancers, which are important for driving gene expression programs that mediate differentiation and cell identity. Whether there are sex differences in Brd4-bound enhancer usage during brain masculinization and how these contribute to sex-biased gene expression are still unknown. Current methods using ChIP-seq and RNA-seq reveal snapshots of epigenetic mechanisms across development, however the destructive nature of these methodologies is a limitation which precludes our ability to directly associate the profiled epigenome to its eventual matured state. We have recently developed Calling Cards, a unique platform to cumulatively record protein-DNA interactions over time. In this study using Calling Cards, we have generated a genome wide profile of Brd4 enhancer usage in male and female mouse brains pre-testosterone surge (E13-E17) and through the surge (E13-P5). We found that in E17 males, Calling Card insertions were enriched in genomic regions associated with neurodevelopmental disorders and autism spectrum conditions (ASC), while many of the top enhancers in E17 females were associated with congenital renal hypoplasia, a predominantly female biased condition. At P5 post-testosterone surge, ASC was the top enriched ontology for both males and females, however males had twice the number of genes present in the annotated list compared to females. Our preliminary results provide a "ground truth" profile of Brd4-bound enhancer usage across brain masculinization and the perinatal testosterone surge. We anticipate that by using this recording technology, we can capture transient enhancer usage and identify sex-biased Brd4 activity that would otherwise be missed by using standard snapshot technologies. This can have broad implications for understanding the sex-biased gene regulation and mechanisms contributing to autism spectrum conditions.

Disclosures: **A. Yen:** None. **R.D. Mitra:** None. **J.D. Dougherty:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.12

Topic: A.02. Postnatal Neurogenesis

Support: Sigrid Juselius Foundation
Leon Levy Foundation
NIH Grant NS114545

Title: Histone bivalency regulates the timing of differentiation and glial-guided migration in developing cerebellar granule cells

Authors: *K. MÄTLIK[1], E.-E. GOVEK[1], M. R. PAUL[1], E. KORB[2], T. S. CARROLL[1], C. D. ALLIS[1], M. E. HATTEN[1];
[1]The Rockefeller Univ., New York, NY; [2]Penn Epigenetics Institute, Perelman Sch. of Medicine, Dept. of Genet., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Developing neurons undergo a complex series of morphological and gene expression changes to transition from neuronal progenitors to mature postmitotic neurons. While the general mechanisms of epigenetic regulation in developing neurons are starting to emerge, the dynamics of chromatin landscape that regulate gene expression in specific types of neurons across neurodevelopment are largely unknown. Here, we used RNA-seq and ChIP-seq to characterize gene expression and histone post-translational modifications in a specific neuron type, the mouse cerebellar granule cell (GC), during key stages of neurodevelopment: neurogenesis, glial-guided migration, and maturation. We discovered that proliferating GC progenitors exhibit a preponderance of H3K4me3/H3K27me3 bivalent domains at GC lineage-specific genes, suggesting that histone bivalency is critical for regulating gene expression dynamics during GC development. We next used a fluorescent probe binding H3K4me3 and H3K27me3 bivalent domains to identify truly bivalent chromatin in individual GC progenitor cells and differentiated GCs. Lastly, using an inhibitor of H3K27 methyltransferases EZH1 and EZH2 in cultures of GCs and organotypic *ex vivo* slices, we found that loss of bivalency perturbs the developmental progression from GC progenitor proliferation to glial-guided migration and neuronal maturation. In conclusion, these results suggest that histone bivalency is required for the developmental transition from neuronal progenitor stage to mature postmitotic neurons and have yielded insight into the chromatin mechanisms that regulate key stages of neuronal development in a specific CNS neuron type *in vivo*.

Disclosures: K. Mätlik: None. **E. Govek:** None. **M.R. Paul:** None. **E. Korb:** None. **T.S. Carroll:** None. **C.D. Allis:** None. **M.E. Hatten:** None.

Poster

686. Neurogenesis and Differentiation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 686.13

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01 AA016959
T32AA007471

Title: Similar differentiation of cells born during reactive proliferation in female rats following alcohol dependence

Authors: *N. N. NAWARAWONG[1], K. R. THOMPSON[2], R. CLARK[2], K. NIXON[3]; [1]Univ. of Texas at Austin, Austin, TX; [2]Univ. of Texas, Austin, Austin, TX; [3]Pharmacol. & Toxicology, Univ. Of Texas At Austin Inst. For Neurosci., Austin, TX

Abstract: Alcohol use disorder among women has steadily risen over the past decade. Recent studies indicate that females are more susceptible to alcohol-induced brain damage, such as decreases in hippocampal volume in humans and loss of dentate gyrus granule cells in rats. Interestingly, upon abstinence from alcohol dependence, a reactive increase in cell proliferation has been observed in the dentate gyrus of both male and female rats, a phenomenon that may correspond to the recovery of hippocampal structure and function. Using a pulse-chase method, our lab has previously reported that this reactive increase produces no change in cellular phenotype on day 35 of abstinence in male rats. However, whether this is similar in females is unknown. Here, at day 35 of abstinence, we examined the phenotype of cells born during peak ethanol-induced reactive proliferation (T7). Female Sprague Dawley rats of a similar age (PND 65-70) were gavaged with either a 25% (w/v) ethanol diet or an isocaloric control diet every 8 hours for 4 days. Ethanol-treated rats received a mean dose of 10.4 ± 0.3 g/kg/day, which produced peak blood ethanol concentrations (BECs) of 374.7 ± 23.2 mg/dL as measured on the third day of the binge. Withdrawal behaviors, assessed 10-28 hours post final dose, averaged 0.9 ± 0.3 out of 4 with a maximum score of 2.7 ± 0.3, all of which was similar to past male work. At T7 (peak reactive proliferation), bromodeoxyuridine (BrdU, 300mg/kg; i.p.) was administered and brains were harvested 28 days later (T7+28). Following transcardial perfusion, brains were sectioned on a vibrating microtome at 40μm and processed utilizing both 1) BrdU immunohistochemistry (DAB) and 2) triple-label immunofluorescence for BrdU, neuronal nuclei (NeuN, a mature neuronal marker), and glial fibrillary acidic protein (GFAP, astrocytes). We found a 73% increase ($p<0.05$) in T7 labeled BrdU+ cells 28 days later in the dentate gyrus of ethanol-treated females compared to controls. To assess cell fate, approximately 30 BrdU+ cells per rat were examined for co-labeling with NeuN or GFAP. In control rats, BrdU+ cells co-labeled with NeuN 81.2 ± 4.7% and GFAP 5.1 ± 1.9%. Despite the increase in T7 labeled BrdU+ cells in ethanol-treated rats, the phenotypic proportions were similar to controls at 84.2 ± 3.2% BrdU+/NeuN+ and 8.3 ± 2.8% BrdU+/GFAP+. Taken together, this data suggests that while the ethanol-induced increases in cellular proliferation at T7 remains detectable 28 days later, the rate of cellular differentiation into neurons and phenotypic proportions of the dentate gyrus remain unchanged.

Disclosures: **N.N. Nawarawong:** None. **K.R. Thompson:** None. **R. Clark:** None. **K. Nixon:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.01

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

Support: NIH R01 Grant HD052731
NIH Grant 1T32HL139438-01A1

Title: Mef2c transcriptional activation drives experience-dependent development of layer 4 to layer 2/3 excitatory synapses in sensory cortex.

Authors: J. N. PUTMAN[1,2], Z. ZHANG[1,2], N. KHANDELWAL[1,2], J. R. GIBSON[1,2], K. M. HUBER[1,2];
[1]Dept. of Neurosci., [2]O'Donnell Brain Inst., UT Southwestern Med. Ctr., Dallas, TX

Abstract: Experience and activity-dependent transcriptional activation is an understudied candidate mechanism for development and refinement of specific cortical circuits. Here we establish that the activity-dependent transcription factor Myocyte-Enhancer Factor 2C (MEF2C) is selectively required for excitatory synaptic development from Layer (L)4 to L2/3 neurons in mouse primary somatosensory (S1) barrel cortex. Postnatal deletion of gene *Mef2c* in L2/3 neurons causes a cell autonomous and selective weakening of excitatory synapses from L4, whereas inputs from contralateral S1 or frontal cortex are unaffected. Deletion of *Mef2c* 2-3 weeks postnatally has no effect on L4→L2/3 synaptic strength, indicating an early developmental role for MEF2C in synapse formation. Sensory deprivation by whisker trimming weakens L4→L2/3 synaptic strength and is rescued by postnatal expression of transcriptionally active MEF2C (MEF2-VP16), suggesting that MEF2C transcriptional activation drives experience-dependent development of L4→L2/3 synapses. In humans, loss-of-function mutations in *Mef2c* cause MEF2C Haploinsufficiency Syndrome (MCHS); characterized by intellectual disability, epilepsy, and autism. Postnatal homozygous or heterozygous *Mef2c* deletion in excitatory neurons using BAC-CaMKII-iCre also exhibit weak L4→L2/3 excitatory synaptic inputs; an effect not observed in heterozygous *Mef2c* deletion only in postsynaptic L2/3 neurons. These results suggest a role for MEF2C in presynaptic L4 neurons for synapse development onto L2/3 neurons. Ongoing experiments are testing this possibility. In contrast to postnatal *Mef2c* deletion, germline heterozygous deletion of *Mef2c*, modeling MCHS, had normal L4→L2/3 synaptic strength suggesting that compensatory mechanisms form normal L4 to L2/3 circuits with prenatal *Mef2c* deletion.

Disclosures: J.N. Putman: None. **Z. Zhang:** None. **N. Khandelwal:** None. **J.R. Gibson:** None. **K.M. Huber:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.02

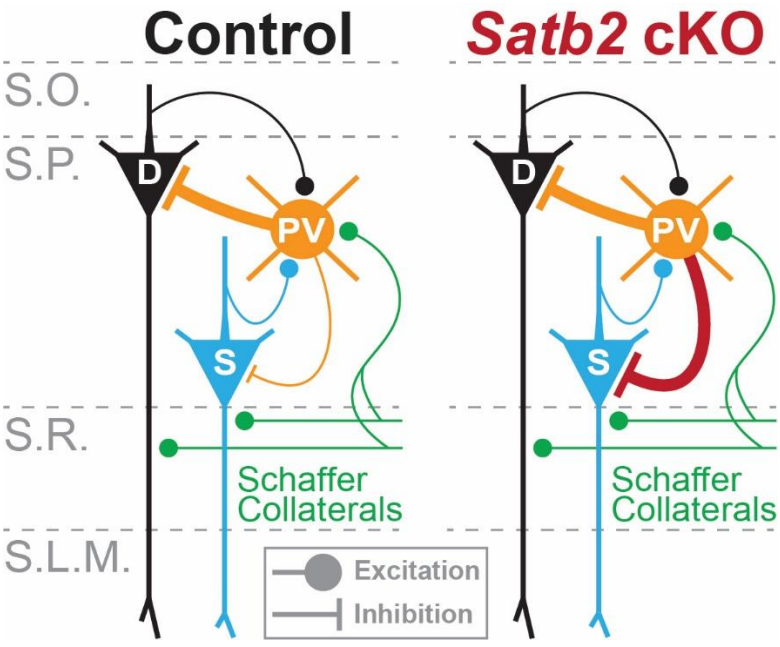
Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH R01MH124870
SFARI Pilot Award #724187

Title: The transcription factor Satb2 regulates pyramidal neuron integration into hippocampal circuits

Authors: *M. A. HANSON, D. NAGARAJAN, N. BIBI, A. H. MARSHALL, J. C. WESTER; Dept. of Neurosci., The Ohio State Univ., Columbus, OH

Abstract: Pyramidal cells (PCs) in CA1 provide the output of hippocampal computations to the rest of the brain. These CA1 PCs can be parsed based on laminar position into two subgroups: deep and superficial. It is hypothesized that deep and superficial PCs are functionally distinct, due in part to their differential synaptic connectivity with local inhibitory interneurons. In particular, parvalbumin basket cells (PVBCs) preferentially inhibit deep PCs, resulting in enhanced feedforward inhibition of afferent input from CA3 Schaffer collaterals. The mechanisms regulating this differential circuit integration of deep and superficial CA1 PCs are unknown. The transcription factor *Satb2* is crucial for the differentiation of neocortical PC subtypes, and it is preferentially expressed in superficial CA1 PCs. Thus, we hypothesized it may play a role in the differentiation and circuit integration of hippocampal PC subtypes. We conditionally knocked out (cKO) *Satb2* from excitatory neurons during early development. We then performed paired whole-cell recordings between PVBCs and deep and superficial PCs in brain slices from juvenile control and *Satb2* cKO mice. Strikingly, we found that *Satb2* cKO abolished biased PVBC inhibition of deep PCs by preferentially increasing PVBC inhibition of superficial PCs. To examine the impact of this change in synaptic strength on feedforward inhibition, we recorded the responses of each PC subtype to Schaffer collateral stimulation in the presence and absence of GABA blockers. With inhibition blocked, we found that *Satb2* does not regulate the strength of excitatory Schaffer collateral synapses. With inhibition intact, in control mice, we observed greater feedforward inhibition onto deep PCs compared to superficial. However, in *Satb2* cKO mice, feedforward inhibition increased selectively onto superficial PCs, resulting in excitatory responses of comparable amplitudes in both superficial and deep PCs. We conclude that *Satb2* expression in superficial PCs maintains differential feedforward inhibitory circuitry between deep and superficial layers in CA1.



Disclosures: **M.A. Hanson:** None. **D. Nagarajan:** None. **N. Bibi:** None. **A.H. Marshall:** None. **J.C. Wester:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.03

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

Support: NIH Intramural Award to CJM

Title: Regulation of somatostatin interneuron excitability by GluN1/GluN3a excitatory glycine receptors influences hippocampal network dynamics throughout development

Authors: *J. KIM, A. VLACHOS, K. PELKEY, C. J. MCBAIN;
Section on Cell. and Synaptic Physiol., Eunice Kennedy Shriver Natl. Inst. of Child Hlth. and Human Develop. (NICHD), Natl. Inst. of Hlth. (NIH), Bethesda, MD

Abstract: Hebb's postulate "Neurons that fire together wire together" is a foundational theory describing relationships between the precise timing of neuronal firing with synaptic plasticity. To satisfy the rule, repetitive synchronized activity is critical for nascent circuit formation as well as learning and memory within mature neural circuits. Prototypical examples of such immature network dynamics are giant depolarizing potentials (GDPs), which are observed around the first postnatal week in the hippocampus. GDPs are intrinsically generated recurring spontaneous waves of neuronal depolarization synchronously experienced across the network, driving synaptic maturation. Interestingly, GDPs are paced by GABAergic transmission which, despite serving as the dominant inhibitory transmitter throughout the mature CNS, provides depolarizing influence early in development due to reversed chloride gradients in immature neurons. Amongst the relatively sparse but highly diverse population of GABAergic interneurons, accumulating evidence indicates that one subtype, somatostatin expressing interneurons (SOMIs), serve as hub elements largely responsible for coordinating GDPs in the neonatal hippocampus. Recently, SOMIs were reported to express conspicuously high levels of *GRIN3A* throughout development and we have determined that SOMI excitability is strongly influenced by non-conventional GluN1/GluN3A diheteromeric receptors from early postnatal to adult ages. These NMDA receptors (NMDARs) are distinct from the ubiquitously expressed GluN2-containing conventional NMDARs, in being voltage independent (ie. Mg^{2+} insensitive) and gated solely by glycine, a co-agonist at conventional NMDARs. Our evidence further indicates that these GluN1/3A excitatory glycine receptors (eGlyRs) strongly influence SOM interneuron pacemaking firing activity in the developing hippocampus with dramatic consequences for GDPs throughout the dentate, CA3 and CA1 hippocampal subregions. In the mature hippocampus, we obtained evidence implicating SOMI eGlyRs in regulating sharp wave ripples, network oscillations associated with memory consolidation. Finally, our data are consistent with SOMI eGlyRs being tonically engaged by endogenous glycine rather than phasically from afferent

inputs, consistent with prior observations that conventional NMDAR co-agonist binding sites are tonically occupied. Collectively, the data suggest that eGlyRs influence SOMI excitability to regulate synchronized network rhythms associated with circuit and memory formation, yielding novel insight into physiological roles of the notoriously enigmatic GluN3A subunit.

Disclosures: J. Kim: None. **A. Vlachos:** None. **K. Pelkey:** None. **C.J. McBain:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.04

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

Support: KAKENHI JP 21H05702
KAKENHI JP 21K15199

Title: Golgi apparatus polarization facilitates dendritic refinement in the developing neocortex

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Abstract: Dendritic refinement is a critical process in neuronal circuit maturation, through which individual neurons establish specific connectivity with their target axons. Here, we demonstrate that the polarity formation of the Golgi apparatus localization in developing neurons is a key step of dendritic refinement. We found that layer 4 (L4) spiny stellate neurons (barrel cells) in the neonatal mouse barrel cortex transiently exhibited a unique Golgi distribution pattern, which was laterally biased toward the barrel center. This Golgi polarization peaked at postnatal day 5-7 (P5-7) and disappeared by P15, which matched with the developmental time course of the barrel cell dendritic refinement. Golgi polarity perturbation resulted in failed formation of dendritic orientation toward the barrel center and response specificity to their principal whiskers in barrel cells. Genetic ablation of NMDAR, which is a key player in dendritic refinement, in barrel cells impaired Golgi polarity. Our results highlight activity-dependent Golgi dynamics in developmental neuronal circuit refinement.

Disclosures: N. Nakagawa: None. **T. Iwasato:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.05

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

Support: SFARI Bridge to Independence Award

Title: Striatal regulation of cortical activity during postnatal development

Authors: *T. DEEMYAD[1], R. PEIXOTO[2];
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Abstract: The postnatal maturation of the mammalian brain is highly dependent on experience and activity-dependent mechanisms. A previous study has shown that the establishment of corticostriatal connectivity onto striatal medium spiny neurons (MSNs) is affected by activity imbalance of the striatal direct and indirect output pathways. Silencing of neurotransmitter release in D1, and D2 MSNs in striatum, during the second postnatal week, resulted in opposing changes in striatal mEPSCs (Kozorovitskiy et al., 2012). Importantly, these changes were not induced by sparse manipulations of MSNs suggesting that they are driven by changes in network activity across the cortico-basal ganglia-thalamic loops. To directly test whether manipulations of striatal activity affect cortical activity during postnatal development, we ablated D1 and D2 MSNs by unilaterally injecting of pAAV-flex-taCasp3-TEVp virus in the striatum of D1-Cre or A2A-Cre. This strategy induces cell-autonomous apoptosis in a cre dependent manner during the period of natural MSN apoptosis, minimizing toxicity to adjacent non-cre+ cells. In the same pups, pGP-AAV-syn-jGCaMP8s-WPRE was injected to L2/3 of both dorsal anterior cingulate cortices (ACC) at P1 to study the neuronal cortical activity at P13; P16 and >P60. Green fluorescence from the genetically encoded calcium indicator GCaMP8s was imaged simultaneously from layer 2/3 of ACC in both hemispheres. Our results show that ablation of D1 MSNs results in a decrease in frequency of spontaneous neuronal cortical activity in ipsilateral compared to the contralateral hemisphere as early as P13 without affecting the amplitude of responses. In contrast, ablation of D2 MSNs, increase the frequency of spontaneous cortical activity later at P16. These changes in spontaneous cortical firings are preserved up to adulthood (i.e>P60). These results suggest that early developmental dysfunction of the striatum can alter cortical activity.

Disclosures: T. Deemyad: None. **R. Peixoto:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.06

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

Support: NIMH grant MH067842
The Saban Research Institute of Children's Hospital Los Angeles Pre-Doctoral Award

Title: Single cell gene expression analysis and spatial organization of excitatory neuron populations in the developing primary visual cortex

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Abstract: The primary visual cortex (V1) is involved in the execution of diverse social and sensory behaviors. This variety in behavioral outputs requires heterogenous neuron populations with different molecular phenotypes and subcortical projection patterns. We have demonstrated through immunocytochemical mapping that a distinct subgroup of cortical projection neurons express *Met*, a pleiotropic gene that encodes the multifunctional c-Met receptor tyrosine kinase (MET). *Met* expression peaks in the mouse V1 between postnatal days (P) 7-14, corresponding with rapid synaptogenesis, after which protein levels decrease. Very little is known about the whether there are unique transcript signatures of *Met* expressing (*Met* +) cortical neuron subtypes at these developmental timepoints. To understand how *Met* expression during early development influences cortical neuron heterogeneity and circuit formation, we performed single cell RNA sequencing on mouse V1 at P8. We show for the first time that expression of the gene encoding MET's sole ligand, *Hgf,* is largely confined to subsets of astrocytes in V1. In addition, we confirm that *Met* is primarily expressed in excitatory neurons in V1 of P8 mice and demonstrate that only a small subpopulation of inhibitory neurons express *Met*. Cluster analysis reveals that *Met* is enriched in subgroups that are also enriched for canonical cortical layer and projection type markers in postnatal mice, such as *Satb2, Cux2, Bcl11b, Fezf2, Tle4,* and *Tbr1*. In addition, we demonstrate that *Met* expression is enriched in cortical layers 2/3, layer 5, and layer 6 in V1 at this developmental timepoint. Interestingly, *Met* is only enriched in one of two layer 5 subclusters, suggesting that *Met*+ layer 5 cortical neurons fall into a specific layer 5 subclass. Differential gene expression (DGE) analyses between *Met*+ and *Met*- neurons is being performed to identify gene expression patterns that define *Met*+ subpopulations within each layer. Additional clustering of all *Met*+ neurons and DGE analysis between different *Met*+ populations across cortical layer-specific clusters will elucidate the molecular heterogeneity within the *Met*+ subclass of neurons. Gene ontology analysis will elucidate cellular and physiological pathways that distinguish *Met*+ neurons from other neurons at this developmental age. And finally, Hiplex RNAScope is being used to validate and further investigate the transcriptomes and topology of different populations of Met+ neurons in the P8 primary visual cortex.

Disclosures: R. Ali Marandi Ghoddousi: None. **K.L. Eagleson:** None. **Z. Rady:** None. **P.R. Levitt:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.07

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

Support: NS076661
NS097537

Title: Hyperactive ERK1/2 in glutamatergic neurons alters connectivity in the mouse cortex

Authors: *K. P. REES[1], G. R. BJORKLUND[2], T. RICHARDSON[1], K. RIORDAN[1], J. M. NEWBERN[1];
[1]Sch. of Life Sci., [2]Sch. of Biol. and Hlth. Sci., Arizona State Univ., Tempe, AZ

Abstract: Glutamatergic neurons comprise 80% of the total neuron population in the cerebral cortex, however, the function of the RAS/RAF/MEK/ERK signaling cascade within this subpopulation of cells is not well understood. Clearly defined mutations within this pathway cause syndromes known as the RASopathies. Clinical symptoms include intellectual disability, developmental delay, cardio-facial deficits, and in some cases hypotonia. A majority of RASopathies are attributed to hyperactivation of ERK1/2 signaling. Individuals with Neurofibromatosis Type 1 (NF1) and Noonan Syndrome (NS), two common RASopathies, exhibit aberrant structural connectivity in diffusion tensor imaging (DTI) studies, however, the contributions of axonal versus oligodendrocyte deficits to this phenotype are not fully understood. Here, we used a conditional genetic approach to delineate the neuron autonomous effects of hyperactive ERK1/2 in glutamatergic neurons of the mouse cortex. We have previously found reduced corticospinal tract (CST) axon extension in these mutants. We now show that this defect is layer V neuron autonomous using a Cre-dependent reporter and anterograde viral tracing. We have also implemented retrograde viral tracings to better understand input into primary motor cortex (M1). Moreover, we show enhanced activated ERK1/2 in spatially distinct sub compartments of neurons. We also explored oligodendrocytes in these neuron Cre-lines to better understand axonal and oligodendrocyte contributions, if any. The relationship between structural and functional connectivity has not been explored in these mutants, we therefore investigated the expression of activity dependent genes response to glutamatergic signaling. Using both pan-glutamatergic and layer V directed approaches, we found that ERK1/2 hyperactivation led to cell autonomous alterations in ARC expression, but not FOS. Overall, our data shows that glutamatergic neuron ERK1/2 hyperactivation during embryogenesis is sufficient to alter both structural and functional connectivity in the mature, adult mouse cortex. Future work will be aimed at elucidating the direct ERK1/2 mediated molecular mechanisms important for circuit formation.

Disclosures: K.P. Rees: None. **G.R. Bjorklund:** None. **T. Richardson:** None. **K. Riordan:** None. **J.M. Newbern:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.08

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

Support: Grant-in-Aid for JSPS Research Fellow Grant Number JP21J15115 to C.K-N.
Grant-in-Aid for Scientific Research (KAKENHI) Grant Number JP20H03346 to T.I.
Grant-in-Aid for Scientific Research (KAKENHI) Grant Number JP21K18245 to T.I.
Grant-in-Aid for Scientific Research (KAKENHI) Grant Number JP16H06459 to T.I.
Collaborative Research Project (2021-#20011) of Brain Research Institute, Niigata University to T.I.

Title: Brainstem-specific NMDAR ablation in the mouse unveils aspects of somatosensory circuit refinement during postnatal development

Authors: *C. KIMURA-NAKAJIMA[1,2], A. SUZUKI[1,2], T. IWASATO[1,2];
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Abstract: The whisker-barrel system in rodents is an excellent model of activity-dependent neural circuit formation. Tactile information from the whiskers reaches through the brainstem and thalamus to the cortex layer 4, where there are whisker-related patterns called barrelettes, barreloids, and barrels, respectively. These patterns are formed during a postnatal week, in which NMDA receptors (NMDARs) play key roles (Li et al., Cell 1994; Kutsuwada et al., Neuron 1996; Iwasato et al., Neuron 1997, Nature 2000; Arakawa et al., J. Neurosci. 2014). To uncover specific roles of brainstem NMDARs in somatosensory circuit refinement, we here generated Bs[K]-NR1KO and Bs[KH]-NR1KO mice, in both of which NMDARs are specifically ablated in the brainstem. In Bs[K]-KO mice, brainstem barrelettes were absent but cortical barrels were present, albeit partially. Cre-mediated gene knockout was incomplete in the brainstem ventral trigeminal principal nucleus (vPrV) of these mice. In Bs[KH]-KO mice, Cre-mediated gene disruption occurred in most vPrV neurons, and both of barrelettes and barrels were absent. These results suggest that brainstem NMDARs indirectly contribute to cortical circuit maturation by providing a template of whisker-map information. We also found that, when NMDARs were ablated in the thalamus of Bs[K]-KO mice, barrels disappeared. These unique Bs[K]-KO mouse phenotypes suggest that the developing thalamus may serve for cortical circuit refinement not by simply relaying a brainstem-derived template but also by compensating an incomplete template, in which thalamic NMDARs play a role. This study provides direct evidence for the role of brainstem NMDARs for cortical circuit formation and highlights aspects of subcortical NMDAR functions.

Disclosures: C. Kimura-Nakajima: None. **A. Suzuki:** None. **T. Iwasato:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.09

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

Support: NIH IPR Grant ZIAMH002959

Title: Development of inhibitory connection from cortical VIP to SST GABAergic neurons

Authors: *S. LEE, P. STEVENSON, A. R. INACIO, S. NASKAR;
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Abstract: Disinhibition mediated by vasoactive intestinal polypeptide (VIP)-positive GABAergic interneurons (INs) is a robust circuit motif found in all cortical areas. VIP INs inhibit other types of cortical GABAergic INs, but its inhibition of dendrite-targeting somatostatin (SST)-positive INs is particularly strong, leading to the disinhibition of pyramidal neurons. This cortical disinhibitory circuit motif has been shown to play an important role in sensorimotor integration, selective attention, gain control, and circuit plasticity. However, the mechanisms by which this robust circuit motif emerges throughout the cortex during early development is largely unknown. Specifically, little is known about the developmental mechanisms of inhibitory synapses from GABAergic INs to other GABAergic INs. To study the developmental process of VIP INs to SST INs connections, we first determined the temporal profile of synaptic connectivity from VIP INs to SST INs. We found that VIP INs provide functional synaptic connections to SST INs as early as postnatal day (P) 7, while pyramidal neurons received inhibition from VIP INs later, starting from P13. We then asked whether the spontaneous activity of VIP INs during this early postnatal window affects the connectivity from VIP INs to SST INs in adulthood. Using a chemogenetic approach, we manipulated the activity of VIP INs during two time periods - first, during the establishment of connectivity from VIP INs to SST INs (P5-12), and second, from VIP INs to pyramidal neurons (P13-20). Alteration of the activity of VIP INs during the earlier time window, P5-12, permanently impairs the strong synaptic connectivity from VIP INs to SST INs in the cortex. However, the manipulation of VIP INs activity during the later window does not affect the connectivity from VIP INs to neither SST INs, nor pyramidal cells. Taken together, we found that VIP INs preferentially form connections to SST INs earlier than to other cell types, and that the emergence of this inhibitory-to-inhibitory connection is governed by activity of the presynaptic VIP INs. Our results suggest that the activity in VIP INs during early development can significantly affect the top-down modulation mediated by cortical disinhibitory circuits later in life.

Disclosures: S. Lee: None. **P. Stevenson:** None. **A.R. Inacio:** None. **S. Naskar:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.10

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

Support: NIH Grant U54 MD007601

Title: The Critical Role of Selenium in Perineuronal Net and GABAergic inhibitory circuit development

Authors: *A. SASUCLARK, M. PITTS;
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Abstract: The development of parvalbumin interneurons (PVIs) is critical to the formation of cortical circuits and the maintenance of synchronous network activity. Parvalbumin interneurons are categorized by their high oscillatory firing rate which makes them susceptible to the effects of increased oxidative stress. Changes to PVIs antioxidant defense mechanisms leaves the cell vulnerable to oxidative damage and consequently, developmental stalling. Selenoproteins, one of the major redox enzyme families, are necessary for the proper development of PVIs. Neuron specific knockout models for Trsp (gene encoding the selenocysteine tRNA), GPx4, and total body knockout for selenoP, reveal reduced PVI expression, cognitive impairments, and death in model organisms. During development PVIs develop a special extracellular matrix surrounding their soma and proximal dendrites known as a perineuronal net (PNN). This lattice-like matrix helps stabilize synaptic connections onto PVIs and provides scaffolding for the formation of neural networks. PNNs have been suggested to assist in managing excess oxidative stress, however this mechanism is not fully explored. We hypothesized that disruption to selenium homeostasis generates excess oxidative stress, which impairs PNN formation and alters the balance of excitatory/inhibitory inputs onto PVIs. To test this hypothesis, we isolated primary cortical neurons from E16 mouse embryos and plated them on glass coverslips and microelectrode array (MEA) plates. Neurons were maintained in serum-free media supplemented with sodium selenite (0 - 1000 nM). We observed the development of cortical networks by assessing electrical activity in our MEA system weekly for 6-weeks. Additionally, we conducted immunocytochemical analysis and antioxidant activity on our cells after 4-weeks of development, utilizing antibodies against PV, vGlut1, VGAT, and a lectin against PNNs. We found that in our 10 nM and 1 uM selenium conditions PNNs develop poorly, exhibiting lower expression and being fewer in number compared to our 100 nM condition. When we conducted parallel experiments in vivo in mice, we found that mice provided deficient selenium (0 uM) had PNNs with weaker expression, and larger and fewer holes in the lattice matrix, compared to mice provided optimal selenium (10 uM). We also observed differences in the electrical activity of our primary cultures, with our 10 nM condition exhibiting higher burst frequency compared to our 100 nM condition. Overall, our results show that selenium is an important modulator of PNN maturation and suggests that selenium deficiency impedes proper development of GABAergic inhibitory circuits.

Disclosures: **A. Sasuclark:** None. **M. Pitts:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.11

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

Support: NIH Grant DC007695

Title: The role of spontaneous activity in maturation of the calyx of held nerve terminal and its synaptic target in the medial nucleus of the trapezoid body

Authors: *D. HELLER[1], E. AMICK[1], S. M. YOUNG, Jr.[2], H. VON GERSDORFF[3], G. SPIROU[1];
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Abstract: The formation of neural circuits in early development can occur independent of neural activity, but their maturation and refinement is an activity-dependent mechanism. Intrinsic patterned spontaneous activity (SA) occurs in several brain regions during development, including the visual and auditory sensory systems. Interestingly, SA in these sensory systems occurs prior to the onset of external stimulation (in mice, ear canals and eyes open after P10), highlighting the importance of stimulus-independent activity during neural circuit formation. In the developing murine auditory system, intrinsic SA originates in the cochlea, beginning at birth, and propagates throughout the ascending auditory pathway. The calyx of Held (CH) is the primary terminus of globular bushy cells (GBCs), whose cell bodies are located in the ventral cochlear nucleus (VCN), and innervates principal cells (PCs) in the medial nucleus of the trapezoid body (MNTB). The CH:MNTB synaptic connection is utilized as a model system for studying the role of SA in neural circuit formation, in part because growth of the CH occurs rapidly (postnatal day (P)2-P6) resulting in mono-innervation, and key biophysical properties of the synaptic partners have been characterized. Previous manipulations to eliminate SA at the developing CH have involved genetic strategies that also affect cochlear function, and may induce homeostatic compensatory mechanisms in GBCs. To overcome this confounding factor, direct manipulation of synaptic transmission through viral vector mediated, rapid-onset expression of tetanus neurotoxin (TeNT) targeting GBCs was employed to silence activity at the CH:MNTB synaptic connection. Following unilateral high titer viral vector injections into the VCN at P0, mCherry fluorescence (co-expressed with TeNT) was detectable within 48 hours in CHs innervating the contralateral MNTB. Compared to non-transduced ipsilateral MNTB control recordings (n = 7), whole-cell patch-clamp recordings from transduced P6 MNTB PCs (n = 4) showed a decrease in the frequency (0.6 ± 0.1 Hz vs 4.0 ± 2.5 Hz; $p < 0.05$) and amplitude (61.8 ± 27.7 pA vs 73.9 ± 33.3 pA; $p < 0.05$), and increase in the decay rate (1.2 ± 0.5 ms vs 0.7 ± 0.3 ms; $p < 0.0001$) of spontaneous excitatory postsynaptic currents. MNTB PCs innervated by transduced calyces showed delayed transition from tonic to phasic firing (0% phasic/100% tonic vs 71% phasic/29% tonic) and increased input resistance (0.4 ± 0.2 GΩ vs 0.2 ± 0.1 GΩ; $p < 0.075$) compared to ipsilateral controls. This study is ongoing and highlights an important role

for SA triggering rapid growth of the CH and the synchronous maturation of the MNTB PC physiological properties.

Disclosures: **D. Heller:** None. **E. Amick:** None. **S.M. Young:** None. **H. von Gersdorff:** None. **G. Spirou:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); syGlass.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.12

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

Support: JSPS KAKENHI JP20H03346
JSPS KAKENHI JP21K18245
JSPS KAKENHI JP16H06459

Title: Spontaneous Activity in the Whisker-Innervating Region of Neonatal Mouse Trigeminal Ganglion

Authors: *P. BANERJEE[1,2], F. KUBO[1,2], H. NAKAOKA[3], R. AJIMA[1,2], T. SATO[1], T. HIRATA[1,2], T. IWASATO[1,2];
[1]Natl. Inst. of Genet., Mishima, Japan; [2]Dept. of Genet., SOKENDAI, Mishima, Japan; [3]Sasaki Inst., Tokyo, Japan

Abstract: Correlated spontaneous activity occurs in certain systems of the developing mammalian brain during the early postnatal period and is thought to be important for the establishment of precise and mature neural circuits following the Hebbian principles of plasticity. In the mouse somatosensory system, the barrel cortex layer 4 excitatory neurons exhibit spontaneous activity in a patchwork-type pattern during the first postnatal week (Mizuno et al., 2018, Nakazawa et al., 2020). Our previous studies revealed that this spontaneous activity in the cortex is blocked by administration of a local anesthetic to the whisker pad, but not by transection of the infra-orbital nerve (Mizuno et al., 2018). Based on these results, we hypothesized that the trigeminal ganglion (TG) in the periphery is the source of spontaneous activity in the neonatal barrel cortex. To investigate whether the neonatal TG shows spontaneous activity or not, we established a system for imaging activity in the TG *ex vivo*. We identified the whisker-innervating region in the TG by application of DiI to the whisker pad. By using a transgenic mouse line expressing a genetically encoded calcium indicator (GCaMP6s) in the TG neurons and the *ex vivo* calcium imaging system, we observed that the neurons in the whisker-innervating region of TG generate sporadic spontaneous activity during the early postnatal period. A modest percentage of neurons showed some evident correlated activity, and these neurons were mostly located close to one-another. The spontaneous activity in TG was majorly demonstrated by the medium-to-large diameter sensory neurons and was inhibited by chelation

of extracellular calcium. Moreover, it was mostly diminished by adulthood. This spontaneous activity in the TG during the first postnatal week may contribute to thalamocortical circuit refinement as the source of patchwork-type spontaneous activity in the barrel cortex.

Disclosures: **P. Banerjee:** None. **F. Kubo:** None. **H. Nakaoka:** None. **R. Ajima:** None. **T. Sato:** None. **T. Hirata:** None. **T. Iwasato:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.13

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

Support: NIH Grant DP2 MH125812
Young Investigator Grant from the Brain and Behavior Research Foundation (UMD)
Seed grant from the Brain and Behavior Institute (UMD)

Title: Melanopsin-dependent local protein translation in developing retinohypothalamic axons

Authors: *R. GUPTA[1], T. A. ALEXANDER[1], S. M. MITCHELL[1], A. T. BELEW[2], N. M. EL-SAYED[2], C. M. SPEER[1];
[1]Dept. of Biol., [2]Cell Biol. and Mol. Genet., Univ. of Maryland, College Park, MD

Abstract: Local protein translation in retinal ganglion cell (RGC) axons enables rapid responses to cell-cell signaling cues during visual system development. Local translation occurs before eye-opening during a time when light detection is mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs) that express the photopigment melanopsin. In this study, we tested the hypothesis that melanopsin signaling regulates local protein translation in developing ipRGCs. Using a knock-in mouse that expresses Cre-recombinase in place of endogenous melanopsin ($Opn4^{Cre}$), we labeled ribosomal proteins with a floxed $Rpl22^{HA}$ line and developed an ipRGC-specific Translating Ribosome Affinity Purification (TRAP) assay. To examine pathway-specific local protein translation, we isolated ribosomes and sequenced the associated translating mRNAs from ipRGC cell bodies in the retina and axons in the dorsal lateral geniculate nucleus (dLGN) and suprachiasmatic nucleus (SCN). We performed these experiments before (P8) and after (P15) eye-opening for comparison with adult (P60) translatomes in both control and melanopsin knockout mice ($Opn4^{Cre/Cre}$::$Rpl22^{HA/+}$). Principal component analysis revealed global differences in the sub-compartment translatomes of ipRGC somata/dendrites in the retinae versus axons in the SCN and dLGN. Differential expression (DE) and gene set enrichment analyses highlight developmental shifts in axonal local protein translation from regulators of neurite growth and synaptogenesis at P8 to proteins involved in synaptic function and maintenance at maturity (P60). Retinohypothalamic and retinogeniculate axons translated an overlapping set of mRNAs as well as hundreds of pathway-specific transcripts across development including

known regulators of axon guidance and neurite growth. Genetic deletion of melanopsin caused upregulation of local protein translation solely in ipRGC axons projecting to the SCN at P8. Our study highlights pathway-specific developmental changes in local protein translation within ipRGC projections and suggests a role for visual experience before eye-opening in the formation of retinal projections to the brain's master circadian pacemaker.

Disclosures: R. Gupta: None. **T.A. Alexander:** None. **S.M. Mitchell:** None. **A.T. Belew:** None. **N.M. El-sayed:** None. **C.M. Speer:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.14

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

Support: NIH grant DP2MH125812
Institutional Startup support provided by the University of Maryland

Title: Super-resolution imaging of activity-dependent subsynaptic domain plasticity in the developing visual system

Authors: *C. ZHANG[1], S. YADAV[2], C. M. SPEER[3];
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Abstract: Super-resolution fluorescence microscopy enables the study of pre/postsynaptic protein aggregates in subsynaptic domains (SSDs) that are co-aligned across the synapse to facilitate synaptic transmission. Changes in SSD number or alignment may be regulated by spontaneous neural activity as a mechanism contributing to synaptic maturation in the developing brain. To test this, we measured SSD properties during the activity-dependent competitive refinement of eye-specific retinal inputs to the dorsal geniculate nucleus (dLGN) of the thalamus. Using volumetric Stochastic Optical Reconstruction Microscopy (STORM) imaging we analyzed ~80,000 eye-specific retinogeniculate synapses during the first postnatal week (P2 to P8) in wild-type (WT) mice and a transgenic line with abnormal spontaneous retinal activity caused by the genetic deletion of the beta 2 subunit of the nicotinic acetylcholine receptor (B2KO). We identified eye-specific synapses by combining pre/postsynaptic immunohistochemical labeling (VGluT2/Bassoon/Homer1) with monocular anterograde tracing using Cholera Toxin Subunit B conjugated with Alexa Fluor 488. In other experiments, we used a cre driver line ($ET33^{Cre}$) to reconstruct a subset of ipsilateral-pathway axons and investigate correlations between synaptic development and axon refinement. Applying voxel intensity-based and deep-learning analysis methods in parallel, we found that postsynaptic Homer1 proteins condensed into fewer SSDs with enriched protein content during development in controls. B2KO mice experienced an opposite effect where Homer1 SSD number increased while protein

enrichment in individual SSDs decreased. In both wild-type and B2KO mice, pre/postsynaptic SSD development did not reflect synaptic competition between the two eyes. By comparing the distribution of pre/postsynaptic proteins across the synapse, we found that SSDs were spatially aligned across the synapse similarly for all ages/genotypes/eye-of-origin. This work demonstrates the developmental and activity-dependent regulation of SSDs underlying synaptic competition and highlights new capabilities of volumetric super-resolution imaging as a tool for studying circuit development in situ.

Disclosures: **C. Zhang:** None. **S. Yadav:** None. **C.M. Speer:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.15

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

Support: NIH Grant R01 EY029323
NIH Grant R01 EY014454
NIH Grant DP2 MH125812

Title: Expansion microscopy (ExM) imaging of retinofugal circuit development

Authors: *C. HERNANDEZ[1], J. B. DEMB[2], C. M. SPEER[1];
[1]Biol., Univ. of Maryland, College Park, MD; [2]Yale Univ., Yale Univ., New Haven, CT

Abstract: Connectivity within visual circuits changes dramatically during early development as neural activity and molecular cues regulate retinal ganglion cell (RGC) synaptogenesis and axonal refinement. Studies of RGC circuit development will benefit from the application of new tools for high resolution imaging with molecular labeling information in situ. Volumetric super-resolution fluorescence imaging by expansion microscopy (ExM) is one strategy that utilizes hydrogel chemistry to physically expand biological samples and thereby enable nanoscale analysis of synaptic properties in brain tissue. In this work, we report our experimental approach for studying RGC synaptic connectivity in the mouse retina and brain by combining immunohistochemical synaptic protein staining, cellular labeling of RGCs and postsynaptic target neurons, and ExM imaging to achieve an ~4x isotropic increase in spatial resolution. Using cre-dependent TIGRE 2.0 and mononucleotide repeat frameshift (MORF) reporter mice we drove strong fluorescent protein expression in ipsilateral eye-specific ($ET33^{Cre}$) and ON alpha RGC ($Opn4^{Cre}$) projections to central brain targets. We combined this axon labeling with antibodies against presynaptic (VGluT2 / Bassoon) and postsynaptic (Homer1 / AMPAR) proteins to measure RGC synaptic output maturation during the refinement of retinogeniculate and retinohypothalamic axons. In parallel, we characterized the molecular organization of inhibitory input to ON alpha RGCs in the retina using antibodies against presynaptic (Bassoon / VGAT) and postsynaptic (Gephyrin / GABAR / GlyR) proteins to identify amacrine cell

synapses. We describe our sample labeling and ExM processing approach for investigating visual circuit development with molecular labeling information, cell-type-specificity, and synapse-level resolution in situ.

Disclosures: C. Hernandez: None. **J.B. Demb:** None. **C.M. Speer:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.16

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

Support: NSERC CGS-Masters
HBHL Fellowship
CIHR Foundation grant FDN-143238

Title: Investigating the functional roles of Wnt3A during retinotectal circuit development

Authors: *R. MCPHEDRAIN, E. S. RUTHAZER;
Neurol. and Neurosurg., McGill Univ. Integrated Program in Neurosci., Montreal, QC, Canada

Abstract: Investigating the functional roles of Wnt3A during retinotectal circuit developmentAuthors*R. A. MCPHEDRAIN, E. S. RUTHAZER ; Neurology and Neurosurgery, McGill University, Montreal, QC
DisclosuresR. A. McPhedrain: None, **E. S. Ruthazer**: None
AbstractThe development of topographic maps in the visual system requires both genetic and sensory experience-dependent factors, but how these different mechanisms interact is poorly understood. Previous studies have implicated Wnt3A as a key retrograde factor for topographic axon guidance and receptive field (RF) plasticity, suggesting that it could facilitate circuit development through both experience-dependent and experience-independent pathways. In the present study, we aimed to clarify the functional role of Wnt3A in the developing retinotectal circuit of *Xenopus laevis* tadpoles. We first used a transgenic reporter line (pbin7Lef-dEGFP) for canonical Wnt signaling to confirm the presence of active Wnt signalling in the optic tectum during retinotopic refinement. To determine the effect of Wnt3A on synaptic physiology, we over-expressed XWnt3A in postsynaptic tectal neurons, recording miniature excitatory postsynaptic currents (mEPSCs), paired-pulse ratio (PPR), and AMPAR/NMDAR ratios. We found that XWnt3A expression increased mEPSC frequency and AMPAR/NMDAR ratios, with no change in mEPSC amplitude or PPR, suggesting Wnt3A could be playing a postsynaptic role in recruiting AMPARs to silent, NMDAR-only synapses. Over-expression of XWnt3A in tectal neurons also increased dendritic branch length after an 8-hour imaging period. Moreover, subjecting animals to visual stimulation, but not darkness, resulted in increased dendritic branch length of XWnt3A-expressing neurons relative to EGFP controls, suggesting that XWnt3A promotes dendritic branch growth through a sensory-dependent mechanism. We also evaluated

the influence of Wnt signaling in regulating retinal ganglion cell (RGC) axon morphology, showing that the disruption of presynaptic Wnt signalling through the expression of a dominant-negative XDsh-ΔPDZ construct increases axon branch number over 4 days. Together, these results demonstrate a multifunctional role for Wnt3A signalling at both pre- and postsynaptic sites during retinotectal circuit refinement. These pleiotropic functions of Wnt signaling provide important insight into how signaling pathways can be dynamically regulated to coordinate circuit development.

Disclosures: R. McPhedrain: None. **E.S. Ruthazer:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.17

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

Support: NIH R01EY019498
NIH R01EY013528
P30EY003176
NSF GRFP
K99EY030909

Title: Identification and testing of cerebellin-4 as a candidate factor mediating type-specific connectivity between retinal ganglion cells and their presynaptic partners

Authors: *J. TWORIG, R. MORRIE, A. TIRIAC, M. B. FELLER;
Mol. and Cell Biol., Univ. of California, Berkeley, Berkeley, CA

Abstract: Direction-selectivity in the retina is mediated by asymmetric inhibitory connections between starburst amacrine cells (SACs) and direction-selective ganglion cells (DSGCs). This wiring occurs in a DSGC subtype-specific manner, such that individual SAC dendrites preferentially synapse onto DSGCs that are tuned to stimuli moving antiparallel to the SAC dendrites (Briggman et al., *Nature*, 2011). Thus, any given DSGC subtype receives input from SAC dendrites that are oriented in that DSGC's null direction. The molecular basis of subtype-specific SAC-DSGC wiring is unknown, but it is likely that DSGCs tuned to motion in different axes express distinct markers that permit synaptogenesis with SAC dendrites oriented in a certain direction. To test this, we have performed RNA sequencing on isolated ON-OFF DSGC populations tuned for either nasal or ventral motion. Differential expression analysis revealed a variety of candidate genes with known functions in cell adhesion or synaptogenesis. We validated expression of several candidates using fluorescent in situ hybridization and immunohistochemistry. We will report progress on testing the role of one candidate, the inhibitory synaptic organizer cerebellin-4 (Cbln4), in the development of direction-selective tuning. Cbln4 is expressed in a subset of retinal ganglion cells which exhibit asymmetric,

ventrally-oriented dendrites. We are currently targeting these cells for whole-cell voltage clamp recording and morphological analysis in wildtype and Cbln4 conditional knockout retinas to determine whether Cbln4 plays a role in inhibitory synaptic development or dendritic morphogenesis.

Disclosures: **J. Tworig:** None. **R. Morrie:** None. **A. Tiriac:** None. **M.B. Feller:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.18

Title: WITHDRAWN

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.19

Title: WITHDRAWN

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.20

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

Support: KAKENHI (21K18245, 20H03346, 16H06459) to TI
JST SPRONG (JPMJSP2104) to AN

Title: Elucidate the mechanism of neural circuit refinement in mouse brain during postnatal development using a rapid protein depletion system

Authors: *A. NIHASHI[1,4], R. AJIMA[2,4], Y. SAGA[2,4], M. KANEMAKI[3,4], T. IWASATO[1,4]; [1]Lab. of Mammalian Neural Circuits, [2]Lab. of Mammalian Develop., [3]Lab. of Mol. Cell Engin., Natl. Inst. of Genet., Mishima, Japan; [4]Dept. of Genet., SOKENDAI, Hayama, Japan

Abstract: Precise neuronal connectivity is established via activity-dependent circuit reorganization during postnatal development. We previously found that the NMDA receptor plays key roles in cortical circuit refinement in the neonatal mouse by using gene knockout approaches (Iwasato et al., Neuron 1997, Nature 2000; Mizuno et al., Neuron 2014). In the current study, we aim to elucidate precise developmental stage-specific roles of NMDA receptors in cortical circuit reorganization. For this purpose, we use the auxin-inducible degron 2 (AID2), which is a newly developed protein knockdown system (Yesbolatova et al., Nat. Commun. 2020). A target protein fused with the mAID tag can be rapidly degraded by 5-Ph-IAA administration in the presence of OsTIR1(F74G). The AID2 system can degrade the mAID-fused target proteins efficiently in most organs of the mouse. However, the previous study that used the adult mouse reported that the AID2 is inefficient in the brain (Yesbolatova et al., 2020). Therefore, before using the AID2 system for the study of neuronal circuit refinement, we needed to examine whether the AID2 system works in the neonatal mouse brain or not. We evaluated the efficiency of AID2-mediated protein degradation using mAID-EGFP reporter mice. Our results confirmed inefficient target protein degradation in the adult reporter mouse brain. In contrast, EGFP signal became undetectable quickly within 3 hours after 5-Ph-IAA administration in the reporter mouse brain at postnatal day 5, which is a promising result. To apply the AID2 system for NMDA receptor function analyses, we generated NR1-mAID knock-in mouse, in which the mAID was fused with the C-terminus of the NR1, the essential NMDA receptor subunit. In the conference, our recent results and future plans will be discussed.

Disclosures: A. Nihashi: None. **R. Ajima:** None. **Y. Saga:** None. **M. Kanemaki:** None. **T. Iwasato:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.21

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

Support: NIH R01MH045573
Del Monte Institute for Neuroscience

Title: Myelin maturation in macaque striatum follows temporal and spatial patterns during development

Authors: *H. O. AWEIS[1], K. H. WANG[2], S. N. HABER[3,4];
[1]Univ. of Rochester, Henrietta, NY; [2]Dept. of Neurosci., [3]Pharmacol. & Physiol., Univ. of Rochester, Rochester, NY; [4]Neurosci., Harvard Med. Sch., Boston, MA

Abstract: The striatum is essential for emotional and behavioral development; however, the underlying morphology contributing to these functions has not been well defined. Myelinogenesis is a critical process of postnatal development. It is necessary for saltatory

conduction of nerve impulses which facilitate complex connectivity of the CNS and enhances skill acquisition. Longitudinal imaging studies show ongoing myelination and protracted white matter growth through adulthood; however, its expansion in the striatum is unknown. The striatum is the primary input nucleus of the basal ganglia and receives overall topographic input from the cortex. These projections are generalized by three broad regions with functional associations: dorsolateral (motor), central (cognition), and ventromedial (emotion/motivation). The dorsolateral striatum receives input from motor and somatosensory cortical areas. The central striatum receives widely convergent input from frontal cortex areas including anterior cingulate cortex (ACC), dorsomedial prefrontal cortex (dmPFC), dorsolateral prefrontal cortex (dlPFC), and ventrolateral prefrontal cortex (vlPFC) which function in cognitive control and behavioral flexibility. The ventromedial striatum receives input from ventral medial prefrontal cortex (vmPFC) and orbitofrontal cortex (OFC) and is associated with the limbic system. The goal of this study is to determine if there are age-related and regional patterns of myelin maturation. We investigated five developmental time points in male macaque via immunohistochemistry, stained for myelin basic protein, and analyzed optical density (OD) of gray matter striatal myelin. The selected experimental ages and their behavioral milestones are as follows: 5-weeks, monkeys emit appropriate responses to social cues; 3-months, fear of strangers and ability to modulate fear; 6-months, initiate grooming with others; 1-year, completion of maternal protection and weaning; 3-years, puberty and beginning of adolescence. Preliminary results on one cohort of animals show age-related increases in gray matter myelin OD. We also noticed regional differences in expression along the ventromedial-dorsolateral axis. At pre-adolescence, dorsolateral regions myelinated first and were most densely myelinated. Central regions were myelinated to a lesser extent and ventromedial regions were least myelinated. By adolescence, all regions achieved the same level of myelination. We are analyzing two additional cohorts. Our findings of spatial and temporal myelin patterns contribute to the understanding of functionally associated morphological changes during development.

Disclosures: H.O. Aweis: None. **K.H. Wang:** None. **S.N. Haber:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.22

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

Support: Dr. Stanley Ho Medical Development Foundation
RGC/CRF C4055-19G

Title: Deficits in myelination lead to poorer neural encoding of speech in preterm infants

Authors: *N. NOVITSKIY[1], P. H. Y. CHAN[1,2], M. S. M. CHAN[1], C. M. LAI[1], S. H. S. LAM[2], T. Y. LEUNG[3], T. F. LEUNG[2], P. C. M. WONG[1];

[1]Dept. of Linguistics & Modern Languages, and Brain and Mind Inst., [2]Dept. of Paediatrics, [3]Dept. of Obsterics and Gynaecology, Chinese Univ. of Hong Kong, Hong Kong, China

Abstract: About one-third of infants who are born preterm are diagnosed with language impairment (Sansavini *et al.*, 2010). The neural underpinning of this deficit may be attributed to the disruption of either synaptogenesis or myelination in the auditory neural system during the perinatal period. We addressed this question by obtaining data of neural encoding of speech from preterm and term infants, more specifically focusing on measures of the frequency-following response (FFR) - a neurophonic component of the EEG. Three-channel 20 KHz-sampled EEG was recorded from 45 early preterm (gestational age 34 weeks or less) and 45 full-term (gestational age 38 weeks or more) sex-matched Cantonese-learning infants. During the recording, subjects listened passively in their sleep to random repetitions of 1860 instances of three different Chinese speech stimuli differing in lexical tone. Twelve FFR measures were extracted after 80-1500 Hz filtering and epoching. Since synaptogenesis is responsible for the overall growth of electrical activity and myelination enhances neural synchronicity, FFR phase-locking measures are more likely associated with myelination, while measures related to power change are more likely associated with synaptogenesis (Anderson *et al.*, 2015). Individual FFR measures were extracted and subjected to Principal Component Analysis and k-means cluster analysis, which resulted in two groups of empirically-derived components we interpreted to be likely myelination-related (Group 1) and synaptogenesis-related (Group 2). Three-way FDR (False Discovery Rate)-corrected ANCOVA revealed that only the Group 1 ($F(1,265)=7.5$, $p=0.007$, $\eta_p^2 =0.027$) but not Group 2 ($F(1,265)=1.09$, $p=0.297$, $\eta_p^2 =0.004$) component was impaired by prematurity. Among the 12 individual measures, only two Group 1 measures, Maximal Inter-Trial Phase Coherence and Response Consistency showed such an effect. The effect of age at EEG was present both in Group 1 measures such as FFR Signal-to-Noise Ratio and Pitch Strength and Group 2 measures such as Lower-Frequency Power and Mid-Frequency Power, consistent with previous findings (Novitskiy *et al.*, 2022). Our data provide preliminary support to the hypothesis that disruption of myelination but not synaptogenesis leads to language impairment due to preterm birth. Findings from this study suggest that neural encoding of speech may serve as a screening test for preterm infants' language developmental problems (Wong *et al.*, 2021).

Disclosures: **N. Novitskiy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent pending. **P.H.Y. Chan:** None. **M.S.M. Chan:** None. **C.M. Lai:** None. **S.H.S. Lam:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent pending. **T.Y. Leung:** None. **T.F. Leung:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent pending. **P.C.M. Wong:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Foresight Language and Learning Solutions Limited founder, patent pending.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.23

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

Support: NIH R01 EY031597

Title: Experience-dependent circuit consolidation in the Xenopus optic tectum

Authors: *C. R. MCKEOWN, R. L. FAULKNER, H. T. CLINE;
Scripps Res., La Jolla, CA

Abstract: Sensory input directs circuit development. In the developing *Xenopus laevis* visual circuit, enhanced visual experience promotes synaptogenesis, dendritic arbor elaboration, the refinement of topographic maps, maturation of neuronal response properties, and rehabilitation of the injured visual circuit. However, the mechanisms by which enhanced visual experience drives these processes remain largely unknown. We electroporated the calcium indicator GCaMP6f into the neural progenitor cells in optic tectum. This labels an age-related cohort of optic tectal neurons from which we image visually-evoked neuronal responses *in vivo* as neurons mature. We collected *in vivo* time-lapse images of visually-evoked calcium transients in the same cells over multiple time points in animals that were exposed to short-term visual experience (STVE) or ambient light conditions. A majority of GCaMP+ tectal neurons failed to show visually-evoked responses at the first imaging timepoint, but exposure to just 4h of STVE significantly increased the frequency and magnitude of visually-evoked calcium spikes compared to controls, consistent with previous electrophysiological findings that STVE promotes the maturation of neuronal response properties and integration of developing neurons into the tectal circuit. Surprisingly, imaging the same cells after a subsequent 16h overnight period indicated that the magnitude and reproducibility of visually-evoked calcium transients were increased further. Moreover, significantly more neurons responded to the visual stimulus after the overnight period in the STVE group as compared to controls. The enhanced visual responsivity of neurons detected the day after STVE was greater than that seen with exposure to two separate STVE epochs, suggesting that unique plasticity events were induced overnight. Our *in vivo* time-lapse data tracking visually-evoked calcium responses in individual neurons within an age-related cohort demonstrates longitudinal visual experience-driven changes in calcium responses within individual neurons in the cohort. These data suggest that a relatively brief exposure to visual stimulation rapidly increases neuronal maturation and circuit integration and furthermore that this same visual stimulation epoch induced delayed plasticity events that occurred during the overnight period which further consolidated the experience-dependent circuit maturation. Future studies will use this *in vivo* longitudinal imaging and analysis pipeline to examine candidate plasticity mechanisms regulating visual experience-dependent neuronal integration into the functional visual circuit.

Disclosures: C.R. McKeown: None. **R.L. Faulkner:** None. **H.T. Cline:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.24

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

Support: Stanford Bio-X Bowes Graduate Fellowship

Title: Embryonic Activity-Dependent Formation of Cortical Neuronal Assemblies

Authors: *D. C. WANG[1], F. SANTOS-VALENCIA[2], J. B. DING[3], K. M. FRANKS[2], L. LUO[1]; [1]Stanford Univ., Stanford, CA; [2]Neurobio., Duke Univ., Durham, NC; [3]Neurosurg., Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Neuronal activity plays a vital role in the assembly of neural circuits throughout development, and the architecture of these developing circuits shapes how both sensory and spontaneous activity are processed in early life. While these interactions have been explored in many afferent sensory circuits, the role of activity in shaping intracortical networks remains largely unexplored. Using Targeted Recombination in Active Populations (TRAP), a technique to non-invasively gain genetic access to highly active neurons during a defined time window, I found that the primary olfactory (piriform) cortex is uniquely robustly active in embryonic cortex. Piriform neurons have an ensemble representation of odor and a high degree of recurrent connectivity which may be selectively enhanced between ensemble members. Embryonically active neurons thus may establish a small number of proto-ensembles through Hebbian plasticity, and well-connected ensembles may promote pattern completion to facilitate the olfactory learning and behavior that are crucial for neonatal survival. Embryonically active piriform cell types are predominantly glutamatergic and those known to have high recurrent connectivity within piriform cortex. Using optogenetic stimulation of embryonically active neurons in acute brain slices from P4-7 mice, I found that these neurons are indeed more likely to be connected to each other rather than embryonically inactive neurons of similar cell type. Importantly, these neurons do not receive more total synaptic inputs, suggesting they have selectively increased connectivity to each other. Lastly, using in vivo Neuropixels recordings of awake P6-10 mice, I recorded populations of individual piriform cortical neurons and isolating embryonically active neurons via optotagging. Preliminarily, embryonically active neurons appear to be more broadly responsive to odors with enhanced preferential tuning to maternal odors. Ongoing experiments to silence these neurons either embryonically or postnatally will be conducted to investigate the role of activity in shaping their preferentially connectivity and postnatal tuning to maternal odors.

Disclosures: D.C. Wang: None. **F. Santos-Valencia:** None. **J.B. Ding:** None. **K.M. Franks:** None. **L. Luo:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.25

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

Support: CONACYT for the Ph.D. fellowship 823584

Title: Differences in global functional network connectivity between premature and full-term infants

Authors: *N. LÓPEZ GUERRERO[1], S. ALCAUTER[2];
[1]Inst. De Neurobiologia. Univ. Nacional Autónoma de México, Querétaro, Mexico;
[2]Neurobiología Conductual y Cognitiva, Inst. De Neurobiologia. Univ. Nacional A, Queretaro, Mexico

Abstract: Premature infants, born before 37 weeks of gestation can have consequences on development, even when no anatomical lesions are evident (Rogers et al.,2018).Resting state functional (MRI) naturally sleeping babies allows the characterization of the brain functional connectome, showing decreased long range connectivity (Smyser et al., 2010). Preterm infants have shown alterations in connectivity measures globally (Gozdas et al., 2018).We included 393 preprocessed structural-functional datasets from the developing Human Connectome Project (Hughes et al., 2017), acquired between week 37-44 weeks of postmenstrual age (PMA) and with no radiological signs of white matter lesions. For each subject, we estimated the connectivity matrix as the correlation of the BOLD time series between all possible pairs of the 90 regions within the neonate AAL atlas (Shi et al., 2011). Subsequently, these matrices were thresholded to keep only the ten percent of the highest connections. From these thresholded matrices we computed graph theory measures as clustering coefficient, node strength, global efficiency and shortest path length, using the Brain Connectivity Toolbox. Using a 1-way ANCOVA, controlling for the PMA at scan and sex, we compared graph theory measures between seven groups of infants. All graph theory measures showing a significant effect between groups were identified, with post hoc tests (Tukey's HSD). Clustering coefficient and node strength showing significant differences between the preterm and term infants (Figure 2A-2B) and shortest path length and global efficiency showing significant differences between at least one group of preterm and term infants (Figure 2C-2D). Premature infants show reduced measures of integration (longer path lengths and reduced global efficiency) and segregation (lower clustering coefficients) of the network. Gozdas et al.(2018) Brain structure & function, 223(8).Hughes et al.,2017) Magnetic Resonance in Medicine, 78(2).Rogers et al.(2018). Journal of neurodevelopmental disorders, 10(1). Shi et al., (2011) , PloS one, 6(4).

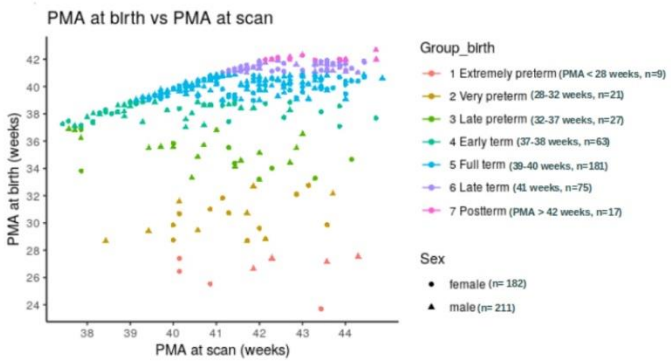

Figure 1. PMA of the sample. PMA at birth and at scan for the sample here explored.

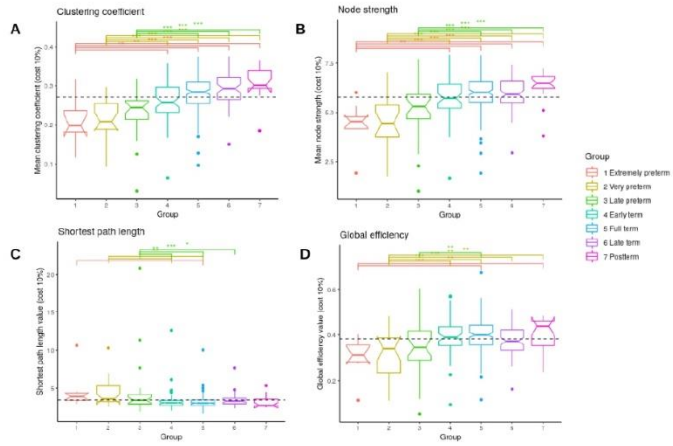

Figure 2. Graph theory measurement for the seven groups.They show significant differences between term and premature infants (lines on top represent the comparisons with p< 0.05, post hoc Tukey HSD tests, the dotted line is the average). A) Mean Clustering coefficient. B) Mean node strength. C) Shortest path length. D) Global efficiency. The clustering coefficient, node strength and global efficiency increases as the PMA at birth increases, controlling for age at scan and sex, while shortest path length decreases as the PMA at birth increases.

Disclosures: **N. López Guerrero:** None. **S. Alcauter:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.26

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

Support: NIH Grant P20GM103436
NIH Grant P20GM106396

Title: Neurodevelopmental effects of embryonic zebrafish exposure to real-world psychotropic drug mixtures

Authors: E. SIPES[1], S. ANDERSON[1], B. SUBEDI[2], *D. R. HAMMOND-WEINBERGER[1]; [1]Biol., [2]Chem., Murray State Univ., Murray, KY

Abstract: Wide ranges of drugs with overlapping targets in the nervous system contaminate drinking water sources. Psychotropic medications are among the most commonly prescribed drugs in the U.S., and a significant portion of these drug residues are discharged into the receiving water bodies. These drug residues eventually reach the drinking water, cross maternal biological barriers, and can alter the embryonic nervous system. Exposure of zebrafish embryos to specific combinations of drugs has resulted in nervous system abnormalities and misexpression of genes implicated in autism, Alzheimer's, and schizophrenia. Thus, chronic exposure to sub-therapeutic doses of these drugs represents a viable risk to human mental health. With the prevalence of such disorders ever-increasing, so does the urgency of understanding how environmental exposure increases risk. Thirty-six psychotropic drug residues were measured in discharged wastewater from treatment facilities and receiving creeks. Zebrafish (*Danio rerio*) larvae were exposed to the environmental relevant mixtures of drug residues. The extracted RNA from fish homogenates was sequenced using RNA-Seq. The high dose cocktail mixture exposure group revealed the largest group of differentially expressed genes. The top 20 differentially expressed sequences in each exposure group comprise 82 unique transcripts corresponding to 74% annotated genes, 7% non-coding sequences, and 19% uncharacterized sequences. Among 61 differentially expressed sequences that corresponded to annotated protein-coding genes, 23 (38%) genes or their homologs have documented nervous system expression in fish or other organisms. Several of the differentially expressed sequences are associated primarily with the immune system, including several major histocompatibility complex class I and interferon-induced proteins. Quantitative RT-PCR and *in situ* hybridization are being used to quantify and explore nervous system-specific changes in gene expression following drug exposure. As a measure the functional consequences of this type of exposure, a battery of larval behaviors that are disrupted in neurodevelopmental disorder models are being tested following drug exposure. By raising zebrafish in dosed water as a proxy for prenatal human exposure through contaminated drinking water, these experiments identify sensitive behaviors and genes that are expressed in developing neural tissues.

Disclosures: E. Sipes: None. **S. Anderson:** None. **B. Subedi:** None. **D.R. Hammond-Weinberger:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.27

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

Support: DFG Grant KI 1816/6-1
DFG Grant KI 1816/7-1
DFG Grant HO 2156/5-1
DFG Grant HO 2156/6-1
DFG Grant PR 1274/4-1
Thüringer Aufbaubank 3D-CONTRAST

Title: Placental transfer of NMDA receptor autoantibodies impairs correlated spontaneous activity in the developing hippocampus

Authors: M. MAJOROS[1], C. ZHANG[2], J. GRAF[1], J. KREYE[3], H. PRÜSS[3], K. HOLTHOFF[1], *K. KIRMSE[2];
[1]Jena Univ. Hosp., Jena, Germany; [2]Univ. of Würzburg, Würzburg, Germany; [3]Charité - Universitätsmedizin Berlin, Germany and German Ctr. for Neurodegenerative Dis. (DZNE) Berlin, Berlin, Germany

Abstract: N-methyl-D-aspartate receptors (NMDARs) are essential for normal brain development. Maternal autoantibodies (ABs) against the NR1 (GluN1) subunit of NMDARs have been shown to actively cross the placenta, reaching the developing brain through the immature blood-brain barrier. However, how NR1 ABs influence neuronal circuit development is largely unknown. Here, we examine the hypothesis that placentally transferred NR1 ABs impair the activity-dependent development of the hippocampus by interfering with the generation of correlated spontaneous activity in early life. We use a passive-transfer model in which pregnant mice are intraperitoneally injected with either human monoclonal NR1 or non-reactive isotype-matched control ABs. We confirm that maternal ABs can be detected in the serum of the offspring, and immunohistological stainings reveal NR1 AB deposits preferentially in hippocampal dendritic layers at birth. Using two-photon Ca^{2+} imaging from CA1 pyramidal cells *in vitro*, we demonstrate that placentally transferred NR1 ABs desynchronize spontaneous network activity in the neonatal CA1. Neuronal desynchronization results from both a decrease in the number of neuron pairs whose activity is significantly correlated and a reduced coupling strength. Collectively, our data indicate that placental transfer of NR1 ABs can profoundly affect NMDAR-dependent network activity during the first postnatal week. Our data suggest a mechanism by which placentally transferred NR1 ABs can induce long-term effects on neurodevelopment.

Disclosures: M. Majoros: None. **C. Zhang:** None. **J. Graf:** None. **J. Kreye:** None. **H. Prüss:** None. **K. Holthoff:** None. **K. Kirmse:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.28

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

Support: CIHR Grant 168873

Title: Investigating Postnatal Development of Claustrum Circuits and Connectivity to The Prefrontal Cortex

Authors: *T. SHAKER, G. J. DAGPA, J. C. JACKSON;
Physiol., Univ. of Alberta, Edmonton, AB, Canada

Abstract: The claustrum (CLA) is a small subcortical nucleus that is extensively interconnected with high-order brain centers, primarily the prefrontal cortex (PFC). Recent evidence suggests that innervation between the CLA and the PFC is implicated in complex cognitive processes, such as consciousness and attention. Nevertheless, the developmental time course of circuit maturation within the CLA as well as the onset of synaptic connectivity between the CLA and the PFC remains elusive. To investigate postnatal development of CLA networks in mice, we employed immunohistochemistry in combination with neural tracing from postnatal day (P) 1 up to P55. We used the widely established CLA marker Nr4a2 to delineate the CLA throughout development. Immunohistochemical analysis of CLA-specific markers revealed distinct maturation trajectories among different cell types. Excitatory neurons and somatostatin-expressing inhibitory neurons largely mature by P7. On the other hand, parvalbumin-expressing (PV+) inhibitory neurons are absent up to P14, but their number increases between P21 and P28. To determine the timeframe of connection formation between the CLA and the PFC, we injected anterograde and retrograde neural tracers into the PFC of Ai9 transgenic mice at seven-day intervals from P1 up to P42, and assessed the number of fluorescent cells 14 days post injection. We found that the majority of CLA-PFC projections are established by P14, whereas PFC-CLA projections do not fully develop until after P28, thus suggesting that CLA inputs may contribute to postnatal development of local PFC networks. We are currently testing the effect of chemogenetic modulation of PFC network activity on PV expression in CLA inhibitory neurons to elucidate whether maturation of PV+ inhibitory neurons in the CLA is gated by the excitatory synaptic drive of PFC inputs.

Disclosures: T. Shaker: None. **G.J. Dagpa:** None. **J.C. Jackson:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.29

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

Support: ZIAMH002898

Title: Widespread genetic modification of the primate brain through in utero AAV injections

Authors: *A. RIBEIRO GOMES[1], N. HAMEL[1], S. MASTWAL[1], D. IDE[2], G. DOLD[2], K. H. WANG[3], D. A. LEOPOLD[1];
[1]Section on Cognitive Neurophysiol. and Imaging, Lab. of Neuropsychology, Natl. Inst. of Mental Health, Natl. Inst. of Hlth., Bethesda, MD; [2]Section on Instrumentation, Natl. Inst. of Mental Health, Natl. Inst. of Hlth., Bethesda, MD; [3]Dept. of Neuroscience, Del Monte Inst. for Neuroscience, Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: The development of germline transgenic mouse models led to the routine expression of genes of interest for basic research and therapeutic applications. Genetically engineered mice have been a valuable tool, but much of what remains to be learned on the aspects of neural circuitry and behavior most relevant for human cognition and psychiatric disease requires biomedical models more closely related to humans. Genome editing technologies in non-human primates (NHP) are costly and time consuming. Thus, there is a need for simpler and complementary methods to introduce transgenes in nervous system cells. The direct delivery of adeno-associated virus (AAV) into the adult typically does not lead to extensive labeling of the brain, even in the case of intraventricular injections. However, studies in the neonatal mouse have demonstrated that AAV injections into the immature brain are more likely to distribute broadly and lead to widespread transgene expression. Because primates are born at a more mature developmental state than mice, equivalent manipulations in NHPs need to be carried out during the fetal period. In the present study, we developed a method to deliver AAV viral particles into the fetal brain using ultrasound-guided injections. In both rats and marmosets (*Callithrix jacchus*), we targeted viral injections to the cerebral ventricular system in a minimally invasive procedure. This method led to the dense and ubiquitous expression of transgenes throughout the cerebral cortex and other structures within the central and peripheral nervous system. We injected 340+ rat fetuses (up to 8 fetuses per litter; 5-10 minutes per injection) and 14+ marmoset fetuses (up to 3 per litter; 10-30 minutes per injection), with no observable risk to pregnancy. Commercially available AAV constructs led to transgene expression in both neuronal and non-neuronal cells. At present we are using this method to target neural subpopulations, both by incorporating specific upstream regulatory regions in the viral construct and by varying the postconceptual timing of the injection. In addition to fluorescent reporters, we have begun transducing neurons across the brain with light-sensitive opsins, with preliminary findings suggesting successful functional expression. This newly developed technique for creating widespread transgene expression across the brain provides new tools to study anatomical and functional properties of distinct cell populations in traditionally non-transgenic model organisms, particularly in NHPs, offering powerful experimental possibilities to explore structure-function relationships underlying behavior.

Disclosures: A. Ribeiro Gomes: None. **N. Hamel:** None. **S. Mastwal:** None. **D. Ide:** None. **G. Dold:** None. **K.H. Wang:** None. **D.A. Leopold:** None.

Poster

687. Neural Circuit Maturation and Remodeling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 687.30

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

Support: NIH F31HD106891
NIH R01DK106476
NIH T32DK007563

Title: Developmental programming of neural circuits integrating drinking and feeding

Authors: *S. R. SWEET[1], R. B. SIMERLY[2];
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Abstract: Development of hypothalamic neural circuits occurs largely during the early postnatal period and is influenced by a variety of environmental factors, a process known as developmental programming. Drinking and feeding are distinct but coordinated responses to homeostatic need-states, as indicated by the phenomenon of dehydration-anorexia, but our understanding of how changes in the neonatal environment impact neural circuits that integrate feeding and drinking remains rudimentary. Previous data suggests that agouti-related peptide (AgRP) neurons originating in the arcuate nucleus of the hypothalamus (ARH) are substrates of developmental programming, as they respond to nutritional cues during a postnatal critical period of development to reach downstream targets, such as the paraventricular nucleus of the hypothalamus (PVH), to regulate energy balance. Because inputs to the PVH from the median preoptic nucleus (MePO) are known to be essential for fluid regulation and converge with inputs from AgRP neurons, the PVH represents a possible node of integration for drinking and feeding. However, little is known about how these convergent inputs develop. As a first step, we used Fos labeling to determine the age at which dehydration signals, caused by hypertonic saline (HS) treatment, reach the PVH in wild-type neonatal mice. The results indicate that neurons in the MePO respond to the HS stimulus by the end of the first week of life and densities of Fos-labeled nuclei in the PVH peak during the second postnatal week. This timecourse precedes innervation of the PVH by AgRP neurons, which is followed closely by innervation of the MePO. Based on these developmental observations, we hypothesized that hyperstimulation of MePO neurons in neonatal mice with HS exposure may impact formation of AgRP circuitry, as well as alter metabolic physiological responses. To test this hypothesis, neonatal mice were exposed daily to HS treatment from postnatal day (P) 5 to P15 and immunohistochemistry was used to evaluate the density of AgRP innervation in the MePO and PVH of the mice at P60. Adult mice that received HS treatment from P5-P15 displayed significantly reduced densities of AgRP axons in the PVH, as well as increased food intake and energy expenditure after a fast. Taken together, these results suggest that postnatal hyperactivation of neural circuits regulating drinking can impact development of convergent AgRP circuits, with lasting consequences for energy balance regulation. These findings expand our appreciation of environmental signals that impact hypothalamic development and provide new insight into developmental programming of energy homeostasis.

Disclosures: S.R. Sweet: None. **R.B. Simerly:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.01

Topic: A.07. Developmental Disorders

Support: Ministry of Science and Technology (MOST), Taiwan Scholarship 110-2926-I-A49-001-MY4
Ministry of Science and Technology (MOST), Taiwan Grant 110-2321-B-A49A-502
Ministry of Science and Technology (MOST), Taiwan Grant 110-2628-B-A49A-509
Ministry of Science and Technology (MOST), Taiwan Grant 110-2634-F-075-001
Ministry of Science and Technology (MOST), Taiwan Grant 110-2634-F-A49-005
Mt. Jade Young Scholarship Award from Ministry of Education, Taiwan
National Yang Ming Chiao Tung University and the Ministry of Education (Aim for the Top University Plan), Taipei, Taiwan

Title: Exploring the trajectory of age-related brain complexity changes in individuals with autism spectrum disorder

Authors: *I.-J. CHI[1], A.-C. YANG[1,2];
[1]Inst. of Brain Science, Col. of Medicine, Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan;
[2]Digital Med. Centere, Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: Autism spectrum disorder (ASD) exhibits the core symptom of restrictive and repetitive behaviors. The underlying mechanism of the symptom may be explained by the loss of brain complexity theory. Although previous studies have adopted different measurements and participants with the specific age range to investigate brain complexity in ASD, an integrated and cross-age study is needed. We aim to determine whether the brain complexity varies with age and differs among brain regions across developmental stages from childhood to young adulthood in individuals with ASD. The functional magnetic resonance images of 531 participants with ASD and 571 controls from Autism Brain Imaging Data Exchange dataset were analyzed. The brain complexity was measured using sample entropy of the blood oxygen level-dependent signal obtained from each gray matter voxel. First, we used the general linear model to investigate the differences in brain complexity between ASD and controls at voxelwise level as well as parcellated 90 brain regions. The p-value was corrected for multiple comparison with the false discovery rate method and was set at 0.001 (t=2.34). Second, to build a smoother age trajectory of brain complexity, all participants were grouped using partially overlapping sliding age-windows at a step of 5 years. Finally, we used the cluster analysis to identify a subset of brain regions that have similar time course of proportion of voxels with abnormal brain complexity across age groups. We found that the brain regions with the most proportion of voxels with abnormal brain complexity in ASD group included right middle orbital frontal gyrus, right anterior cingulate, and right parahippocampal gyrus. The highest proportion of abnormal brain complexity voxels was found to be at the age group of 8-12 years (1.72%), and then such

proportion was decreased at the age of 15-19 years, with almost no difference from the controls (0.02%); however, at the age of 22-26 years, the proportion slightly rebounded (0.23%). Three clusters were identified: cluster 1 contains middle orbital frontal gyrus, anterior cingulate cortex, and fusiform, which has a higher impact on brain complexity in childhood and adulthood. Cluster 3 contains parahippocampal gyrus, insula, and middle cingulate cortex, which mainly affects brain complexity in childhood. Finally, cluster 2 is the brain region with the lowest correlation on the change in brain complexity, which contains post cingulate cortex and precuneus. Taken together, these findings suggest that brain complexity of individuals with ASD changes with age and the dominated brain regions with abnormal brain complexity also differ at each developmental stage.

Disclosures: I. Chi: None. **A. Yang:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.02

Topic: A.07. Developmental Disorders

Support: Office of Research Computing at George Mason University (URL: https://orc.gmu.edu)
NSF Grant 1625039
NSF Grant 2018631
NIMH R01MH100028, PI: Pelphrey

Title: Age-related differences in brain response to biological motion stimuli in a sex-balanced sample of autistic and typically-developing youth.

Authors: *E. GERSON[1], G. MCQUAID[2], A. JACK[2];
[1]Psychology, George Mason Univ., Falls Church, VA; [2]Psychology, George Mason Univ., Fairfax, VA

Abstract: Age-related differences in brain response to biological motion stimuli in a sex-balanced sample of autistic and typically-developing youth.
AuthorsE. Gerson, G. McQuaid, A. Jack; George Mason University, Fairfax, VA; The GENDAAR Consortium.
DisclosuresE. Gerson: None. G. McQuaid: None. A. Jack: None.
Autism Spectrum Disorder (ASD) is a neurodevelopmental condition which affects social behaviors; yet, limited research has addressed the neurodevelopment of social processing systems in ASD. Furthermore, despite documented sex-related differences in social behaviors in ASD samples, age-by-sex interactions in social processing within these samples are not yet understood. The present study used a point-light display paradigm of biological motion with whole-brain functional magnetic resonance imaging (fMRI) to explore brain activation in

response to social stimuli in a relatively sex-balanced sample of ASD (*n* = 94, 48 male) and typically-developing (TD; *n* = 113, 59 male) individuals aged 8 to 17 years.[1] In analyses where groups were directly compared, a matched sample (*n* = 184) was used to account for variations in head motion. Using FSL v. 6.0.4 (fmrib.ox.ac.uk/fsl), we tested for effects related to age, sex, diagnosis, and autism-related social features, as well as interactions between these variables. Corrections were performed in FSL's Randomise with threshold-free cluster enhancement, 10,000 permutations, and corrected $p < .05$. Age was negatively correlated with activation of the action observation network in TD females (Figure 1), and positively correlated with activity in the right anterior insula in TD males (Figure 2). No age effects survived non-parametric permutation-based corrections in the ASD males or females. Diagnostic, age, and social features did not survive non-parametric permutation-based corrections. These findings highlight the importance of further research to understand the development of neural systems for social processing in ASD versus TD males and females.
Figure 1. Age Positive Main Effect TDf
Figure 2. Age Negative Main Effect TDmFootnotes[1] Jack A, Sullivan CAW, Aylward E, Bookheimer SY, Dapretto M, Gaab N, Van Horn JD, Eibott J, Jacokes Z, Toregerson CM, Bernier RA, Geschwind DH, McPartland JC, Nelson CA, Webb SJ, Pelphrey KA, Gupta AR; GENDAAR Consortium. A neurogenetic analysis of female autism. Brain. 2021 Jul 28; 144(6): 1911-1926. doi: 10.1093/brain/awab064. PMID: 33860292; PMC8320285

Disclosures: **E. Gerson:** None. **G. McQuaid:** None. **A. Jack:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.03

Topic: A.07. Developmental Disorders

Title: No difference in extra-axial cerebrospinal fluid volumes in children and adolescents with neurodevelopmental and psychiatric disorders

Authors: *M. PETERSON, C. WHETTEN, A. M. CLARK, J. A. NIELSEN;
Brigham Young Univ., Provo, UT

Abstract: Autism spectrum disorder is associated with structural and functional disruptions in the brain, including an increase in extra-axial CSF volume in early childhood. A series of studies investigating this volume in children between the ages of 6 months and 4 years found that extra-axial CSF volume was predictive of an autism diagnosis and symptom severity (Shen et al., 2013; Shen et al., 2017, Shen et al., 2018). Following these studies, an accelerated longitudinal study found that an increased volume of this fluid in autism may be constrained to children younger than 3 years of age (Peterson et al., 2021). However, the specificity of an increased volume of extra-axial CSF to autism remains largely unknown. In the present study, we examined extra-axial CSF volume in children and adolescents ages 5-21 years with no diagnosis,

an autism diagnosis, or a different neurodevelopmental or psychiatric disorder diagnosis. It was hypothesized that an elevated extra-axial CSF volume would be found in autism compared with typical development and the other diagnostic group. To test this hypothesis, a cross-sectional dataset of 446 T1-weighted MRI scans (85 autistic, 60 typically developing, and 301 other diagnosis) was used (Alexander et al., 2017). An analysis of covariance was used to examine differences in extra-axial CSF between these groups with the covariates of mean-centered age, mean-centered age^2, scan site, sex, mean-centered estimated total intracranial volume (eTIV), mean-centered eTIV^2, a mean-centered age by group interaction, and a mean-centered age2 by group interaction in R 4.0.2 using the package car. A significant effect of age on extra-axial CSF volume was found ($F(1, 433) = 44.85$, $p < .001$) in addition to a significant eTIV effect ($F(1, 433) = 132.56$, $p < .001$). Interestingly, there was neither a significant effect of diagnostic group on extra-axial CSF volume ($F(2, 433) = 2.69$, $p = .07$), nor a significant group by age interaction ($F(2, 433) = 0.34$, $p = .72$). Additionally, no significant differences between groups were observed after re-centering age at 5 ($F(2, 433) = 1.23$, $p = .29$), 10 ($F(2, 433) = 2.74$, $p = .07$), 15 ($F(2, 433) = 2.27$, $p = .11$), and 20 ($F(2, 433) = 1.95$, $p = .14$) years. In contrast to our hypothesis but in congruence with previous findings of no group differences in extra-axial CSF volume between autistic and neurotypical individuals 3-42 years old, we found no group differences in extra-axial CSF volume between 5-21 years. These results indicate that an increased volume of extra-axial CSF may be limited to autistic individuals younger than 5 years.

Disclosures: **M. Peterson:** None. **C. Whetten:** None. **A.M. Clark:** None. **J.A. Nielsen:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.04

Topic: A.07. Developmental Disorders

Support: ZIA-MH-002920-09

Title: Individuals with autism spectrum disorder exhibit atypical connectivity patterns from social regions in the anterior temporal lobes

Authors: *J. SHAO, A. PERSICHETTI, J. DENNING, S. GOTTS, A. MARTIN;
Lab. of Brain and Cognition, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Impaired social communication is a core behavioral phenotype in individuals with autism spectrum disorder (ASD). Consistent with these behavioral deficits, atypical functional connectivity between social processing regions in the anterior temporal lobes (ATL) and the rest of the social network is commonly observed in ASD individuals. However, it is not clear how the functional organization within the ATL is altered in ASD. We used long-range patterns of functional connectivity to uncover the functional organization of the ATL in ASD individuals and contrasted it with the organization in typically developing (TD) individuals. We analyzed

high-quality resting-state fMRI data (8 minutes 10 seconds) from 70 high-functioning ASD individuals (14 female) and 70 TD individuals (19 female). The groups were matched on age, IQ, head motion, and temporal signal-to-noise ratio (tSNR). We first parcellated the ATL by calculating the functional connectivity between voxels within the ATL (defined as any temporal lobe voxels anterior to y=-35 in Talairach space) and all voxels outside of the temporal lobes. We then thresholded the resultant correlation matrices and clustered the group-average matrices using the Infomap algorithm. We required parcels to replicate across 10 randomized split-half samples of the data (35 participants in each half per group). We further compared our ASD and TD parcellations using two other metrics: the eta^2 coefficient (a measure of similarity between the parcels) and functional laterality (specifically, hemispheric segregation and integration). We found three main group differences: First, the parcellation resulted in 38 distinct functional regions in the ASD group compared to 34 in the TD group. Second, the average pairwise eta^2 coefficient across parcels was significantly weaker in the ASD group compared to the TD group ($t_{(69)}=4.36$, $p<10^{-5}$). Third, parcels in the right hemisphere of the TD group connected to regions in both hemispheres (hemispheric integration), while the ASD group failed to show this pattern of hemispheric integration (interaction contrast, $p<0.05$). In addition, parcels in the left hemisphere showed a weaker within hemisphere connectivity (hemispheric segregation) in the ASD group (interaction contrast, $p<0.05$). These results were most prevalent in and around the superior temporal sulcus and temporal pole. Our results suggest that the functional organization of anterior temporal lobe regions in ASD individuals is more fractionated and less cohesive relative to matched TD controls. Additionally, the functional laterality of ATL regions differs between the ASD and TD groups.

Disclosures: J. Shao: None. **A. Persichetti:** None. **J. Denning:** None. **S. Gotts:** None. **A. Martin:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.05

Topic: A.07. Developmental Disorders

Title: Characterization of brain responses to social and non-social images in autistic children

Authors: *S. NAGABHUSHAN KALBURGI[1], A. KEY[2], J. W. BODFISH[2], P. R. LEVITT[3]; [1]Children's Hosp. of Los Angeles, Los Angeles, CA; [2]Vanderbilt Univ., Nashville, TN; [3]Children's Hosp. Los Angeles and Univ. of Southern California, Los Angeles, CA

Abstract: Brain activity underlying behavioral differences in social (SOC) and nonsocial (non-SOC) attention in autism can be studied using electroencephalography (EEG). In autistic adults, a decreased late positive potential (LPP) response is observed to SOC images, indicating reduced motivational salience to SOC information which may reflect reduced downstream allocation of attentional and cognitive resources required for information processing. In this study, we

investigate LPP responses to SOC and non-SOC images in autistic children. We also examine the brain network dynamics and the pattern of neuronal activation in response to SOC and non-SOC images in autistic children using microstate and time-frequency analysis. EEG was collected while 13 autistic (ASD) and 13 typically developing (TD) age- and gender-matched children between the ages of 8-14 years passively watched images on a screen. The SOC images consisted of faces with positive affect and the non-SOC images were objects of high autism interest (HAI). EEG was preprocessed and event related potentials (ERP), microstates and time-frequency metrics were extracted in response to SOC and HAI. The amplitudes and latency of the LPP responses were calculated. Microstate analysis was conducted to examine brain network dynamics and time-frequency analysis was conducted to study the patterns of neuronal activation. Brain behavior correlations were examined. ERP analysis showed decreased LPP amplitudes in ASD in response to SOC compared to TD children. Microstate analysis revealed that the salience network is not activated in response to SOC in ASD at the group level. Time-frequency analysis indicated this may be due to stronger neuronal activation in response to HAI and a lack of neuronal activation to SOC in the autism group. The results suggest the lack of activation of the salience network may explain differences in attention to SOC information at the behavioral level. This may be the underlying mechanism for the differences in attentional and cognitive processes involved in processing social information in ASD.

Disclosures: S. Nagabhushan Kalburgi: None. **A. Key:** None. **J.W. Bodfish:** None. **P.R. Levitt:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.06

Topic: A.07. Developmental Disorders

Support: University of Missouri Research Board Grant (PI: Beversdorf)

Title: Relationship between MR Spectroscopy detected neurometabolites and changes in social behaviors in a pilot, open-label trial of memantine in adults with autism spectrum disorder

Authors: *N. NAIR[1], J. P. HEGARTY, II[3], C. M. CIRSTEA[2], M. GU[3], C. APPLING[2], D. BEVERSDORF[2];
[1]Dept. of Psychiatry, [2]Univ. of Missouri, Columbia, MO; [3]Stanford Univ. Sch. of Med., Pao Alto, CA

Abstract: Background: Increased glutamatergic/excitatory activity and decreased GABAergic/inhibitory activity has been reported in autism spectrum disorder (ASD). Memantine is an N-methyl-D-aspartate (NMDA) glutamatergic antagonist studied for the treatment of core ASD symptoms, with mixed results. We examined whether glutamatergic (and other neurometabolite) levels were associated with and predicted response to memantine in an

exploratory pilot study. Methods: Ten adult participants with ASD underwent proton magnetic resonance spectroscopy (^{1}H-MRS) imaging at baseline and behavioral assessments before and after 12-weeks of open-label memantine. LCModel was used to quantify Point RESolved Spectroscopy detected concentrations of glutamate+glutamine (Glx), N-acetylaspartate (NAA), creatine+phosphocreatine (Cr+PCr), and myo-inositol (Ins), within the left dorsolateral prefrontal cortex (LDLPFC) and right (R) posterolateral cerebellum. Post-treatment scores on Clinical Global Impressions-Improvement (CGI-I) for social interaction and changes in scores on the Social Responsiveness Scale (SRS) baseline vs. posttreatment were the outcome measures. CGI-I scores post-treatment were used to classify the participants into two groups, responders (scores 1-3; n=5) and non-responders (scores 4-7; n=5). Independent samples t-tests, partial correlations and linear hierarchical regression models (SPSS) were used to determine between-group differences in neurometabolite concentrations and associations between neurometabolites and behavioral scores. Results: Responders and non-responders did not significantly differ in Glx levels in either region of interest. Responders, however, had higher levels of NAA in LDLPFC compared to non-responders (9.78(0.71) vs. 6.61(1.65) IU, t=-3.56, p=0.024). Linear hierarchical regression revealed that Glx (B=-1.07, p=0.02) and Ins (B=0.58, p=0.04) levels in LDLPFC predicted post-treatment CGI social scores (R^2 adj = 0.86, F=9.19, p=0.05). Changes in SRS scores posttreatment correlated with baseline Cr+PCr levels in the DLPFC (r=-0.956, p=0.04). Discussion: Our pilot data suggest that interactions between Glx and the neurometabolite associated with glial integrity (Ins) may help predict treatment response to memantine in ASD. Those with highest baseline NAA, a putative neuronal marker, and Cr+PCr, a brain energy metabolism marker, were also found to respond better to treatment with memantine. These preliminary results may explain some of the mixed results reported in previous trials of memantine in ASD. Future studies will need to examine these results in a larger sample.

Disclosures: **N. Nair:** None. **J.P. Hegarty:** None. **C.M. Cirstea:** None. **M. Gu:** None. **C. Appling:** None. **D. Beversdorf:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Past Speaker for Biogen. F. Consulting Fees (e.g., advisory boards); Stalicla Biosci, Quadrant Biosci, Scioto Biosci, Impel Pharma, YAMO Pharma.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.07

Topic: A.07. Developmental Disorders

Support: NIH P20-GM103650
NSF 1632849
BBRF 26282
NIH R15 MH122935

Title: Evidence of wide-spread white matter compromise in autism spectrum disorder: a large-scale diffusion imaging study using repository data

Authors: *S. OTTO[1], Y. YANG[2], L. RAY[2], J. TRAVERS[2], M. MONTERO[2], J. J. HUTSLER[4], S. M. HAIGH[3];
[2]Psychology, [3]Dept. of Psychology and Inst. for Neurosci., [1]Univ. of Nevada, Reno, Reno, NV; [4]Univ. of Nevada, Reno, NV

Abstract: Autism Spectrum Disorder (ASD) pathology involves multiple distributed neural networks. Abnormal white matter (WM) connectivity has been implicated as a potential mechanism for perturbed neural functioning across these networks. Much of the existing literature surrounding WM connectivity in ASD has primarily focused on children, while little is known about the structural and behavioral profile across the lifespan into adulthood. Diffusion MRI (dMRI) has developed into a promising technique to investigate complex brain network connectivity *in vivo* and its application in clinical populations is rapidly gaining popularity because of its sensitivity to microstructural changes in WM. The present study used diffusion MRI repository data from a large sample to investigate the degree to which WM diffusion is abnormal in ASD compared to IQ-matched neurotypical controls (NT). dMRI data was acquired from the ABIDE II repository, Carnegie Mellon University, and the University of Pittsburgh. We analyzed a total of 336 subjects (187 ASD, 149 NT) using Tract Based Spatial Statistics (TBSS). Due to the nested nature of the data, robust linear mixed-effects modeling was used to examine if group differences in diffusion measures were indicated while controlling for several covariates. To investigate the relationship between diffusion and symptomatology, we used Confirmatory Factor Analysis (CFA) and regression models to determine if the diffusion measures were predictive of diagnosis and behavioral symptom severity. Compared to NT controls, individuals with ASD showed significantly decreased fractional anisotropy (FA), increased mean diffusivity (MD) and increased radial diffusivity (RD). These results were evident across the entire brain. CFA and regression analyses found that the biological measures of FA, MD, AD and RD were not predictive of behavioral outcome on ADOS or SRS scores. These results suggest that WM compromise begins early in ASD and persists throughout adulthood. Due to the nonlinear and dynamic nature of brain development in ASD, it is difficult to isolate aberrant changes in WM connectivity that might reflect core ASD symptomatology. Focusing more efforts on adults with ASD may provide a better understanding of which of these changes are sustained beyond development and maturation. Our findings highlight the need for longitudinal studies to better understand how age-related changes in WM diffusion properties may relate to the behavioral profile often seen in ASD. Furthermore, measures of cognitive performance may be more suitable indicators in determining relationships between biological markers and behavioral outcome.

Disclosures: S. Otto: None. **Y. Yang:** None. **L. Ray:** None. **J. Travers:** None. **M. Montero:** None. **J.J. Hutsler:** None. **S.M. Haigh:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.08

Topic: A.07. Developmental Disorders

Support: NIMH Grant R01MH116147 to P.M.T.
NIMH Grant F32MH122057 to K.E.L.

Title: Assessing the utility of advanced diffusion-weighted brain MRI in characterizing white matter differences in autism

Authors: *S. M. BENAVIDEZ[1], K. E. LAWRENCE[1], E. LALTOO[1], J. T. MCCRACKEN[2], P. M. THOMPSON[1];
[1]Imaging Genet. Center, Mark and Mary Stevens Neuroimaging & Informatics Inst., USC, Marina del Rey, CA; [2]Dept. of Psychiatry and Biobehavioral Sci., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Autism is a neurodevelopmental condition characterized by differences in social communication and repetitive and restricted behaviors. Autism has previously been associated with altered brain white matter when using the traditional diffusion-weighted MRI model, diffusion tensor imaging (DTI). Such prior work reported microstructural alterations that are indicative of reduced white matter integrity and myelination. Although DTI is the most widely-used diffusion model, it is limited by its inability to model crossing fibers in the brain. This investigation thus aimed to characterize white matter microstructure alterations in autism using an advanced diffusion model, the tensor distribution function (TDF), to determine if white matter alterations were more discoverable when using a method that models multiple fiber populations. Here we analyzed diffusion-weighted MRI scans from 438 subjects (264 subjects with autism, 174 neurotypical controls) pooled across ten different studies; the harmonization method ComBat was used to correct for inter-scanner variability. We calculated the DTI metrics fractional anisotropy (FA^{DTI}), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD); TDF was used to calculate FA^{TDF}. Tract based spatial statistics (TBSS) was used to create white matter skeletons, and the average of each diffusion metric was extracted along the full white matter skeleton (full WM) or the corpus callosum (CC), a major white matter tract previously implicated in autism. We found significantly altered white matter microstructure in autism across FA^{DTI}, MD, RD, and FA^{TDF}. For both FA^{DTI} and FA^{TDF}, those diagnosed with autism showed reduced white matter integrity in comparison with neurotypical controls for the full WM (FA^{DTI}: $p = .02$, $\beta = .23$; FA^{TDF}: $p = .002$, $\beta = .31$) and the CC (FA^{DTI}: $p < .001$, $\beta = .43$; FA^{TDF}: $p < .001$, $\beta = .44$), on average. Autism was also associated with greater MD in the CC ($p = .003$, $\beta = -.30$), as well as greater RD in the full WM ($p = .013$, $\beta = -.22$) and CC ($p < .001$, $\beta = -.48$), compared to neurotypical controls. For our primary analyses of interest, we assessed the relative sensitivity of the DTI and TDF models to autism-related alterations in white matter microstructure. The TDF model showed greater sensitivity to white matter differences in autism than DTI for both the full WM and the CC (Full WM: FA^{DTI} $\beta = .23$, FA^{TDF} $\beta = .31$; CC: FA^{DTI} $\beta = .43$, FA^{TDF}:$\beta = .44$). In sum, our analyses demonstrate the utility of the advanced diffusion model TDF in characterizing white matter microstructure alterations in autism.

Disclosures: **S.M. Benavidez:** None. **K.E. Lawrence:** None. **E. Laltoo:** None. **J.T. McCracken:** Other; Consultant for Roche, TRIS Pharmaceuticals, Octapharma, and GW Pharmaceuticals. Research contracts from Roche, Octapharma, and GW Pharmaceuticals for research unrelated to this abstract. **P.M. Thompson:** Other; Research grant from Biogen, Inc. for research unrelated to this abstract..

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.09

Topic: A.07. Developmental Disorders

Support: NIMH Grant R21MH115297
The Beatrice and Samuel A. Seaver Foundation

Title: Examining atypical corollary discharge signaling with electroencephalography in autism spectrum disorder

Authors: *J. TRAYVICK[1], S. B. GUILLORY[2], C. S. MCLAUGHLIN[3], E. L. ISENSTEIN[4], K. N. THAKKAR[5], D. MATHALON[6], J. H. FOSS-FEIG[1];
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Abstract: The ability to distinguish between self-generated versus externally generated sensory events is a process critical to prediction, self-monitoring, and differentiating relevant and irrelevant stimuli. Corollary discharge (CD) signals are the neurobiological pairing between motor output and sensory experiences during self-generated actions. CD allows for the suppression of sensory responses to self-generated action and, thus, differentiation between externally and self-generated actions. Sensory and motor symptoms represent key features of autism spectrum disorder (ASD) and might be influenced by deficits in CD signaling. Work in typically developing individuals reveals suppressed sensory responses to self-generated stimuli compared to externally generated events, thought to index CD. This study used electroencephalography (EEG) to test for atypical CD processes in ASD. We hypothesized that suppression in self-generated sensory events would be present in typically developing (TD) controls but reduced in ASD. High-density EEG was recorded from 36 children with ASD (M = 11.53 ± 2.65 years, 9 females) and 37 typically developing controls (M = 12.49 ± 2.66 years, 14 females). The motor-auditory paradigm consisted of 75 trials and had three conditions: motor control, self-generated, and externally-generated. In the motor control condition, participants pressed a button every 2-3 seconds. In the self-generated condition, participants generated an auditory stimulus when they pressed a button. In the externally generated condition, participants

passively listened to tones played 2-3 seconds apart. Each condition was run twice. In each trial, event-related potentials were time-locked to the onset of the auditory stimulus or button press. N1 mean amplitudes were calculated from the Cz central electrode. Suppression of the N1 response was determined by calculating the difference between the externally-generated and self-generated (minus motor control) conditions. An independent samples t-test was used to compare suppression of the N1 response in ASD versus TD controls. Children with ASD showed significantly weaker N1 suppression (0.27 ± 0.32 μV) compared to TD controls (-1.01 ± 0.25 μV), $t(71) = -3.14$, $p = 0.002$, supporting our hypothesis. Indeed, our findings support deficits in CD signaling in ASD and might help to better understand deficits in self-monitoring, prediction, and sensitivity to external sensory events in the population. Future research in this area might improve our understanding of neural bases for core features of the ASD phenotype.

Disclosures: J. Trayvick: None. **S.B. Guillory:** None. **C.S. McLaughlin:** None. **E.L. Isenstein:** None. **K.N. Thakkar:** None. **D. Mathalon:** None. **J.H. Foss-Feig:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.10

Topic: A.07. Developmental Disorders

Support: The Schindler Foundation

Title: Language development in neurotypical children and children with autism spectrum disorder using the N400 event-related-potential component and functional magnetic resonance imaging

Authors: *K. TOFFOLO, E. FREEDMAN, J. FOXE;
Univ. of Rochester, Rochester, NY

Abstract: During speech comprehension, prediction may facilitate faster language processing in which the ongoing context of a sentence can be used to predict sentence outcome by limiting subsequent word likelihood. Context-dependent predictions are influenced by semantic and syntactic comprehension, which can be measured via electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). Two event-related potentials (ERPs), the N400 and P600 components, respond to context-dependent violations with amplitude modulations, and are suggested to measure semantic and semantic/syntactic processing respectively. Similarly, prior fMRI studies have shown separate regional activation in response to semantic or syntactic information. Neuroimaging research suggests that predictive processes and language skills are refined throughout development, where with age, there are reductions in amplitude and latency in the N400 and P600 and gradual activational segregation of syntactic and semantic processing. However, language development is not characterized well using these neuroimaging methods in tandem and these developmental changes may be different in other populations. Behavioral

research has suggested that the language abilities of individuals with Autism Spectrum Disorder (ASD) develop differently. The purpose of this study was to use EEG and fMRI to characterize language development, specifically semantic and syntactic processing, in neurotypical (NT) children and children with ASD. Using a standardized semantic stimulus set (Toffolo et al. 2022) and a syntactic stimulus set, our study compared language processing between NT (n=13) and ASD (n=5) children across three distinct age groups: 6-7, 8-9, and 10-12 years. Preliminary data suggested differences in language processing between children with and without ASD. In NT children, both the N400 and P600 ERP components matured throughout language development in response to semantic errors, showing reductions in amplitude, latency, and bilateral scalp topography with age. As a whole, they also showed activational differences in response to semantic and syntactic errors. In response to semantic errors, the ASD N400 ERP component had reduced amplitudes when compared to the NT N400. Furthermore, functional activation did not differ between semantic and syntactic error contrasts in children with ASD. Neither experimental group showed a P600 in response to syntactic errors. The outcomes of this study could benefit individualized intervention and provide information on developmental language trajectory with complementary information from fMRI and EEG methodologies.

Disclosures: K. Toffolo: None. **E. Freedman:** None. **J. Foxe:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.11

Topic: A.07. Developmental Disorders

Support: NSERC Discovery Grant
Canada First Research Excellence Fund (CFREF)

Title: Quantitative fMRI Meta-Analysis Reveals Aberrant Hemispheric Lateralization of Both Language and Face Processing in Autism Spectrum Disorder

Authors: *L. M. SOLOMON-HARRIS, B. L. HARTMAN, T. J. DUNN, Z. A. YAPLE, W. D. STEVENS;
Psychology, York Univ., Toronto, ON, Canada

Abstract: Autism spectrum disorder (ASD) is characterized in part by difficulties in communication and social interaction, which have been reflected in atypical processing of language and faces in the brain. While these may be separate and unrelated domains of cognitive impairment, some evidence suggests that they may be interrelated. Importantly, language and face processing are typically lateralized towards the left and right cerebral hemispheres, respectively. There is convergent evidence across several neuroimaging studies supporting the hypothesis that communication deficits in ASD are associated with reduced left hemispheric lateralization of language processing. However, there is a lack of functional MRI (fMRI) studies

that focus on the rightward lateralization of face processing in ASD. Here, we report the first quantitative meta-analysis of fMRI studies on both language and face processing in ASD (36 articles on language comprising 599 ASD and 620 typically developing (TD) participants; 28 articles on face processing comprising 437 ASD and 470 TD participants). This work extends previous fMRI meta-analyses, which investigated either language or face processing alone in a small number of studies, by performing cross-domain analyses to examine the relationship between these cognitive domains in the context of ASD across a large number of studies. Results of the present meta-analysis demonstrate that ASD is related to atypical hemispheric specialization of both language and face processing, which is particularly prominent in the posterior superior temporal sulcus (pSTS) in both hemispheres. Atypical lateralization of these cognitive domains was demonstrated both in analyses of foci reported from between-group contrasts (i.e., ASD>TD and TD>ASD) as well as foci reported from within-group contrasts (i.e., ASD and TD groups alone). Previous research has shown that the pSTS is critical for processing the dynamic aspects of faces, multisensory integration, biological motion, and theory of mind, which are all cognitive functions that are frequently impacted in ASD. The present results suggest that reduced hemispheric specialization of the pSTS could be a critical aspect of atypical functional brain organization in ASD.

Disclosures: L.M. Solomon-Harris: None. **B.L. Hartman:** None. **T.J. Dunn:** None. **Z.A. Yaple:** None. **W.D. Stevens:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.12

Topic: A.07. Developmental Disorders

Support: NIH U54HD083211/P50HD103537
NIH/NCATS KL2TR000446
NIH/NIDCD F31 DC015696-01A1
NIH/NIDCD R21 DC016144
NIH/NIDCD F31 DC020129-01A1
NSF NRT grant DGE 19-22697

Title: Audiovisual Speech Processing Efficiency and Links with Language in Autistic and Non-Autistic Children

Authors: *K. DUNHAM[1], J. I. FELDMAN[2], D. SIMON[3], S. EDMUNDS[4], A. TU[5], W. KUANG[6], J. CONRAD[7], P. SANTAPURAM[8], M. T. WALLACE[1], T. G. WOYNAROSKI[1]; [1]Vanderbilt Brain Institute; Dept. of Hearing and Speech Sci., [2]Dept. of Hearing and Speech Sci., [3]Vanderbilt Brain Inst., Vanderbilt Univ., Nashville, TN; [4]Psychology, Univ. of South Carolina, Columbia, SC; [5]Otolaryngology and Communication Sci., Med. Col. of Wisconsin, Milwaukee, WI; [6]Pediatrics, Los Angeles County and Univ. of Southern California Med. Ctr., USC, Los

Angeles, CA; [7]Intrnl. Med. and Pediatrics, Univ. of Illinois Hosp., Chicago, IL; [8]Anesthesiol., Columbia Univ. Irving Med. Ctr., New York City, NY

Abstract: Explaining individual differences in language understanding and use in autistic children is critical because language has been repeatedly linked with long-term outcomes in this population. Theory suggests that audiovisual speech processing efficiency may explain variability in language understanding and use across children on the autism spectrum. Audiovisual speech processing efficiency can be operationalized as amplitude differences in the event-related potential (ERP) response to audiovisual speech versus auditory-only speech. Prior work indicates that in neurotypical adults, the ERP amplitude is suppressed, particularly at the P2 component, in response to audiovisual speech compared to auditory-only speech. This phenomenon, known as P2 amplitude suppression, has been observed in non-autistic children, but has yet to be measured in autistic children. Furthermore, it is unknown whether this neural index explains individual differences in language in autistic children. This project evaluated the theoretical association between P2 amplitude suppression and language in a sample of autistic and non-autistic children (n=25 per group) between 5.5 and 12.4 years old matched on chronological age and biological sex. Electroencephalography (EEG) was collected while children watched videos of audiovisual (auditory speech + synchronous mouth movements) and auditory-only (auditory speech + still image of the face) speech. The raw EEG signal was sampled at 1000 Hz and referenced to vertex (Cz). The amplitude of the P2 component (defined a priori as occurring between 160 ms and 240 ms) measured at Cz was extracted from the average ERP of each participant. Participants also completed standardized receptive and expressive vocabulary assessments. P2 amplitudes in response to auditory-only and audiovisual conditions were compared between groups, and a series of regression analyses was conducted to evaluate associations between amplitude suppression and receptive and expressive vocabulary standard scores. Both groups demonstrated P2 amplitude suppression, on average, in response to audiovisual speech compared to auditory-only speech, and between-group differences in mean amplitude suppression were not significant. However, the degree of amplitude suppression experienced varied considerably across participants and was positively associated with receptive vocabulary scores, but not expressive vocabulary scores, across groups. These results suggest that this neural proxy of audiovisual speech processing efficiency may explain variance in language in autism and may serve as a candidate target for language intervention for autistic children.

Disclosures: K. Dunham: None. **J.I. Feldman:** None. **D. Simon:** None. **S. Edmunds:** None. **A. Tu:** None. **W. Kuang:** None. **J. Conrad:** None. **P. Santapuram:** None. **M.T. Wallace:** None. **T.G. Woynaroski:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.13

Topic: A.07. Developmental Disorders

Support: Office of the Assistant Secretary of Defense for Health Affairs through the Autism Research Program under Award No. W81XWH-16-1-0321.

Title: Baseline skin conductance level as a predictor of the response to propranolol for clinician rated anxiety in Autism spectrum disorder

Authors: *C. APPLING[1], M. PRENDERGAST[1], N. NURAINI[3], D. Q. BEVERSDORF[4], V. DAVILA[5], B. THOMPSON-GORDON[2], B. FERGUSON[6];
[1]Neurosci., [2]Sch. of Med., Univ. of Missouri, Columbia, MO; [3]Neurosci., Univ. of Missouri, Columbia, Columbia, MO; [4]Dept Radiol, Neurol, Psychol Sci, DGS of INP, Univ. of Missouri Columbia, Columbia, MO; [5]Psychology & Neurosci., Baylor Univ., Waco, TX; [6]Univ. of Missouri Thompson Ctr. For Autism, Columbia, MO

Abstract: Autism spectrum disorder (ASD) is characterized by social and communication impairments as well as restrictive repetitive behaviors that begin in early development. In addition to the core symptoms, a large proportion of individuals with ASD have co-occurring anxiety. At this time, no pharmacological agent has proven beneficial for the treatment of core features of ASD, and the efficacy of pharmacological agents targeting anxiety in ASD is unclear. Furthermore, a developmentally dysregulated noradrenergic system may be a significant component in ASD. For example, recent research from our team found positive effects of a single dose of propranolol, a beta-adrenergic antagonist, on conversational reciprocity and language in ASD. As such, we have become highly interested in how the noradrenergic system also affects anxiety. In order to identify patients most likely to respond to propranolol, the following study will determine if skin conductance level (SCL), which is associated with anxiety and adrenergic tone, predicts changes in anxiety after treatment with propranolol. Previously, we examined the effects of an open label 12-week administration of propanol on anxiety in high functioning individuals with ASD and found anxiety levels were significantly lower after treatment compared to baseline. We predict mean baseline SCL will be correlated with the clinician rated Clinical Global Impact Measure–Severity (CGI-S) change score. The participants were previously diagnosed with ASD as confirmed by ADOS-2 and/or ADI-R, all within the age range of 7-24. Prediction of the treatment response to propranolol using SCL may help with future precision medicine efforts to create individualized treatments for those with ASD who seek treatments for anxiety. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense.

Disclosures: C. Appling: None. **M. Prendergast:** None. **N. Nuraini:** None. **D.Q. Beversdorf:** F. Consulting Fees (e.g., advisory boards); Quadrant Biosci, YAMO Pharma, Impel Pharma, Scioto Biosci, and Stalicla Biosci. **V. Davila:** None. **B. Thompson-Gordon:** None. **B. Ferguson:** None.

Poster

688. Autism Pathophysiology: Human Studies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 688.14

Topic: A.07. Developmental Disorders

Title: Interdependence of alerting and executive control networks is associated with ASD and ADHD traits: The locus coeruleus - norepinephrine (LC-NE) system using pupillometry and ERP

Authors: *Y. KIM[1], A. SAUNDERS[2], R. ROZNIAREK[2], K. CORTES[2], A. HAMILTON[2], S. SCHIEBER[2], D. KANTOR[1], D. SCHNEIDER[3], B. KEEHN[1];
[1]Speech, Language, and Hearing Sci., [3]Psychological Sci., [2]Purdue Univ., West Lafayette, IN

Abstract: Attention has been divided in subsystems responsible for alerting, orienting, and executive control, which are supported by independent brain networks. However, a large body of work suggests that the alerting and executive networks do not function independently. Further, the interaction between these networks may be exacerbated in individuals with autism spectrum disorder (ASD). However, the neural mechanism(s) associated with the interdependence of attentional networks remains unclear. Therefore, the current study aims at examining whether the interdependence between alerting and executive networks can be interpreted under the LC-NE framework in relation to ASD and attention-deficit / hyperactivity disorder (ADHD) traits. Participants included 80 college students who scored in the highest (n=40) and lowest (n=40) quartiles based on the Autism Quotient scores. The study included two experiments: 1) a resting eye-tracking task to measure resting, tonic pupil diameter and EEG, and 2) a cued-flanker paradigm to measure behavioral performance and cue- and target-induced ERP components and phasic changes in pupil size. For the resting task, participants were asked to look at a black central crosshair, which was displayed on a grey background. For the cued-flanker paradigm, isoluminant stimuli (i.e., five arrows, cue) were presented on a gray background. Participants were instructed respond to the direction of the target center arrow. ASD and ADHD traits were measured using the Broad Autism Phenotype Questionnaire (BAPQ) and Conners ADHD Adult Rating Scales (CAARS). For cued-flanker RT, both the alerting and congruency effects, as well as the interaction between these factors were significant (all *ps* <.001). The significant interaction was due to larger congruency effect (incongruent-congruent) in the cued compared to the no-cue condition (*p*<.001). The alerting-congruency interaction score (Cued congruency effect - no-cue congruency effect) was positively related to BAPQ total and CAARS inattentiveness scores (all *ps* <.05). Pupillary and electrophysiological indices of the LC-NE system are currently being processed and will be included in conference presentation. Consistent with prior reports, our results show the interdependence of alerting and executive control attention networks. As hypothesized, such interdependence is associated with greater ASD and ADHD traits. These findings expand our understanding interplay between attentional processes, and suggests that they may be linked to social and non-social symptoms associated with ASD and ADHD. Future work will investigate how this may be linked to atypical LC-NE activation.

Disclosures: Y. Kim: None. **A. Saunders:** None. **R. Rozniarek:** None. **K. Cortes:** None. **A. Hamilton:** None. **S. Schieber:** None. **D. Kantor:** None. **D. Schneider:** None. **B. Keehn:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.01

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant R01-MH091424

Title: Viral-mediated (Poly I:C) inflammation in the neonatal cerebellum induces the chemokine CCL5 and its receptors CCR1 and CCR5.

Authors: *M. PEREZ-POUCHOULEN[1], C. DIONISOS[2], M. M. MCCARTHY[1];
[1]Pharmacol., [2]Program in Neurosci., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: We previously identified the second postnatal week as a critical period of Purkinje neuron development mediated by prostaglandin E2 and estradiol in the neonatal rat. Furthermore, inflammation caused by Poly I:C during the second postnatal week reduces the Purkinje dendritic tree size. Using a custom made NanoString® gene array that included a large number of immune related genes, we determined that 11-day-old male pups treated with Poly I:C reacted with a significant increase in *CCL5*, a chemotactic cytokine that attracts T cells, eosinophils, and basophils to the site of inflammation. Poly I:C treatment also increased the expression of two receptors for ccl5, CCR1 and CCR5 in the cerebellar vermis in both males and females at PN11. These two receptors are crucial for CCL5 inflammatory effects and could play an important role in regulating the developing dendritic tree of Purkinje neurons. In-situ hybridization (RNAscope®) for specific transcripts revealed that most microglia express CCR1 and CCR5 under inflammatory and non-inflammatory conditions in both males and females. Poly I:C treatment also increased the total number of $CCL5^+$ cells in the developing cerebellum and these were determined to be both natural killer cells and T cells. These findings suggest an important role for CCL5 and other immune cells in mediating inflammation in the developing cerebellum. NIH Grant R01-MH091424 to M.M.M.

Disclosures: M. Perez-Pouchoulen: None. **C. Dionisos:** None. **M.M. McCarthy:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.02

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH (NTRAIN/NICHD K12HD093427)
SNSF Postdoc.Mobility (P2EZP3_191858)
Wings for Life Spinal cord research foundation (WFL-US-18/20)
Craig Neilsen Foundation Pilot grant (727694)

Title: Molecular specification of cortico-brainstem versus corticospinal projection neurons in development

Authors: *J. KAISER[1], P. PATEL[1], F. DÜNDAR[2,3], J. PEREZ-TETUAN[1], E. SIEGER[1], N. ANGIRA[1], V. SAHNI[1,4];
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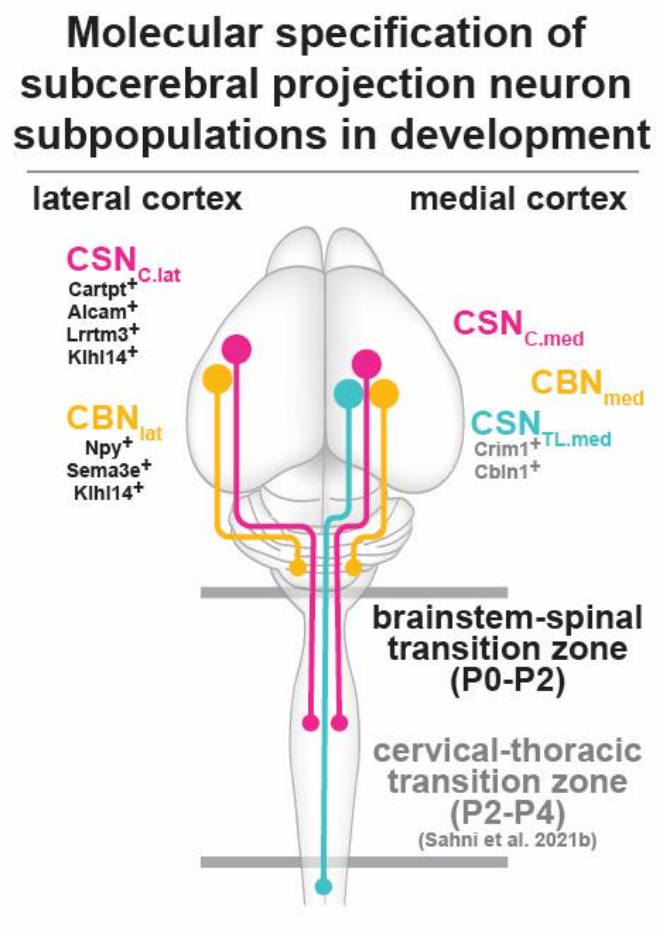
Abstract: Skilled motor control requires precise connections between subcerebral projection neurons (SCPN) in the cerebral cortex and their appropriate subcerebral targets in the brainstem or spinal cord. The brainstem is an important motor control center and cortical projections to the brainstem serve distinct motor control functions than corticospinal projections. However, mechanisms controlling cortico-brainstem versus corticospinal projections during development remain unknown. Here, we show that the transition between the brainstem and cervical cord distinguishes cortico-brainstem from corticospinal neurons from the earliest stages of SCPN axon extension in white matter. We used high throughput single-cell RNA sequencing of FACS-purified SCPN, retrogradely labeled from either the cerebral peduncle (labeling both cortico-brainstem and corticospinal neurons) or the cervical cord (labeling corticospinal neurons only) at critical times of axon extension. We identify that cortico-brainstem and corticospinal neurons are molecularly distinct: We establish Neuropeptide Y (Npy) as specifically enriched in cortico-brainstem neurons in lateral cortex, while CART prepropeptide (Cartpt) delineates cervical-projecting corticospinal neurons. Our results highlight molecular specification of cortico-brainstem vs. corticospinal projections well before these axons reach their appropriate segmental target and suggest a broad molecular program over SCPN axon targeting to distinct subcerebral targets early in development. These findings are likely to inform future investigations of motor circuit development, as well as approaches aimed at enhancing motor recovery after central nervous system damage.



Disclosures: **J. Kaiser:** None. **P. Patel:** None. **F. Dündar:** None. **J. Perez-Tetuan:** None. **E. Sieger:** None. **N. Angira:** None. **V. Sahni:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.03

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: A Cure for Ellie

Title: The role of antisense oligonucleotides in RNA modification in leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation

Authors: ***M. AMANAT**, S. GUANG, S. BAEK, M. YING, A. FINE, A. FATEMI, C. NEMETH;
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Abstract: Objectives: Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is an inherited white matter disease, caused by mutations in the *DARS2* gene, affecting different nervous system structures including the pyramidal tract, cerebellum, and dorsal column. Most patients have one mutation in the splicing site in intron 2, leading to reduced exon 3 inclusion in mature mRNA and no functional protein, and a second downstream mutation. To date, no cure exists for this disease. Antisenseoligonucleotides (ASOs) consist of single-stranded, modified ribonucleic or deoxyribonucleic bases that bind the complementary sequences in mRNA. The heteroduplex formation of ASO-mRNAs can activate RNase H leading to mRNA degradation, induce translational arrest by steric hindrance of ribosomal activity, or affect mRNA maturation through splicing modification. This *in vitro* study aimed to assess the efficacy of ASOs on *DARS2* mRNA in an attempt to increase inclusion, and reduce exclusion of exon 3. **Methods:** Neural progenitor cells (NPCs) were derived from induced pluripotent stem cells of three LBSL cases and one healthy control. Each patient line harbored one of two different mutations (c.228-20_21delTTinsC or c.228_17C>G) in intron 2. First- and second-generation ASOs with different mechanisms were designed; one to target an intronic splicing silencer (ASO1) and one to activate splicing enhancer (ASO2). A combination of ASOs was tested in parallel (Cocktail). Three doses of each ASO (50 nM,100 nM, and 150 nM) were administered to NPCs using Lipofectamine3000 and P3000transfection reagents. RT-qPCR was conducted to measure *DARS2* mRNA with/without exon 3. **Results:** Data from 40 NPC samples showed that ASOs in different doses increased the expression of *DARS2* transcripts including exon 3, compared to untreated. Maximum effect was mostly observed at the 100 nM dose. Across the three LBSL cell lines, *DARS2*transcripts including exon 3 were 2.57, 6.57, and 5.85 times higher with ASO1; and 1.88,5.41, and 4.47 times higher with ASO2, compared to untreated. The Cocktail showed the greatest increases of exon 3 inclusion at 2.26, 8.33, and 7.76X. Exon 3 expression in was close to healthy control after treatment and was 1.2 to 1.6 fold higher than control in one LBSL cell line. The expression of DARS2 transcripts lacking exon 3 was reduced to1.5-to 4-fold below baseline. **Conclusion:** ASOs and their combination are effective in modifying the splicing of*DARS2* mRNA to increase the expression of exon 3. Future studies need to assess the level of corrected protein and the functional consequences of this effect. Future work will also assess the safety profile of these ASOs.

Disclosures: M. Amanat: A. Employment/Salary (full or part-time):; Kennedy Krieger Institute. **S. Guang:** None. **S. Baek:** None. **M. Ying:** A. Employment/Salary (full or part-time):; Kennedy Krieger Institute. **A. Fine:** A. Employment/Salary (full or part-time):; Kennedy Krieger Institute. **A. Fatemi:** A. Employment/Salary (full or part-time):; Kennedy Krieger Institute. **C. Nemeth:** A. Employment/Salary (full or part-time):; Kennedy Krieger Institute.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.04

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: Harvard Catalyst Five Senses Pilot Grant Program

Title: Abnormal fetal brain development in human fetuses with non-syndromic isolated structural musculoskeletal birth defects

Authors: E. AHMAD[1], C. VELASCO-ANNIS[2], E. YANG[2], A. GHOLIPOUR[2], H. FELDMAN[2], P. E. GRANT[2], *L. VASUNG[2];
[1]Fetal Neonatal Neuroimaging and Developmental Sci. Ctr., [2]Boston Children's Hospital/Harvard Med. Sch., Boston, MA

Abstract: Proprioception (sense of self-movement, force, and body position) is altered in several congenital conditions that fall into the category of non-syndromic isolated musculoskeletal structural birth defects of the body (niMSBDs). However, to what extent are proprioceptive stimuli important for prenatal brain development and whether fetuses with niMSBDs have abnormal brain development remains a critical knowledge gap. Thus, we aimed to identify whether fetuses with niMSBDs, compared to the controls, have altered brain development before birth.From the hospital database, we retrospectively collected *in-vivo* structural T2-weighted MRI of 69 fetuses (30 controls and 39 cases with niMSBDs including arthrogryposis, skeletal dysplasia, short long bones [ICD-10-CM codes: Q74.3, Q68.8, Q74.9, Q66.8, Q69, Q70-73, Q79.9]) between 17-37 gestational weeks (GW). The study was approved by the institutional review board. Fetal brain MRIs were automatically reconstructed and segmented using state-of-the-art MRI tools ensuring high accuracy and reproducibility. We calculated the volumes (in mm^3) of transient fetal compartments (ganglionic eminence, proliferative zones, subplate zone, intermediate zone, and cortical plate), lateral ventricles, and other brain regions (limbic, basal ganglia with the thalamus, cerebellum). Relative hemispheric volumes (% hemisphere) were calculated, log-transformed, and used as a dependent variable. The robust regression method was used to identify and downweight any extreme values. We hypothesized that the dependent variable will be explained by the following factors or covariates: hemisphere (left-right), age (in GW), brain zone/region, and group (control or niMSBDs). We also included the interaction term (region*group) to provide region-specific group differences. Sex wasn't taken into consideration due to a large number of missing data. The resulting *p*-values were adjusted by the Holm procedure to limit the familywise type I error rate to 5%.Compared to the controls, fetuses with niMSBDs had significantly smaller intermediate zone (-51.2±7.5% SE) and cerebellum (-47.4±8.0% SE) after correction for multiple comparisons. Our results indicate that early development of the cerebellum and intermediate zone might be altered in fetuses with niMSBDs.

Disclosures: E. Ahmad: None. **C. Velasco-Annis:** None. **E. Yang:** None. **A. Gholipour:** None. **H. Feldman:** None. **P.E. Grant:** None. **L. Vasung:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.05

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH R01 NS124660

Title: Investigation of a human disease variant in GSX2 which alters DNA binding specificity and leads to basal ganglia agenesis

Authors: *L. TWEEDIE[1,2], J. SALOMONE[1,2], S. QIN[1], B. CAIN[1], B. GEBELEIN[1], K. CAMPBELL[1];
[1]Div. of Developmental Biol., Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [2]Med. Scientist Training Program, Univ. of Cincinnati Col. of Med., Cincinnati, OH

Abstract: The striatum, a major component of the basal ganglia, is known to derive largely from neural progenitors in the lateral ganglionic eminence (LGE) during embryogenesis. Gsx2, a homeobox transcription factor, is necessary for the correct patterning of neural progenitors in the LGE and ultimately the specification of distinct neuronal subtypes, such as striatal projection neurons. Mice carrying germline *Gsx2* null alleles show severe agenesis of the striatum and do not survive after birth. A recent report in humans (De Mori et al., (2019) *Brain*, 142: 2965-2978), identified a homozygous null allele and another homozygous mutation within the GSX2 homeodomain (HD) which changes the "Q" to "R" at amino acid 251 (i.e. $GSX2^{Q251R}$). Both mutations are viable, and the children show similar severe agenesis of the basal ganglia and neurological symptoms including spastic tetraparesis, dystonia, and intellectual impairment. Preliminary electrophoretic mobility shift assays (EMSAs) using mouse Gsx2 with an analogous mutation (i.e. $Gsx2^{Q252R}$) show that while this mutant protein retains binding to the high affinity GSX2 site TATTA, it prefers binding sites typically bound by K50 HDs (i.e. like Otx) rather than the usual Q50 HD sites. We therefore hypothesized that the $Gsx2^{Q252R}$ mutation leads to aberrant DNA binding and thus a modified gene regulatory network (GRN) that alters LGE progenitor specification and striatal differentiation. To determine the impact of this human variant on basal ganglia development, we generated a mouse model with the $Gsx2^{Q252R}$ HD mutation using a CRISPR-Cas9 approach. Importantly, the $Gsx2^{Q252R}$ protein is observed to be stable and nuclear localized in embryonic mutant brains. Preliminary characterization of these mutant mice indicates an intermediate phenotype between *Gsx2* null and WT animals, both for gene expression changes and striatal size. These data support the idea that $Gsx2^{Q252R}$ maintains proper regulation of some targets but does not regulate, or inappropriately regulates, other genes. To better understand the impact of this HD mutation on the *Gsx2* GRN, we utilized CRISPR-Cas9 to introduce the human variant on a $^{2xFLAG}Gsx2$ background to make $^{2xFLAG}Gsx2^{Q252R}$ mice. These mice are being used for CUT&RUN analysis to determine the DNA binding profile of this mutant protein and compare it with our published findings for WT Gsx2 using the $^{2xFLAG}Gsx2$ mice (Salomone et al., *Genes & Development*, 35: 157-174). Finally, $Gsx2^{Q252R/Q252R}$ mice are viable postnatally (unlike germline null *Gsx2* mice), allowing us the future opportunity to investigate behavioral changes as a result of this mutation.

Disclosures: L. Tweedie: None. **J. Salomone:** None. **S. Qin:** None. **B. Cain:** None. **B. Gebelein:** None. **K. Campbell:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.06

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: University of Scranton, Faculty Research Internal Grant

Title: Hypoplasia of dopaminergic neurons by hypoxia disrupts swimming development of larval zebrafish

Authors: *J.-H. SON[1], A. GERENZA[1], G. BINGENER[1], J. BONKOWSKY[2];
[1]Univ. of Scranton, Scranton, PA; [2]Univ. of Utah, Salt Lake City, UT

Abstract: Hypoxic injury to the developing human brain increases the risk of permanent behavioral deficits, but the precise mechanisms of hypoxic injury to the developing nervous system are poorly understood. In this study, we have characterized the effects of developmental hypoxia (1% pO_2 from 24-48 hours post-fertilization (hpf)) on diencephalic dopaminergic neurons (DA) in larval zebrafish and their development of swimming behavior. We found that hypoxia reduced the number of diencephalic DA neurons at 48 hpf immediately following hypoxia. Further, returning zebrafish larvae to normoxia following hypoxia (i.e., hypoxia-recovery, HR) induced reactive oxygen species (ROS) production in a time-dependent manner. Real-time qPCR results showed that HR caused upregulation of proapoptotic genes including *p53*, *caspase9*, and *caspase3*, suggesting the potential for ROS-induced cell death. With HR, we also found an increase in TUNEL-positive dopaminergic DA neurons, a corresponding persistent reduction in the number of diencephalic DA neurons by increased apoptosis, and impaired swimming behavior subsequently. The present study provides new insights for understanding the mechanisms of motor disability related to developmental hypoxic injury.

Disclosures: J. Son: None. **A. Gerenza:** None. **G. Bingener:** None. **J. Bonkowsky:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.07

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH Pioneer Award DP1NS106665
Paul G. Allen Frontiers Group
Travis Roy FDN, MA Spinal Cord Injury Research

Title: Purification and subcellular molecular investigation of human subtype-specific growth cones and their parent somata

Authors: *M. PETER, A. K. ENGMANN, K. OZKAN, H. E. MCKEE, J. D. MACKLIS; Harvard Univ., Cambridge, MA

Abstract: During development, distinct subtypes of neurons and areas of the brain form specific connections to construct functional circuitry. Growth cones (GCs) of diverse projection neuron subtypes must navigate complex extracellular environments to reach distant, subtype-specific targets. These axon-terminal structures respond to substrate-bound and diffusible signals in a subtype- and context-specific fashion to construct, e.g., functional cortical and cortical output circuitry. Recent studies strongly indicate that subcellular localization of RNA and protein molecular machinery specific to GCs likely underlies the precise functions of GCs during circuit development, and maturation into subtype-specific functional synapses. While great progress has been made identifying signals that guide elements of axonal growth, it is increasingly clear that subcellular, local GC biology critically controls precise circuit and appropriate synapse formation, maintenance, and function. Our laboratory has recently developed integrated experimental and analytical approaches enabling high-throughput, high-depth transcriptomic and proteomic investigation of purified GCs from subtype- and stage- specific cortical projection neurons *in vivo* in mice. This approach has revealed unanticipated complexity of GC molecular machinery and GC enrichment of transcripts and proteins in subtype-specific mouse GCs, so highly GC- enriched that they are essentially undetectable above noise in parent somata. Human subcellular GC biology remains essentially unstudied due to inaccessibility of human neurons developing connectivity. Here, we used *in vitro* fused human organoids ("assembloids"), with central characteristics of two distinct CNS regions, to model elements of human subtype-specific development of connectivity. We differentiated human pluripotent stem cells into cortical-like and ventral spinal cord-like organoids, and fused these organoids to recapitulate aspects of cortico-spinal connectivity. These "assembloids" developed axonal connections with GCs at axon terminals, enabling isolation and purification of fluorescently labeled, subtype-specific human GCs, along with parent somata, from neuronal projections resembling corticospinal mouse connectivity. Parallel purification of the GC and soma subcellular compartments from specific and distinct subsets of developing human neurons enables elucidation of normal and genetically perturbed RNA and protein subcellular molecular machinery, RNA trafficking, subcellular translational regulation, and discovery within the context of deeply studied mouse developmental biology.

Disclosures: M. Peter: None. **A.K. Engmann:** None. **K. Ozkan:** None. **H.E. McKee:** None. **J.D. Macklis:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.08

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: JSPS KAKENHI Grant Number JP90348813

Title: Two modes of the corticospinal axon elimination during development

Authors: *N. MURABE[1], S. FUKUDA[2], M. SAKURAI[3];
[1]Teikyo Univ. Sch. of Med., Tokyo, Japan; [2]Teikyo Univ. Sch. of Med. Dept. of Physiol., Tokyo, Japan; [3]Teikyo Univ, Sch. Med., Tokyo, Japan

Abstract: The exuberant projection and later elimination of surplus axons is one of the important mechanisms for refinement of neuronal circuits during development. The corticopontine and corticospinal neurons to the cervical spinal cord initially extend their main axons far beyond the final targets, and thereafter sprout collaterals to their targets, which is followed by distal axon pruning, i.e., pruning back main axons up to their target levels. These targets of the subcortical projections are located at most in the higher level of the spinal cord. However, little is known about the development of corticospinal axons projecting to the lumbar spinal cord. We previously showed that the cervical spinal cord received many axons from a large area of the contralateral cortex including the hindlimb area in early postnatal mice. We used an intersectional strategy to sparsely label the corticospinal axons that at least once projected to the cervical spinal cord C7 on P7. AAV2-retro encoding Cre was injected into the gray matter at the C7 on P7; and later AAV1-Cre-dependently expressing mCherry was injected into hindlimb area of the contralateral cerebral cortex on P70. Axons labeled with mCherry extend beyond the C7 spinal cord to the lumbar spinal cord. In the lumbar cord, a large number of labeled fibers entered the gray matter while the cervical gray matter received much fewer fibers. They developed robust arborization in the lumbar cord, exhibiting meshwork structure, whereas axons in the cervical gray matter showed only poor branching. These results suggest that corticospinal neurons in the hindlimb area first innervate the cervical gray matter as well as the lumbar spinal cord, but they prune proximal branches later, makes a clear contrast to distal axon pruning in corticocervical projection neurons.

Disclosures: **N. Murabe:** None. **S. Fukuda:** None. **M. Sakurai:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.09

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: Brian's Hope

Title: Novel combination N-acetylcysteine-4-phenylbutyrate dendrimer (NAC-D-4PBA) drug to reduce endoplasmic reticulum stress and inflammation in ABCD1 KO mice

Authors: *I. L. GAROFOLO;
Neurosci. Res., Kennedy Krieger Inst., Baltimore, MD

Abstract: Use of novel combination *N*-acetylcysteine and 4-phenylbutyrate dendrimer (NAC-D-4PBA) nanomedicine to reduce endoplasmic reticulum stress and inflammation in mouse model of X-linked Adrenoleukodystrophy

Garofolo I[1], Sharma A[2], Kannan S[3], Fatemi A[1,4], Kannan RM[2], Nemeth CL[1,41]Moser Center for Leukodystrophies at Kennedy Krieger, Kennedy Krieger Institute, Baltimore, MD, USA;[2]Center for Nanomedicine, Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, MD, USA[3]Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA [4]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA;

X-linked Adrenoleukodystrophy (X-ALD) is a neurodegenerative disorder stemming from mutations in the *ABCD1* gene which encodes the ATP-binding cassette (ABC) peroxisomal transporter of very long chain fatty acids (VLCFA). As a result, mutations in *ABCD1* result in accumulation of VLCFA in plasma and cells of all tissues leading to inflammatory demyelination as well as endoplasmic reticulum (ER) stress. X-ALD is associated with a variety of phenotypes, from the severe and fatal childhood cerebral ALD to the adult-onset peripheral neuropathy, adrenomyeloneuropathy (AMN), complicating treatment strategies. Advances in dendrimer nanoparticle therapeutics have allowed for targeted delivery of intracellular components across the blood-brain barrier. We have demonstrated efficacy of the anti-inflammatory/antioxidant dendrimer *N*-acetylcysteine conjugate (D-NAC) in patient derived cells to increase total glutathione and reduce inflammation. Furthermore, in mice, dendrimer 4-Phenylbutyrate (D-4PBA) increased ABCD2 expression and reduced neuronal VLCFA in the spinal cord. Here, we test the efficacy of a novel conjugate combining dendrimer with NAC and 4PBA (NAC-D-4PBA) in the ABCD1 deficient mouse. Preliminary data show successful brain and spinal cord penetration of the combined conjugate with NAC-D-4PBA-CY_5 accumulating in neurons and microglia in the ventral horn of the lumbar spinal cord. Future studies will determine the efficacy of NAC-D-PBA to demonstrate the combined ability of limiting microglial inflammation and reducing ER stress concurrently in the ALD mouse. These studies are further expected to improve neurobehavior scores in rotarod and open field tests from baseline, demonstrating positive effects of NAC-D-4PBA on motor coordination. Determining feasibility and efficacy of NAC-D-4PBA via intracellular and neurobehavioral modalities will grant access to further therapeutic opportunities in X-ALD research.

Disclosures: I.L. Garofolo: None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.10

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: CIHR
NSERC

HBHL
Weston Brain Institute

Title: Afferent modulation of neuronal survival in the mammalian striatum

Authors: *A. F. SADIKOT[1], V. V. RYMAR[2];
[1]McGill Univ., Montreal Neurolog. Inst., Montreal, QC, Canada; [2]Neurol. and Neurosurg., Montreal Neurolog. Insitute, Montreal, QC, Canada

Abstract: Factors that determine developmental survival of striatal neuron subpopulations remain unclear. We determined if the survival of striatal neurons in rodent brain is dependent on major glutamatergic or dopaminergic inputs. Glutamatergic or dopaminergic inputs were lesioned in neonatal Sprague-Dawley rats and unbiased stereology was used to quantify neuronal subpopulations in young adults, comparing lesioned rats or sham lesioned age-matched controls. Early postnatal lesions of the corticostriatal system did not result in significant striatal neuronal loss quantified on Nissl stains, but there was a decrease in neuronal size. Early postnatal lesions of the dopaminergic or thalamostriatal systems resulted in loss of striatal neurons in young adults. On the other hand, quantitative analysis in a mouse model with early genetic loss of dopaminergic neurons (aphakia mutant mouse) reveals no significant neuronal loss in the striatum of young adult offspring compared to wildtype controls. Thus, in addition to a known trophic dependence on their targets, striatal neurons depend on trophic input from afferents for survival. However, this survival dependence is contingent on the source of input, time at which inputs are removed, and the experimental model.

Disclosures: **A.F. Sadikot:** None. **V.V. Rymar:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.11

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: Genetics Training Grant T32GM007413
NIH Office of the Director R24OD026591
NIH National Institute of Neurological Disorders and Stroke R01NS105758

Title: Pioneer Gap Junction Channels in Embryonic Zebrafish Motor Systems

Authors: *R. LUKOWICZ BEDFORD, A. C. MILLER;
Univ. of Oregon, Eugene, OR

Abstract: The development and maturation of motor systems requires the successful development of coordinated communication within and between the nervous system and musculature. One mechanism of communication that is used within both systems are gap

junction channels, which allow for the fast, bi-directional, movement of ions and small metabolites. While gap junction communication is well documented in neural and muscular development and is required for maturation and function in both systems, the molecular identity of the proteins that form the channels remains largely unknown. This is in part due to the large and complex family of channel proteins, called the Connexins in vertebrates, which has 20 individual genes in humans. To probe the molecular identity of the Connexins in a vertebrate motor system we focused on motor neurons and early developing muscle in embryonic zebrafish as it offered a fast developing, accessible system driving an early stereotyped behavior (spontaneous coiling). We used our single cell RNA sequencing atlas that captures all tissues over zebrafish organogenesis (1-5 days post fertilizations, dpf) and identified candidate pioneer *connexins* enriched in neuromuscular development. We identified a previously uncharacterized, conserved, connexin, *gjd4*, that is expressed exclusively in slow muscle at 1 dpf. *gjd4* mutants have weakened spontaneous coiling, disrupted myosin organization and maturation, and disrupted calcium dynamics within slow muscle. This suggests that *gjd4* functions as a pioneering gap junction channel required for slow muscle development and function. We next found that early developing motor neurons express four related orthologues of mammalian Cx36-orthologs (*gjd1a*, *gjd1b*, *gjd2a*, and *gjd2b*). Genetic redundancy may explain why pioneering connexins of the nervous system have not previously been identified - mutant analysis amongst these genes is ongoing. Taken together, we have identified the molecular identity of the pioneering gap junction channels in the embryonic zebrafish motor system and have begun to reveal the contribution of these channels in the development of motor systems. This work was supported by the NIH National Institute of General Medical Sciences, Genetics Training Grant T32GM007413 to RLB, and the NIH Office of the Director R24OD026591 and the NIH National Institute of Neurological Disorders and Stroke R01NS105758 to ACM.

Disclosures: R. Lukowicz Bedford: None. **A.C. Miller:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.12

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH R01 MH090740

Title: Role of Sox8 in direct pathway striatal projection neuron development: a cautionary tale of transgenic reporters

Authors: *P. MERCHAN SALA[1], J. EHRMAN[2], S. ALI[3], L. ERHMAN[3], R. SCHNEIDER[3], D. NARDINI[3], R. WACLAW[3], K. J. CAMPBELL[4];
[1]Cincinnati Children's Med. Ctr., Cincinnati, OH; [2]Cincinnati childrens medical center., cincinnati, OH; [3]Cincinnati childrens medical center, cincinnati, OH; [4]Developmental Biol., Cincinnati Children's Hospl, Cincinnati, OH

Abstract: The striatum is the major component of the basal ganglia and is well known to play a key role in the control of motor function via the indirect (striatopallidal) and direct (striatonigral) output pathways. Imbalances in the activity of these pathways are thought to underlie the behavioral abnormalities observed in a number of childhood neurological disorders including attention deficit hyperactivity disorder (ADHD) and other classical motor disorders. Transcription factors (TFs) such as Isl1 and Ebf1 have been implicated in the proliferation, survival and maturation of direct pathway striatal projection neurons (dSPNs). The well-known glial TF Sox8 is also expressed in dSPNs and we found that it is severely down-regulated in the *Ebf1* but not *Isl1* mutant striatum. We analyzed $Sox8^{lacZ}$ knockout mice (Sock et al, (2001) *Mol Cell Biol* 21: 6951-6959) and found that there is a dramatic reduction in the projections of the direct pathway to the substantia nigra pars reticulata (SNr) in both homozygous and heterozygous animals, despite the fact that the striatum appears normal in size. We observed *DrD1-EGFP*- and substance P-positive fibers abnormally terminating within the globus pallidus of *Sox8* mutants supporting the existence of abnormal projections of the direct pathway. Since Sox8 is also expressed in oligodendrocytes, we wanted to pursue a conditional knockout approach using the EUCOMM *Sox8* allele. We first made a null allele ($Sox8^{tm1d/tm1d}$) which deletes exon 2 of the *Sox8* locus and surprisingly did not observe a reduction in dSPN projections to the SNr. However, replacement of exon 2 with a *lacZ* reporter, i.e. $Sox8^{tm1b/tm1b}$ allele, showed a moderate axon phenotype, similar to that in the original $Sox8^{LacZ/+}$ heterozygous mice, suggesting a possible negative effect of exogenous β-galactosidase protein in dSPN axonal growth. We are currently examining the relative levels of β-galactosidase between the different *Sox8* alleles and correlating that with the axonal phenotypes observed. Despite the divergent axonal phenotypes observed in $Sox8^{lacZ/lacZ}$ and $Sox8^{tm1d/tm1d}$ (i.e., null without *lacZ*) animals, similar alterations in striatal gene expression were observed in both mutants. Taken together, our work on the different *Sox8* alleles indicates that this TF plays a role in the regulation of striatal gene expression but not dSPN axon outgrowth. Moreover, our findings suggest that exogenous reporters such as β-galactosidase or other fluorescent proteins could interfere with cellular functions such as axon outgrowth in developing neurons.

Disclosures: P. Merchan Sala: None. **J. Ehrman:** None. **S. Ali:** None. **L. Erhman:** None. **R. Schneider:** None. **D. Nardini:** None. **R. Waclaw:** None. **K.J. Campbell:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.13

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NINDS award #R01 NS115881-01A1

Title: The impact of environmental context on the development of coordinated movements in rats

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Abstract: Environmental enrichment studies have long emphasized the importance of the context in which an individual is raised on both brain development and behavioral outcomes. Previous work has shown that environmental enrichment accelerates motor development and can actually mediate motor deficits (Marques et al., 2014; Young, Vuong, & Tesky, 2012). However, some limitations of these studies are the highly controlled and static nature of these "enriched" environments. Thus, the current research aims to measure the influence of a more dynamic environment with numerous affordances on the development of coordinated behavior. Specifically, we are interested in determining whether rearing in a semi-naturalistic environment with more diverse movement opportunities can lead to more rapid motor development and increased coordination of the limbs. Pregnant rats (Rattus norvegicus) were housed in either standard laboratory housing (L) or a seminatural outdoor field pen (FP) that was 3000 times larger than a laboratory cage. Following birth, we tracked the motor development of the offspring using a set of three behavioral tasks. From Post-Natal (PN) day 1 to 11, the rat pups underwent a surface righting task (SRT) where they were placed on their backs, and the duration it took to right themselves was timed. Next was an open field task (OFT) that was implemented on PN 6 and continued until PN 22 to capture general activity levels and gross locomotor activity. Following a short break, these same rats were placed through four days of the ladder rung walking (LRW) task at three different developmental time points: PN 24, PN 36, and PN 56. This task had a standard rung arrangement, with a 1 cm gap between each rung, and a variable rung arrangement where the gap size was randomized between a 1 cm - 3 cm gap. All tasks were recorded with a camera for posthoc analysis. We will implement the machine learning algorithm DeepLabCut (Mathis et al., 2018) to quantify the kinematics of their movements and different strategies employed by FP and L rats in all three tasks. Preliminary results show that FP rats have accelerated motor development in the SRT and OFT compared to the L rats. The FP rats also had fewer errors on the LRW tasks in the standard and variable rung arrangements. Collectively, these findings suggest that early environment influences not only accelerate the rate of motor development but also heighten the degree of limb coordination that likely stems from the movement opportunities and affordances available.

Disclosures: F. Gomez: None. **M. Englund:** None. **C. Pineda:** None. **C. Bresee:** None. **L.A. Krubitzer:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.14

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: National Research Foundation of Korea (NRF) grant (No. 2022R1C1C1009774).

Title: Neurodevelopmental evaluation for premature neonates by spontaneous movements analysis using inertial sensors : a methodology

Authors: *S. LEE[1], M. KANG[2], E. KO[2], S. KIM[2], S. MOON[2], Y. MOON[2], J. KWEON[2];
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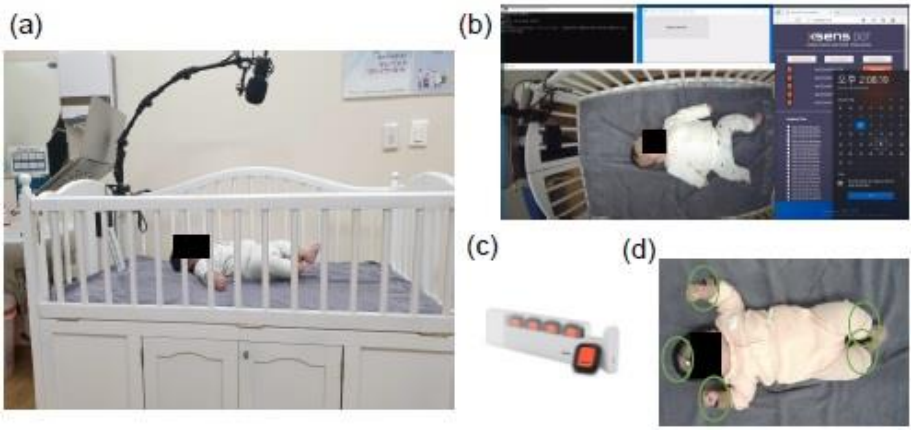
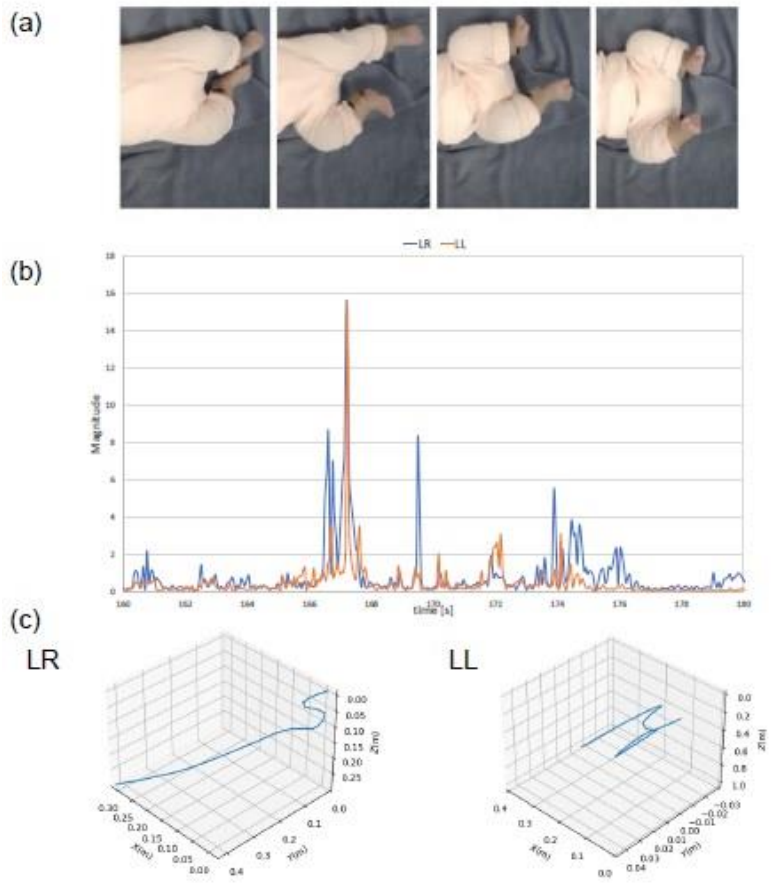
Abstract: Most infants visit the clinic with their parents' suspicions of neurodevelopmental delays. This study aims to suggest a methodology for acquiring multimodal information to utilize for early screening of the risk of developmental delay. The protocol for collecting multimodal information on spontaneous general movements consists of both the video recording and the motion analysis inertial sensor system. The spontaneous movement for at least 5 minutes is recorded with the video camera and audio recording placed high above the infant(Fig1). Using the video, a certified physical therapist performs Prechtl's general movement assessment (GMA) evaluation. Five inertial sensors(Xsens DOT, Netherlands) consisting of 3D gyroscopes, accelerometers, and a magnetometer are attached to the forehead and both wrists and ankles during acquisition (Fig1). The data from the inertial motion analysis system have been compared to the clinically significant findings including age-specific motor optimality scores of GMA based on the simultaneously recorded video. The test protocol was completed by a prematurity infant. The results showed that the data from inertial motion analysis were sufficiently correlated to the specific findings of GMA. The cramped-synchronized general movement was observed during GMA, which showed correlated vector magnitude and position changes of inertial motion analysis (Fig2).





Disclosures: **S. Lee:** None. **M. Kang:** None. **E. Ko:** None. **S. Kim:** None. **S. Moon:** None. **Y. Moon:** None. **J. Kweon:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.15

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH grant NTRAIN/NICHD K12HD093427
Wings for Life Spinal Cord Research Foundation WFL-US-18/20
Craig Neilsen Foundation Pilot grant 727694
NY State (NYS) Spinal Cord Injury Research Board (SCIRB) Postdoctoral Fellowship C33613GG

Title: Microsurgical lesions identify segmentally distinct responses of axotomized corticospinal neurons

Authors: C. RUVEN[1], J. KAISER[1], ***P. PATEL**[1], R. KAWAGUCHI[2], V. V. SAHNI[1,3]; [1]Burke Neurolog. Inst., White Plains, NY; [2]Dept. of Psychiatry and Behavioral Sci., Univ. of California Los Angeles, Los Angeles, CA; [3]Feil Family Brain and Mind Res. Inst., Weill Cornell Med., New York City, NY

Abstract: It is well established that long distance axonal regenerative ability declines with age, however, it is not precisely known how and when corticospinal neurons (CSN) lose this ability during development. This is because established experimental models of neonatal SCI perturb the spinal environment and disrupt potential guidance cues. This makes it difficult to accurately assess the ability of the CNS to support long-distance axon regeneration. To circumvent this problem, we established a novel microsurgical approach to disrupt developing CSN axons in the spinal cord, leaving the spinal environment relatively unperturbed (minimal astrogliosis and microglial activation). In this approach, the developing corticospinal tract (CST) is lesioned under ultrasound guided backscatter microscopy, by using a beveled micropipette vibrating at ultrasonic frequency. Using this novel microsurgical approach, we identified that long-distance CSN axon regenerative ability is not lost uniformly across the spinal cord- it is lost at distinct times at distinct spinal levels. At P4, this ability is fully lost at cervical C2, reduced at thoracic T2, and fully intact at thoracic T11. At P1, this ability is reduced at cervical C2, and almost fully maintained at thoracic T2, albeit regenerating CSN axons traverse the dorsolateral funiculus instead of their normal principal location in the dorsal funiculus. These data suggest that mechanisms limiting CSN axon regeneration are: 1) in effect at significantly earlier developmental times than previously appreciated; and 2) likely different at distinct spinal segments. Our analysis further reveals that this differential loss of axon regenerative ability cannot be explained by overt differences in astrocyte or microglial activation. In summary, we have established a novel, reproducible approach to lesion the developing CST to precisely delineate the developmental decline in long-distance regenerative ability. Future investigations, using this approach, will be able to identify novel molecular mechanisms controlling long-distance axon regeneration. Further, this work also suggests that distinct approaches will be required to effect CST regeneration after SCI at distinct spinal levels.

Disclosures: C. Ruven: None. **J. Kaiser:** None. **P. Patel:** None. **R. Kawaguchi:** None. **V.V. Sahni:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.16

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant F30 AA029261
NIH Grant RO1 AG0728900

Title: Prenatal ethanol exposure alters development of the striatal microcircuit and early motor behavior

Authors: *A. TOUSLEY, B. KOC, P. W. L. YEH, H. H. YEH;
Dartmouth Col., Hanover, NH

Abstract: Developmental motor delays are a common early clinical sign of Fetal Alcohol Spectrum Disorders (FASD) as well as other neurodevelopmental disorders. Individuals with FASD can develop a range of motor symptoms including problems with both gross and fine motor function, and sensorimotor integration. However, the neural circuit level changes that underlie early motor deficits remain underexplored. The striatum, the input nucleus of the basal ganglia, plays an important role in motor learning in adult animals, while the maturation of the striatal circuit has been associated with the development of early motor behaviors. Here we demonstrate that a brief binge exposure to ethanol (5% w/w) in a liquid diet on embryonic days (E)13.5-16.5, results in developmental motor deficits concurrent with alterations in synaptic activity, passive/active properties and morphology in two populations of striatal neurons: GABAergic interneurons (GINs) and striatal projection neurons (SPNs). We performed a series of 9 brief motor behavior tasks on postnatal days (P)0-14. Behaviorally tested animals were then used to complete whole cell-voltage and current clamp recordings of GINs and SPNs in order to assess GABAergic/glutamatergic synaptic activity and their passive/active properties. Cells were filled with biocytin during recording for morphological analysis. We found that GINs demonstrated significantly decreased frequency of GABAergic and glutamatergic spontaneous postsynaptic currents (sPSCs) during the first postnatal week. Both decreased frequency and amplitude of GABAergic and glutamatergic sPSCs were present in GINs at P14. Alternatively, while SPNs exhibited a significant decrease in glutamatergic sPSC frequency during the first postnatal week, this deficit normalized by P14. However, SPNs displayed lower firing threshold during the first postnatal week and a decreased firing rate accompanied by increased soma size during the second postnatal week. These data indicate that SPNs and GINs may be differentially affected by *in utero* ethanol exposure and provide insight into how deficits in each cell population may relate to the onset of early motor behaviors. Ongoing work explores if observed deficits are sex-specific, and if the synaptic deficits may be driven by action potential or spontaneous pre-synaptic transmitter release-mediated mechanisms.

Disclosures: **A. Tousley:** None. **B. Koc:** None. **P.W.L. Yeh:** None. **H.H. Yeh:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.17

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: Else Kröner Fresenius Stiftung: 2019-A03
Deutsche Forschungsgemeinschaft (DFG): KU 3711/2-1, project number:

423633679
Forschungsgemeinschaft (DFG): KU 3711/2-1, project number: 425899996 – SFB 1436

Title: Ultra-high resolution MR Imaging of the human primary motor cortex in ageing and disease

Authors: *A. NORTHALL[1], J. DOEHLER[1], M. WEBER[2], I. TELLEZ[3], S. VIELHABER[2], S. SCHREIBER[2], E. KUEHN[4];
[1]Inst. for Cognitive Neurol. and Dementia Res., [2]Dept. of Neurol., Otto-von-Guericke Univ. Magdeburg, Magdeburg, Germany; [3]Max Delbrueck Ctr. for Mol. Med., Berlin, Germany; [4]Hertie Inst. for Clin. Brain Res., Tuebingen, Germany

Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease causing a loss of motor control, including breathing muscles and other essential muscle groups that cause the death of a patient within a median of three years after initial diagnosis. The disease is characterized by increased iron and depopulation of Betz cells in layer Vb of the primary motor cortex (M1), which connect to the spinal cord to control muscles. Iron accumulation and cellular loss is also present in healthy aging, but neither for the case of aging nor for the case of ALS it is yet clear whether this is specific to particular layers or topographic areas of M1. To investigate layer Vb degeneration in healthy aging and ALS patients, we used ultra-high field 7T-MRI to investigate layer-specific demyelination, iron and calcium accumulation in 20 younger adults, 20 older adults, and 10 patients with ALS after first diagnosis. We tested face, upper limb and lower limb function (tongue kinematics, hand strength/dexterity, walking distance). Quantitative T1 (qT1) images (resolution: 0.5mm for healthy adults, 0.7mm for patients) and quantitative susceptibility mapping images were used as in-vivo proxies of cortical myelin and iron/calcium content, respectively. fMRI data were used to precisely localize body part areas in M1. Decurved qT1 was used to identify four anatomically-relevant cortical compartments in M1 (superficial layers 1-4, layer 5a, layer 5b, layer 6). In healthy adults, we show layer-specific myelin differences between topographic areas (e.g. hand area has more myelin than the face area in layer 6, while the opposite effect is shown in layer 5a). While this topographic myelo-architecture is stable with age (i.e. no myelin differences between younger and older adults), we show age-related iron and calcium accumulation, particularly in the deep layers and lower limb area of M1. Preliminary analysis shows that one left lower limb-onset ALS patient shows reduced myelin in the lower limb area of the right (affected) hemisphere, and increased myelin in the not-yet affected face (bulbar) area of the left hemisphere, compared to a matched control. Analyzing the data of 9 more ALS patients will confirm whether this pattern is replicable. In conclusion, we show that myelin differences exist between topographic areas of M1, which are stable in aging while iron/calcium accumulation is layer- and topographic field-specific. In ALS, we show that topographic area-specific changes in myelin content are associated with symptom onset. Our findings provide novel opportunities for measuring disease progression in ALS, and disentangling the effects of ALS from aging on the complex architecture of M1.

Disclosures: A. Northall: None. **J. Doehler:** None. **M. Weber:** None. **I. Tellez:** None. **S. Vielhaber:** None. **S. Schreiber:** None. **E. Kuehn:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.18

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH DK 126085

Title: Impact of Early Life Stress on Preautonomic Circuits in Neonatal Mice

Authors: *V. GARZA[1], H. ZHENG[2], L. RINAMAN[2];
[2]Psychology, [1]Florida State Univ., Tallahassee, FL

Abstract: Previous studies have demonstrated correlations between early life stress (ELS) and adverse effects on behavior and physiology, including vagally-mediated gastrointestinal functions. The development of neuronal projections to a target and the formation of synaptic connections defines neural circuit formation, which may be disrupted by ELS. In mice, critical periods of vagal circuit development include the first and second weeks postnatal. We hypothesize that ELS will alter the central vagal connectome in mice, producing long-term effects on brainstem, hypothalamic, and limbic forebrain circuits that are synaptically linked to vagal motor neurons. To test this, mice were reared from postnatal day 2 (P2) to P9 under conditions of limited bedding and nesting to elicit ELS by disrupting maternal care; control mice were reared under care as usual (CAU) conditions. On P11, the ventral stomach wall was injected with pseudorabies virus (PRV152) in ELS and CAU mice (n=36; 2 males, 2 females per litter). Pups were perfused 72 hr later (on P14) to permit retrograde transneuronal labeling defining the synaptic organization of pre-vagal motor circuits. The distribution and extent of transneuronal labeling varied within litters and between rearing conditions. In both CAU and ELS mice, consistent labeling was observed in the dorsal vagal complex, reticular formation, diencephalon, limbic forebrain, and visceral cortices, similar to previous results in neonatal rats (PMC6725770). Quantitative analysis of labeling patterns across brain regions will reveal potential effects of sex and/or ELS on central pre-vagal circuitry.

Disclosures: V. Garza: None. **H. Zheng:** None. **L. Rinaman:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.19

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: 1 R01 MH128745
1 R21 MH125367

Title: Defining the functional identity of the mouse paralaminar nucleus

Authors: *D. SAXON[1], V. BUTYRKIN[2], J. POLACKAL[3], P. J. ALDERMAN[4], S. VICINI[6], S. F. SORRELLS[5], J. CORBIN[7];
[1]Georgetown Univ., Washington, DC; [2]Univ. of Maryland, College Park, MD; [3]George Washington Univ., Washington, DC; [4]Neurosci., [5]Dept. of Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; [6]Dept Parmacology & Physiol., Georgetown Univ. Med. Ctr., Washington, DC; [7]Ctr. for Neurosci. Res., Children's Natl. Med. Ctr., Washington, DC

Abstract: The amygdala is a brain region highly involved in social and emotional processing. Amygdala dysfunction is implicated in many developmental and neuropsychiatric disorders, including Autism Spectrum Disorders (ASD) and mood disorders. The paralaminar nucleus (PL) of the human amygdala was recently found to contain a population of neurons that remain immature until adolescence, much later than most neurons in the human brain. Based on the timing of their maturation, these cells may play a key role in social-emotional development during adolescence, and there is evidence that the PL is altered in humans with ASD. However, the functional identity of this unique pool of late-maturing neurons remains largely unstudied. We recently identified and characterized the PL in the mouse, revealing close similarities to the human. Utilizing this mouse model of the PL, we sought to uncover the neuronal diversity of the mature PL, defined by developmental lineage, circuitry, intrinsic electrophysiology, and morphology. We first employed lineage tracing of the mouse PL and revealed that the region is comprised of neurons from multiple developmental lineages, corresponding to known telencephalic progenitor regions. Next, we data-mined the Allen Brain Connectivity Atlas and observed putative inputs to the mouse PL emanating from multiple brain regions. Based on this lineage and circuit heterogeneity, we hypothesized that the PL is comprised of distinct subpopulations serving diverse roles. To test this hypothesis, we are employing multiple tools (patch clamp, circuit tracing and manipulation, morphological reconstruction) to determine diversity, connectivity, and function of mature PL neurons. This continued work will reveal the functional identity of the PL and begin to determine its role in behavior and disease.

Disclosures: D. Saxon: None. **V. Butyrkin:** None. **J. Polackal:** None. **P.J. Alderman:** None. **S. Vicini:** None. **S.F. Sorrells:** None. **J. Corbin:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.20

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Title: Effects of enriched environments in functional brain connectivity

Authors: *E. GONZÁLEZ-PÉREZ[1], J. ORTIZ-RETANA[2], E. PASAYE-ALCARAZ[3], S. ALCAUTER-SOLORZANO[1];
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Abstract: Introduction: Enriched environment (EE) is described as a condition characterized by increased opportunities for exploratory behavior and sensory stimulation (Hebb, 1947). Several studies have shown that EE improves a set of cognitive and motor skills (Guildi et al, 2014). The main networks characterized in resting state is the Default Mode Network (DMN) and Sensorimotor network (SM). Magnetic resonance imaging (MRI) provides an invaluable opportunity to characterize in-vivo the longitudinal developmental trajectories of several structural and functional properties of the human and animal brains, with outstanding anatomical resolutions. The aim of this work is to show the effect of enriched environment in the development of functional brain networks. **Methods:** A total of 21 rats, (EE=9, control=12) in 21, 45 and 90 postnatal days were housed in cages, the standard cages were 34.5 x 49 x 17 cm, while enriched cages were 45.7 x 41.9 x 76.2 cm with a training wheel, different tunnels and toys inside of the box, the environment changed every 3 days. The rats were scanned in each point of age to determine the functional connectivity between regions of the DMN (Retrosplenial cortex and Cingulum) and for SM Network (motor cortices left and right). Images were acquired in a Bruker Pharmascan 70/16US, 7 Tesla MRI Scanner (Bruker, Ettlingen, Germany). Animals were anesthetized with isoflurane at 0.05% concentration for induction and positioning in the scanner bed and a single bolus of 0.010 mg/kg of dexmedetomidine was administered subcutaneously. The animal research protocols were approved by the bioethics committee of the Institute of Neurobiology, UNAM). Images were analyzed with ANTs and FSL routines. The statistical analysis was performed by multiple comparisons using an ANOVA Test in RStudio. **Results**: We found that the brain connectivity between RSCx-Cg1 is significantly different between ages P90 compared to P21 (p=0.008) for control rats. P45 and P21 (p=0.001), P90 and P21 (p=0.002) for enriched rats. No significant differences were found between groups in this network. For the Sensorimotor network we found significant differences between ages P90 compared to P21 (p=0.001) for control group, P45 with P21 (p=0.001) and P90 compared to P21 (p=0.035) for enriched rats and between groups EE and CB in age P45 (p=0.028). **Conclusion**: The brain functional connectivity in rats showed significant changes with ag and different environments along lifespan, proving to be a valuable model of development.

Disclosures: E. González-Pérez: None. **J. Ortiz-Retana:** None. **E. Pasaye-Alcaraz:** None. **S. Alcauter-Solorzano:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.21

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: P50AA26117
T32AA007565

Title: Periadolescent social stress alter binge-like ethanol consumption, anxiety-like behaviors, and microglial function in a sex-dependent manner

Authors: *S. GIRONDA[1], A. SIERRA[3], S. MACAULEY[2], J. WEINER[1];
[1]Wake Forest Univ., Winston Salem, NC; [2]Wake Forest Univ., Winston-Salem, NC; [3]Glial Cell Biol. Lab., Achucarro Basque Ctr. For Neurosci., Leioa, Spain

Abstract: Introduction: Alcohol use continues to be one of the highest-ranked causes of death worldwide. Excessive and maladaptive use of alcohol, clinically defined as alcohol use disorder (AUD), affects nearly 14.4 million people in the United States and 107 million people worldwide. One of the greatest risk factors associated with the development of AUD and binge drinking, early life stress (ELS), has been widely investigated and demonstrated to have a profound impact on the development of the systems associated with an increased vulnerability to maladaptive drinking. Recently, microglia, the resident macrophage, and predominant immune response in the brain, have been implicated as a key mediator between a variety of forms of early life stress and a host of neuropsychiatric disorders, including AUD and anxiety disorders. Here, we sought to establish a mouse model to examine the role of microglia in AUD vulnerability.Methods: C57/BL6 mice were either exposed to a social stress experience (PSS) during periadolescence (PD 14-21) for 30 minutes a day or no stress at all. At weaning, mice were randomly assigned to group-housed cages until ~PD60 when behavioral studies began. Mice were then exposed to a battery of behavioral assays to identify changes in anxiety-like and depression-like behaviors or binge-like ethanol consumption using the drinking in the dark (DID) paradigm. Following the completion of these assays (~PD100), changes in microglia activity were measured using immunohistochemistry.Data and Results: In the open field test female mice exposed to PSS spent significantly less time in the center than control female mice ($p < .01$). In addition, PSS-exposed females exhibited increased latency to feed during the novelty-suppressed feeding test ($p<.05$). In addition, PSS increased ethanol intake in both sexes ($p<.001$). Following a month of the DID procedure, PSS-exposed mice exhibited a reduction in IBA 1+ microglia ($p<.01$) and an increase in activation ($p<.05$) in the ventral hippocampus.Conclusions: PSS exposure leads to increased binge-like ethanol consumption, negative emotion-like behaviors, and alterations in microglia activity. Future studies will employ PSS to determine if microglia play a causal role in the maladaptive behaviors promoted by this model.

Disclosures: S. Gironda: None. **A. Sierra:** None. **S. Macauley:** None. **J. Weiner:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.22

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIH 4 R00MH124434
BBRF NARSAD Young Investigator Award

Title: Worth the risk? Effects of development and early care quality on lateral habenula involvement on infant social behavior flexibility

Authors: *S. HU[1,2], A. GEORGE[1,2], K. PACKARD[1,2], M. SONG[1,2], J. WANG[3], M. OPENDAK[1,2,3];
[1]Kennedy Krieger Inst., Baltimore, MD; [2]Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD; [3]Dept. of Child & Adolescent Psychiatry, NYU Langone Hlth., New York, NY

Abstract: Flexible social behavior is critically important during early life, when environmental demands are in constant flux. Yet, heightened circuit plasticity during this period also renders the infant vulnerable to environmental influences that guide lifelong social behavior. However, the circuit mechanisms linking early experience to lasting social behavior patterns remain unclear. Here, we use a rodent model to study the ontogeny of the lateral habenula (LHb), a key negative regulator of dopaminergic signaling, in social behavior in typical and perturbed development. To perturb development, we used the Scarcity-Adversity model of Low Bedding (SAM-LB) from postnatal (PN) days 8-12, in which the dam is given limited nesting materials.In our first experiment, habenulae were dissected at PN18/PN28 and assayed for levels of CaMKIIβ. In our second experiment, PN18/PN28 rat pups were injected with radiolabeled glucose prior to receiving mild tail shocks or no shocks, alone or with a social partner present. Brains were removed and analyzed with autoradiography. In our final experiment, we bilaterally transduced PN3 pups with the DREADDs receptor hM4Di or control virus in the LHb. To chemogenetically inhibit the LHb, we injected PN18/28 pups with clozapine-N-oxide or saline control prior to peer sociability tests with/without ambient predator odor. We observed an increase in CaMKIIβ expression in PN28 pups compared to PN18 pups, regardless of rearing condition. The increase in CaMKIIβ, which is expressed in excitatory neurons, suggests greater neural activity. In support of this, metabolic imaging showed that at PN28, social presence and shock (threat) were associated with increased glucose uptake in the LHb. Furthermore, chemogenetic inhibition of the LHb at PN28 increased social approach when threat odor was present in control-reared animals. SAM-LB animals showed decreased social approach behavior at baseline at PN28, which was rescued by LHb inhibition. Our results suggest that development and early care influence LHb involvement in processing social and threat cues. Whereas weaning at PN21 typically triggers habenula-dependent inhibition of social approach under threat, early adversity engages LHb-inhibited approach even in the absence of threat. These findings implicate the LHb as a target for early intervention.

Disclosures: S. Hu: None. **A. George:** None. **K. Packard:** None. **M. Song:** None. **J. Wang:** None. **M. Opendak:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.23

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: NIMH 5R01MH119156

Title: Classification of transcriptionally distinct neurons in the lateral septum

Authors: *C. REID[1], C. C. HARWELL[2], M. TURRERO GARCIA[2], D. TRAN[1], S. VU[1], Y. REN[2];
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Abstract: Septal nuclei in the basal forebrain have critical roles in regulating emotional states including fear, anxiety, and aggression. Dysfunction of septal neurons is thought to play a significant role in the pathophysiology of a variety of psychiatric disorders including schizophrenia, bipolar disorder and depression. The septum can be classified into medial (MS) and lateral (LS) regions. The medial septum is composed of cholinergic, GABAergic and glutamatergic neurons that are mainly project to the hippocampus. The lateral septum is composed of GABAergic projection neurons that receive reciprocal input from numerous brain regions known to regulate emotional and motivational states. Despite our growing appreciation for the role of the LS in modulating emotional states, we know very little about the development and diversity of lateral septal neurons (LSNs). The overall aim of this project is to understand the extent of neural diversity in the lateral septum. Our previous work has suggested that a significant proportion of LSNs are derived from progenitors with a history of expressing the transcription factor Nkx2-1. Nkx2-1 is critical for the specification and maturation of cortical interneurons, and we hypothesize it may play a similar role for LSNs. We performed single-nucleus RNA sequencing on young adult Nkx2-1Cre mice crossed with the Sun1:GFP allele, and characterized several putative subgroups of medial and lateral septal neurons. We found that LSNs can generally be categorized into two populations: those with a history of Nkx2-1 expression (Nkx2-1 neurons), and those that highly express the transcription factor Meis2 (Meis2 neurons). We mapped the spatial organization of molecular subgroups using spatial transcriptomics and immunohistochemistry, revealing the discreet arrangement of molecular LSN groups across the rostral-caudal and dorsal-ventral axis of the septum. Using recombinant viruses and mouse Cre lines we labelled subsets of LSNs and investigated their intrinsic physiological properties. Lastly, we traced their efferent and afferent inputs and found patterns of connectivity that are unique to specific molecular subgroups LSNs, suggesting specialized circuit and behavioral functions of these distinctive groups.

Disclosures: C. Reid: None. **C.C. Harwell:** None. **M. Turrero Garcia:** None. **D. Tran:** None. **S. Vu:** None. **Y. Ren:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.24

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: AMED Grant 21gm1310012s0301

Title: Dynamical systems model of embodied memory in early human infancy

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Abstract: A large body of empirical studies have indicated that young human infants can learn and remember an interaction with a specific environment by using a method of reinforcement of limb movement in the interaction with a suspended mobile toy, called “Mobile Conjugate Reinforcement (MCR)” (Rovee-Collier et al. 2000). However, the underlying mechanisms by which such a memory is stored, lost and regained are not clear. Dynamical systems modeling will provide a clue to understand such phenomena involving multiple time scales. In this study, we extended dynamical systems models of MCR paradigm (Kelso & Fuchs 2016, Fujihira & Taga 2022) to examine the mechanisms of forgetting and reactivating memory in infants. Our model has two nonlinear oscillators representing spontaneous limb movements and mobile movements, and three variables *u*, *v*, *m* with different time constants to change the action. *u* immediately integrates signals from the brain and sensory information regarding the mobile and produces motor commands to modulate the limb movements. *v* represents changes in internal state of the brain during learning to determine enhancement or inhibition of action based on the contingency between limb and mobile movements. Over the longer time scale, *m* represents memory formation, retention and forgetting for the motor command generated by *u*. The result of computer simulation reproduced the retention dynamics observed in the MCR paradigm (Rovee-Collier et al. 1980), which was calculated as the time evolution of a ratio of limb movements in the immediate retention test and those in the delayed retention test. The retention ratio gradually decayed, which was governed by the time constant for changes in *m*. Furthermore, after the retention ratio decayed, external forcing of mobile movements immediately elevated the retention ratio, indicating the reactivation of memory. The present study showed that the empirical evidence of memory dissociation in infants can be accounted for by three variables representing the brain dynamics with different time constants. Modeling the emergent properties of action generation in the changing environment with the internal dynamics of the brain poses a new perspective for understanding infants’ learning and memory in terms of embodiment in development.

Disclosures: R. Fujihira: None. **G. Taga:** None.

Poster

689. Development and Brain Connectivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 689.25

Topic: A.08. Development of Motor, Sensory, and Limbic Systems

Support: P50 MH096889

Title: Early life adversity in mice alters structural connectivity within the cingulum that is associated with changes in social behavior

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Abstract: The cingulum bundle is a multi-segmented large white matter tract that connects limbic, thalamic, and cortical regions. Diffusion magnetic resonance imaging (dMRI) has reported decreased fractional anisotropy (FA) and increase mean diffusivity (MD) within the cingulum of individuals exhibiting a variety of psychopathologies (schizophrenia, depression, post-traumatic stress disorder, etc). In adult male and female mice exposed to early life adversity, we examined if the cingulum bundle connectivity is modified using MRI derived metrics and whether differences are associated with behavioral changes. C57BL/6J mice were either assigned limited bedding and nesting (LBN) or normal bedding conditions from postnatal day (PND) 2-9 (n = 13/21 control/LBN males [5 litters], n = 10/7 control/LBN females [3 litters]). Young adult mice (PND 94-161) underwent *ex vivo* MRI (9.4T) volumetric and high-resolution dMRI (5 b0, 30 directions, b=3000mm^2/sec). Regional tissue features were extracted from FA, MD, axial diffusivity (AD), and radial diffusivity (RD) parametric maps. Tractography within the cingulum was performed based on the Australian Mouse Brain Mapping Consortium (AMBMC) atlas. T2 relaxation times and regional volumes were extracted from anatomical T2-weighted images (repetition time=4000ms, echo time=10ms). Social behavior was quantified using the 3-chambered social interaction test. The cingulum in LBN males (but not females) exhibited decreased FA relative to control mice. Within the cingulum bundle, we observed robust correlation between FA and RD, FA and MD, but not AD. Reconstruction of cingulum tracts revealed elevated FA and AD in control males comparted to LBN males. In the 3-chambered social interaction test, LBN males spent significantly less time with the peer and the object. The amount of time spent with peer and object was positively correlated to AD within the cingulum. In summary, the cingulum exhibits male-specific changes following early life adversity including decreased FA and a negative correlation between FA and RD/MD. AD within the tracts was correlated with social behavior. Finally, tractography analysis revealed that a larger cingulum fiber bundle would have no overt change in fiber number. Given the broad brain-wide connectivity of the cingulum bundle, the decrements we observed in mice exposed to early life adversity may have a profound impact on social behavior in adulthood.

Disclosures: B.P. Noarbe: None. **K.M. Wendel:** None. **A.K. Short:** None. **T.Z. Baram:** None. **M.A. Yassa:** None. **A. Obenaus:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.01

Topic: E.03. Basal Ganglia

Support: VIEP BUAP 2021

Title: Intrapallidal injection of cannabidiol modulates the expression of GPR55 in hemiparkinsonian rats

Authors: *F. PATRICIO[1], A. GARCÍA-CAMARILLO[1], A. PATRICIO-MARTÍNEZ[2], I. MARTÍNEZ-GARCÍA[3], J. M. PEREZ-AGUILAR[4], J. AGUILERA[5], I. D. LIMÓN[1];
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Abstract: Cannabidiol (CBD) has been proposed as a pleiotropic molecule that interacts with various targets, inluding the GPR55 receptor. Indeed, localization of GPR55 receptor mRNA has been shown in different brain regions, particularly to the nuclei of the basal ganglia (BG). For this reason, GPR55 receptor protein expression is likely to be present in the indirect pathway of BG, that is, in striatum and *globus pallidus external* (GPe), nuclei that are altered in Parkinson's disease. The present work aimed to evaluate the intrapalidal injection of CBD [10 µM] on the expression of GPR55 receptor in striatum and GPe of hemiparkinsonian rats. Male Wistar rats were used weighing 250-300 g to which 6-hydroxydopamine (6-OHDA) was administered in the nigrostriatal route [16 µg / 2 µL] by stereotaxic surgery. At 20th days, a guide cannula was placed in the GPe to directly administer CBD [10 µM]. Once the cannula was introduced, the CBD was administered at 28th, 29th, and 30th days post-lesion. The results obtained show a decrease in the protein expression of the GPR55 receptor in the GPa of rats with the injection of 6-OHDA plus vehicle. However, the 6-OHDA plus CBD group increased GPR55 receptor expression compared to the 6-OHDA group ($p<0.05$). Finally, the immunoreactivity to evaluate the expression of TH was performed to corroborate the success of the lesion, which showed a decrease in striatum and GPe of all experimental groups with 6-OHDA. In summary, our results suggest that the CBD could have effects on the expression mechanism of GPR55 in GPe, and that the dopaminergic system influences the down-regulation of GPR55.

Disclosures: F. Patricio: None. **A. García-Camarillo:** None. **A. Patricio-Martínez:** None. **I. Martínez-García:** None. **J.M. Perez-Aguilar:** None. **J. Aguilera:** None. **I.D. Limón:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.02

Topic: E.03. Basal Ganglia

Support: Minnesota Partnership for Biotechnology Grant

Title: Evoked Resonant Neural Activity in the Globus Pallidus Pars Interna

Authors: *B. T. KLASSEN, H. D. SIMPSON, K. J. MILLER;
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Abstract: Chronic electrical stimulation of basal ganglia structures ("Deep Brain Stimulation" or DBS), typically targeting the subthalamic nucleus (STN) or globus pallidus interna (Gpi), is an effective treatment for patients with Parkinson disease not sufficiently responding to medications. Effective treatment depends on accurate positioning of the stimulation electrodes within the motor subregions of these targets. Evoked resonant neural activity (ERNA) has been reported to be observed following a brief train of stimuli applied to the motor subregion (dorsolateral region) of the STN and may be a useful biomarker of accurate lead positioning. We explored whether a similar ENRA could be elicited by stimulation in the motor subregion of the Gpi and sought to confirm its absence in structures outside of this circuit. During DBS surgeries in patients with Parkinson disease or essential tremor, recordings were obtained before, during, and after brief trains of stimulation mirroring clinical parameters (11 pulses at 130 hertz, 90 microsecond pulse width, 2.8 mA). In some cases multiple stimulation/recordings were obtained from different sites as the DBS microelectrode was serially advanced toward the final target, and in others we performed stimulation/recording using the implanted chronic stimulating electrode in its final position. We find that ENRA is present in the motor subregion of the Gpi target as well as in STN. ENRA was not observed superior to these targets or in the Vim thalamus. Thus, ENRA may be a biomarker of effective electrode positioning at multiple nodes within the basal ganglia circuits affected by Parkinson disease.

Disclosures: B.T. Klassen: None. **H.D. Simpson:** None. **K.J. Miller:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.03

Topic: E.03. Basal Ganglia

Support: NIMH project #ZIAMH 002032

Title: Unilateral suppression of the ventral caudate nucleus increases motor impulsivity in the rhesus monkey

Authors: *M. SMITH[1], M. A. ELDRIDGE[2], B. RICHMOND[1];
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Abstract: Impulsivity is the tendency towards rapid reactions to stimuli without consideration of the possible consequences. Impulsivity is connected to many mental illnesses, including attention deficit hyperactivity disorder, obsessive-compulsive disorders and addiction disorders. Previous studies have implicated frontostriatal circuits in impulsive behavior. In this study, we examined the effect of unilateral suppression of the ventral caudate on motor impulsivity in rhesus monkeys. Motor impulsivity was modeled by the subjects' inability to complete trials in a reward task that required a bar to be released after a variable wait period. 3 mL of muscimol, a GABA-agonist, was injected into the striatum of the subjects at 0.18 µL per minute. Suppression of the striatal region by muscimol resulted in increased impulsivity (more early bar release errors). Following muscimol testing, a viral construct Lenti-hSyn::hM4Di-GFP containing the hM4Di DREADD (designer receptor exclusively activated by designer drug) was injected into the same region. The virus was injected at 0.5 µL per minute for 20 minutes. Clozapine N-oxide and deschloroclozapine activate the DREADD to suppress neuronal activity. Injections of DREADD activating drugs increased impulsive behavior. Thus, both methods of suppression increased behavioral indicators of impulsivity, supporting the conclusion that this region of the striatum is involved in inhibition of motor impulses.

Disclosures: **M. Smith:** None. **M.A. Eldridge:** None. **B. Richmond:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.04

Title: WITHDRAWN

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.05

Topic: E.03. Basal Ganglia

Support: NIH/NINDS 5R00NS107639-04
Brain and Behavior Research Foundation (BBRF) NARSAD 28690
Conte - NIH/NIMH P50 MH119467
MURI - ARO W911NF-16-1-0474

Title: Characterization of intertrial dopamine dynamics in monkey striatum

Authors: *U. AMJAD[1], J. CHOI[1], A. M. GRAYBIEL[2], H. N. SCHWERDT[1];
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Abstract: Substantial evidence supports the idea that within-trial dopamine (DA) dynamics, as modulated by controlled task events involving rewards and reward-predictive cues, reflect reward prediction error (RPE) and serve as a teaching signal. These teaching signals associate the predictive cues to reward outcomes and have been shown to reinforce rewarding motor future actions, eventually leading to task acquisition. However, the function of DA changes during the intertrial intervals (ITIs), time periods that extend from when one trial ends (outcome) to when the next trial starts and do not contain any explicit reward-related task events, remain relatively uncharacterized. Could DA dynamics during these ITIs influence subsequent trial behaviors, or serve as long-term teaching signals for task performance? We examined DA concentration changes during relatively long ITIs (8 s) as measured by fast-scan cyclic voltammetry from chronically implanted carbon fiber sensors in the striatum of one rhesus monkey performing a visually guided reward-biased saccade task. This task consisted of trials, each of which terminated with either a large or small reward (liquid food) if the monkey successfully made the required sequence of saccades, first to a centrally displayed cue and second to a peripheral target cue; or with an error (i.e. no reward) if the monkey failed to saccade or maintain fixation on any of the displayed cues. DA concentration changes were analyzed over an ITI defined as beginning 2 s after the reward outcome up to the next trial start, 8 s later. Preliminary analysis showed highly variable DA dynamics during the ITI with significant differences that depended on preceding outcomes (e.g. reward or error) as well as subsequent task performance variables. Early results indicate that the DA concentration changes in the caudate nucleus exhibit inverted patterns of ramp-like activity for ITIs depending on whether they were after rewarded or error trials. The time-dependent characteristics of these ITI signals varied across sessions, but the outcome-dependent contrasts remained. These contrasting dynamics were also strongly dependent on session progression. In addition, ITI DA showed different patterns as correlated to subsequent task performance: reaction times and horizontal saccade velocities, suggesting a potential function in reinforcement and invigoration, in accord with existing theories. Collectively, these results indicate a potential link between ITI DA and temporal difference learning theories. DA activity over the ITI may serve as a learning signal, reinforcing rewarding actions across individual trials.

Disclosures: U. Amjad: None. **J. Choi:** None. **A.M. Graybiel:** None. **H.N. Schwerdt:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.06

Topic: E.03. Basal Ganglia

Support: FRQS Grant, Chercheur boursier Junior 2: #283437
NSERC Grant RGPIN-2017-05510
NSERC Canada Graduate Scholarship - Doctoral

Title: Neurotransmitter concentration levels of the basal ganglia predicts intracortical activity of the primary motor cortex

Authors: *S. REMAHI[1,2], M. MABIKA[1,2], S. CÔTÉ[1,2], C. IORO-MORIN[1,3], K. WHITTINGSTALL[1,4], J. NEAR[5], J.-F. LEPAGE[1,2];
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Abstract: Paired pulse transcranial magnetic stimulation (ppTMS) allows the assessment of intracortical inhibitory and excitatory processes of the motor cortex (M1). These inhibitory and excitatory processes reflect signaling pathways involving neurotransmitters such as GABA, the major inhibitory neurotransmitter, and glutamate-glutamine (Glx), an excitatory neurotransmitter, which can also be measured through magnetic resonance spectroscopy (MRS). However, previous studies have shown an absence of relationship between measurements of GABA by MRS in M1 and ppTMS measures, while measures pertaining to glutamate have been inconsistent. Given its role in motor control and influence on intracortical activity of M1, we sought to investigate if neurotransmitter concentration levels within the basal ganglia, which have strong afferences and efferences with M1, exert a significant influence on intracortical circuit activity of M1 in healthy individuals. To achieve this objective, 21 neurologically-healthy, right-handed young adults underwent a 1h TMS protocol using the Magtism Bistim2; the following measures were obtained: resting motor threshold (rMT), short intracortical inhibition (SICI), long intracortical inhibition (LICI), intracortical facilitation (ICF), and the cortical silent period (CSP). TMS was followed by a 1h MRS session (MEGA-PRESS sequence) with the voxel of interest placed over the dorsal striatum, as well as a control voxel located over the occipital cortex. MRS data was processed in Osprey. We generated general linear models, one per TMS item as outcome variable, with GABA+ and Glx as predictors. For the subcortical voxel, two of the five models were significant: SICI (r^2: 0.51, p=0.001) and the ICF (r^2: 0.36, p=0.01) were both positively related to the concentration of Glx (SICI: $\beta = 0.06$, $p = 0.005$; ICF: $\beta = 0.1$, $p = 0.003$); showing that participants with higher concentrations of Glx had weaker SICI inhibition and stronger ICF facilitation. No model using the occipital voxel significantly predicted ppTMS measures. To our knowledge, this is the first demonstration of a relationship between neurotransmitter concentration levels in subcortical regions and intracortical circuit activity of the primary motor cortex. Our results suggest a link between the activity of intracortical circuits of M1 and neurotransmitter concentration levels in subcortical structures heavily involved in motor function. These results may explain, at least in part, the lack of relationship between both measures in previous studies focusing on the cortex.

Disclosures: S. Remahi: None. **M. Mabika:** None. **S. Côté:** None. **C. Ioro-Morin:** None. **K. Whittingstall:** None. **J. Near:** None. **J. Lepage:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.07

Topic: E.03. Basal Ganglia

Support: NIH U19NS113201
NIH F31NS122155
NIH F31NS113385
Burroughs Wellcome Fund Career Award

Title: Striatal dopamine structures the spontaneous behavior of mice across multiple timescales

Authors: *M. JAY[1], J. E. MARKOWITZ[2], W. F. GILLIS[1], J. WOOD[1], T. SAINBURG[1], R. W. HARRIS[1], R. SCOTT[1], D. H. BRANN[1], C. WEINREB[1], M. OSMAN[1], S. A. ROMERO PINTO[3], N. UCHIDA[4], S. LINDERMAN[5], B. L. SABATINI[1], S. R. DATTA[1];
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Abstract: Spontaneous animal behavior is built from action modules that are concatenated by the brain into sequences. However, the neural mechanisms that guide the composition of naturalistic, self-motivated behavior remain unknown. Here we show that endogenous dopamine release systematically fluctuates in both the dorsolateral striatum (DLS) and nucleus accumbens core (NAcc) during spontaneous behavior as mice transition between sub-second behavioral modules, despite the absence of task structure, sensory cues or exogenous reward. Closed-loop optogenetic manipulations across both subregions of the striatum demonstrate that striatal dopamine alters the usage or sequencing properties associated with behavioral modules over minutes, without directly influencing movement initiation or kinematics. These results suggest that behavioral modules represent elemental units of continuous behavior that can be flexibly chosen over time. However, the degree to and manner in which the statistics of spontaneous behavioral modules are altered as a result of optogenetic manipulations varied between the DLS and NAcc, suggesting that dopaminergic subsystems differentially govern action choices during self-generated behavior in an unconstrained mouse.

Disclosures: M. Jay: None. **J.E. Markowitz:** None. **W.F. Gillis:** None. **J. Wood:** None. **T. Sainburg:** None. **R.W. Harris:** None. **R. Scott:** None. **D.H. Brann:** None. **C. Weinreb:** None. **S.A. Romero Pinto:** None. **N. Uchida:** None. **S. Linderman:** None. **B.L. Sabatini:** None. **S.R. Datta:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.08

Topic: E.03. Basal Ganglia

Support: R01 NS104089 NINDS
BSF 2017255

Title: Compartment-specific analysis of cholinergic interneurons in the dorsal striatum reveals a distinct relationship with striosomes

Authors: *Z. B. HOBEL[1], J. M. MALGADY[1], L.-T. YANG[1], J. L. PLOTKIN[1,2,3];
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Abstract: The striatum, the primary input nucleus to the basal ganglia, is a large subcortical structure that receives and integrates a vast array of topographically organized cortical and thalamic inputs and plays a central role in action selection and motor learning. The striatum can be histochemically organized into two compartments known as striosomes and matrix. Relative activity between compartments has been linked to distinct behaviors and they are differentially associated with psychomotor disorders, although the precise function of the compartments is not well understood. The striatum is also enriched in cholinergic interneurons (CINs) which, despite making up <3% of the total neuronal population, provide abundant acetylcholine (ACh) that is critical for numerous aspects of behavior. Although CINs can be found in both compartments, low acetylcholine esterase (AChE) expression in striosomes suggests that ACh influences striosomes and matrix differently. It has been posited that CINs preferentially occupy striosome-matrix boundary regions but a rigorous analysis of CINs by compartment has not been performed. Here we show that CINs in the pre-commissural dorsal striatum of mice exhibit a medial-to-lateral density gradient and a striking compartment-specific organization. While the majority of CINs reside in the matrix, CIN cells bodies are located in striosomes significantly more frequently than would occur by chance, particularly in dorsolateral striosomes between 0.9-0.1 mm bregma, and are correspondingly located in the matrix at a less-than-chance level. A higher-than-chance presence of CINs at inner striosome-matrix boundaries matched that seen in striosome cores. CIN tonic activity, inferred from immunohistochemical staining for phospo-RPS6(Ser240/244), was lower in striosomes than matrix, as was ACh release measured using 2-photon imaging of the ACh sensor ACh1.4. While CIN processes are extensive and famously cross compartment boundaries, these findings raise the intriguing possibility that local striosomal modulation of CIN somatic activity will have a larger impact on striatal ACh release than previously predicted.

Disclosures: Z.B. Hobel: None. **J.M. Malgady:** None. **L. Yang:** None. **J.L. Plotkin:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.09

Topic: E.03. Basal Ganglia

Support: Korea NRF Grant 2020R1A2C1005492
Korea NRF Grant 2021R1A4A1031644
Korea NRF Grant 2021M3A9G8022960
Korea NRF Grant 2022M325E8017907

Title: Two distinct modes of dopaminergic modulation on striatopallidal synaptic transmission

Authors: *Y. LEE[1], E. CHO[1], H.-J. KIM[1], K. MYUNG[3,2], Y. LI[4], J.-I. KIM[1];
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Abstract: Dopamine (DA) and its GPCR receptor control willed movement through D1-direct pathway and D2-indirect pathway within basal ganglia. In a classical model, excessive activity in indirect pathway is one of the circuit mechanisms underlying parkinsonism. Although striatopallidal synapses function as a critical gateway of indirect pathway, the physiological functions of dopamine on striatopallidal synapses remain unclear due to relatively sparse dopaminergic innervation on the external globus pallidus (GPe). Here, we seek to understand how DA through nigropallidal pathway modulates striatopallidal synaptic transmission. Utilizing electrophysiology, optogenetics, GRAB sensor, pharmacology, enhanced confocal imaging, and synapse analysis, we revealed that DA is directly released onto the GPe and there is a marked regional heterogeneity of dopaminergic innervation to the GPe. In addition, we found that dopamine D2-like receptors modulate striatopallidal synaptic transmission via two distinct modes. The treatment of D2-like receptor agonist elevated paired-pulse ratio (PPR) and reduced GABAergic transmission at striatopallidal synapses located in dorsolateral (DL) and ventromedial (VM) GPe. Unexpectedly, however, PPR was not altered by the D2-like receptor agonist at striatopallidal synapses in ventrolateral (VL) and dorsomedial (DM) GPe, even with reduced GABAergic transmission. As potential mechanisms behind these distinct modes of dopaminergic modulation, we further found that D2 and D4 receptors in GPe subregions differentially regulate striatopallidal synaptic transmission through their differences in subcellular expression and sensitivity. In a DA-depleted animal model, nigropallidal dopaminergic fibers innervating each GPe subregion exhibited different susceptibility to 6-OHDA. Furthermore, DA depletion promoted presynaptic D2R-mediated inhibition at striatopallidal synapses in VL and DM subregions of the GPe potentially as a compensatory mechanism of DA loss. To sum up, these results demonstrate that synaptic information conveyed by indirect pathway can be regulated by DA via two distinct modes, which seem to be determined by anatomical locations of striatopallidal synapses in the GPe. Since structural and functional organization of basal ganglia circuits is critical to understanding both DA-related behaviors and DA-depleted pathological conditions such as Parkinson’s disease, our findings will provide new insights into the overlooked role of dopaminergic modulation on striatopallidal synapses and globus pallidus.

Disclosures: **Y. Lee:** None. **E. Cho:** None. **H. Kim:** None. **K. Myung:** None. **Y. Li:** None. **J. Kim:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.10

Topic: E.03. Basal Ganglia

Support: ALTF 827-2018

Title: Identification of action prediction error, a value-free dopaminergic teaching signal that drives learning in an auditory discrimination task

Authors: *H. MARTÍNEZ VERGARA, F. GREENSTREET, S. PATI, L. SCHWARZ, M. WISDOM, F. MARBACH, Y. JOHANSSON, T. MOSKOVITZ, C. CLOPAZ, M. STEPHENSON-JONES;
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Abstract: Frequency-specific plasticity in the posterior striatum (pStr) during auditory discrimination learning suggests it is the locus for forming and storing task-relevant associations. Dopamine signals, thought to reinforce these associations, have been reported to encode information about threat in the pStr, raising the question of how reward-guided associations are formed in this region. Here we show that pStr dopaminergic input is indeed critical for learning and forming frequency-specific associations. We propose a model where dopaminergic input to the pStr forms the value-free half of a dual value-based/value-free dopaminergic learning system. Chronic lesions of the pStr, or the pStr-projecting dopaminergic cells, result in identical learning deficits affecting later learning stages. This is consistent with our dual controller model where initial learning is driven by a value-based system and then rapidly consolidated in a value-free manner in the pStr. Supporting this, optogenetic inhibition of either the direct or the indirect pathways in pStr disrupt behavioural performance specifically in later stages of learning. In line with pStr-projecting dopamine providing a teaching signal we show that temporally-specific optogenetic manipulations of dopamine levels in pStr bias future behaviour. These results, together with our finding of an action-related and value-free dopaminergic signal.

Disclosures: **H. Martínez Vergara:** None. **F. Greenstreet:** None. **S. Pati:** None. **L. Schwarz:** None. **M. Wisdom:** None. **F. Marbach:** None. **Y. Johansson:** None. **T. Moskovitz:** None. **C. Clopaz:** None. **M. Stephenson-Jones:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.11

Topic: E.03. Basal Ganglia

Support: DMRF Award

Title: Striatal cholinergic transmission in a mouse model of mixed dystonia-dyskinesia

Authors: *M. SCARDUZIO[1], K. E. JAUNARAJS[1], J. W. OLSON[2], D. G. STANDAERT[1]; [1]Ctr. for Neurodegeneration and Exptl. Therapeutics, Neurol., [2]Ctr. for Theoretical Neuroscience, Neurol., UAB, Birmingham, AL

Abstract: Hyperkinetic movement disorders, such as dyskinesia and dystonia, are often debilitating and difficult to treat effectively. Several lines of evidence suggest that aberrant striatal cholinergic interneuron (ChI) function may induce or facilitate the development of dyskinesia and dystonia. Clinically, anticholinergic drugs are some of the most effective pharmacological treatments available. Animal models of both disorders (genetic mouse models of dystonia and L-Dopa-induced dyskinesia) have indicated pathophysiological increases in striatal ChI activity and/or function but **to date no direct relationship between dysfunctional cholinergic transmission and dystonic/dyskinetic movements has ever been established.** Most animal models of hyperkinetic movement disorders are problematic because 1) they replicate genetic mutations but not behavior, 2) they involve neurotoxic lesions of relevant brain structures, or 3) behavior is not inducible and/or predictable making it difficult to design appropriate internal controls to establish physiological changes that occur during the onset of a dystonic/dyskinetic attack. To transcend these limitations, we utilized a transgenic mouse model of a human disorder, paroxysmal non-kinesiogenic dyskinesia/dystonia (PNKD), in which reproducible, prominent motor symptoms resembling human hyperkinetic conditions can be induced in an otherwise normally behaving animal upon exposure to certain drugs (caffeine and D2 receptor agonists). **To understand the underlying role of striatal ChI activity on manifestation of dystonia and dyskinesia movements we** used *in vivo* fiber photometry optical imaging of GPCR-based acetylcholine (ACh) sensors to **monitor striatal ACh activity in real time with high temporal resolution in PNKD mice while examining motor behavior**. Caffeine and the D2R agonist quinpirole both induced a complex mixed dystonia-dyskinesia phenotype in male and female PNKD but not in their wild-type (WT) littermates. The motor phenotype in the PNKD mice was manually scored with established dystonia and dyskinesia rating scales. Interestingly, the onset of dyskinetic and dystonic movements correlated with different striatal ACh dynamic profiles, suggesting that they may be driven by specific alterations in the dynamics of striatal cholinergic modulation.
Support: Dystonia Medical Research Foundation (DMRF) Award

Disclosures: M. Scarduzio: None. **K.E. Jaunarajs:** None. **J.W. Olson:** None. **D.G. Standaert:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.12

Topic: E.03. Basal Ganglia

Support: NHRI-EX111-11114NI
MOST 109-2320-B-002-042-MY3

Title: Slitrk1 is pivotal in adult striatal cholinergic neurons: Implication in Tourette syndrome

Authors: *L.-C. CHIOU[1,2], M.-H. CHANG[1], J.-C. DU[1], M. LEE[1,3], H.-J. LEE[1];
[1]Grad. Inst. of Pharmacology, Col. of Med., [2]Grad. Inst. of Brain and Mind Sci., Natl. Taiwan Univ., Taipei, Taiwan; [3]Fac. of Pharmaceut. Sci., UCSI Univ., Kuala Lumpur, Malaysia

Abstract: The *SLIT and NTRK-like 1* (*SLITRK1*) gene mutation and striatal cholinergic interneurons (ChIs) loss are associated with Tourette syndrome (TS), respectively. In mammals, Slitrk1 is widely expressed in striatal neurons at early ages but only present in ChIs in the adult striatum, suggesting Slitrk-1 plays a pivotal role in maintaining the striatal ChIs activity. We thus validated this hypothesis by silencing *Slitrk1* in the striatum of adult mice via bilateral microinjection of *Slitrk1* siRNA in their dorsal striatum. This Slitrk1-knockdown (KD) mice exhibited TS-like stereotypic behaviors, impaired prepulse inhibition, and delayed sensorimotor response, compared with scrambled siRNA-treated control mice. These TS-like characteristics of *Slitrk1*-KD mice correlated temporally with lower Slitrk1 protein levels, fewer Slitrk1-containing ChIs, fewer activated ChIs, and lower evoked dopamine (DA) levels in their striatum. Slitrk1-negative ChIs were less excitable than Slitrk1-positive ChIs in electrophysiological properties. *Slitrk1*-KD mice had lower evoked acetylcholine and DA levels, higher tonic DA levels, and downregulated DA transporters (DAT) in the striatum than scramble controls. Methamphetamine failed to induce hyperlocomotion in *Slitrk1*-KD mice, suggesting their deficit in evoked DA release. Stereotypic behaviors in *Slitrk1*-KD mice were unaffected by intra-striatal blockade of D1 receptors but significantly reduced by haloperidol, a D2 antagonist used for treating TS. Apomorphine induced much more climbing behaviors in *Slitrk1*-KD mice than in scrambled controls, suggesting their D2 receptors (D2Rs) become hyper-responsive. These results suggest that Slitrk1 is pivotal in maintaining adult striatal ChIs activity. Thus, in *Slitrk1*-KD mice, evoked ACh levels are reduced due to fewer activated ChIs, leading to reduced evoked DA release and subsequent compensatory DAT downregulation and elevated tonic DA levels in their striatum. Reduced evoked DA release may also lead to a compensatory hyper-responsiveness of D2Rs, especially presynaptic D2Rs that can be activated by abundant tonic dopamine. This would further inhibit dopamine and ACh release in a vicious circle, ultimately leading to stereotypic behaviors. This study also suggests that *Slitrk1*-KD mice may serve as a preclinical animal model of TS.

Disclosures: L. Chiou: None. **M. Chang:** None. **J. Du:** None. **M. Lee:** None. **H. Lee:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.13

Topic: E.03. Basal Ganglia

Support: NIH NINDS R01 NS104089

Title: Adaptations in cholinergic signaling in the SAPAP3 null mouse model of compulsive behavior

Authors: *J. M. MALGADY, A. T. BAEZ, K. JIMENEZ, J. A. WILKING, J. L. PLOTKIN; Stony Brook University, Dept. of Neurobio. & Behavior, Stony Brook, NY

Abstract: Compulsive grooming in SAP90/PSD-95-associated protein 3 (SAPAP3) null mice is generally accepted as being driven by corticostriatal synaptic dysfunction. Our recent work has expanded on this model, showing that intrinsic excitabilities of dorsolateral striatum direct and indirect pathway spiny projection neurons (dSPNs and iSPNs, respectively) are altered alongside synaptic function. However, little is known about how this aberrant phenotype may be influenced by neuromodulators, such as acetylcholine (ACh) and dopamine (DA). As the two dominant neuromodulators of dSPN and iSPN physiological function, they play a critical role in shaping striatal output. Irregular cholinergic and dopaminergic signaling have been linked with neuromotor disorders and aberrant habit formation, yet a potential role in the Sapap3 null phenotype remains largely unknown. Here, we demonstrate that evoked ACh release is significantly elevated in the dorsal striatum of a novel SAPAP3 null mouse line ($cKI^{-/-}$). We investigated if a potential increase in ACh tone might affect cholinergic signaling in striatal projection neurons. Indeed, using a combination of electrophysiology and 2-photon Ca^{2+} imaging, we show that muscarinic signaling is differentially attenuated in the dendritic spines of dSPNs and iSPNs in SAPAP3 $cKI^{-/-}$ mice. Further, we investigated whether nicotinic receptor mediated DA release was similarly shunted. Strikingly, we find that the α4β2 nAChR- mediated component of evoked DA release is reduced in SAPAP3 $cKI^{-/-}$ mice. Together, these data suggest that pathological cholinergic modulation of striatal function may contribute to compulsive motor behaviors observed in SAPAP3 null mice.

Disclosures: J.M. Malgady: None. **A.T. Baez:** None. **K. Jimenez:** None. **J.A. Wilking:** None. **J.L. Plotkin:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.14

Topic: E.03. Basal Ganglia

Title: Unidirectional dendro-dendritic dopamine synapses between midbrain dopamine neurons with distinct axonal projections

Authors: *S. LEE, N. HAMMER, B. FISCHER, S. STOJANOVIC, J. ROEPER;
Inst. of Neurophysiol., Frankfurt am Main, Germany

Abstract: Midbrain dopamine (DA) neurons are essential for the cardinal brain functions and are inhibited by the activation of D2-autoreceptors (D2R) (Lacey et al., 1987). In vitro electrophysiology demonstrates the presence of synaptic D2R signaling between pre- and post-synaptic DA neurons (Beckstead et al., 2004). Functional dendro-dendritic vesicular DA release between midbrain DA neurons was described by spontaneous D2R-mediated IPSCs recording. (Gantz et al., 2013). Our previous studies showed different expression levels of D2R and GIRK2 in midbrain DA neurons projecting to distinct target areas (Lammel et al., 2008), the functional contribution of D2R signaling is still unknown. In addition, our recent study suggested that midbrain DA neurons are anatomically segregated by their projection sites to the striatum (Farrasat et al., 2019). Based on this study, we recorded electrically evoked, D2R-mediated, sulpiride-sensitive, slow inhibitory postsynaptic currents (eIPSCs). Mean eIPSC amplitudes of lNAcc-projecting DA neurons were significantly larger compared to those of dorsal striatum-projecting DA neurons (lNAcc:27.1±2.5pA, n=21; DMS:16.3±1.4pA, n = 23; DLS:12.5±1.3pA, n=18). We optogenetically stimulated presynaptic DLS-projecting neurons while recording optically-evoked, sulpiride-sensitive D2-IPSC (oIPSC) in lNAcc-projecting DA neurons (lNAccDLS:14.9±3.7pA, n=13). When we inverted the synaptic direction between these DA neurons, little to no oIPSC were evoked (DLSlNAcc:3.6±1.4pA, n=9). To identify potential morphological correlates for dendro-dendritic DA synapses among distinct axonal projection systems, we reconstructed single projection-defined midbrain DA neuron by conducting sparse, AAV-based retrograde GFP labeling. The morphological reconstruction of DLS-projecting DA substantia nigra (SN) neurons revealed that their dendrites spread across a large territory including the substantia nigra reticulata, ventral tegmental area (VTA), as well as the medial SN. In contrast, lNAcc-projecting DA SN neurons displayed a significantly smaller dendritic tree. We also identified a number of dendro-dendritic appositions between distinct DA subpopulations. These morphological results are in accordance with the electrophysiological data demonstrating uni-directional dendro-dendritic dopamine synapses between dorsal striatum and ventral striatum-projecting DA neurons.

Disclosures: S. Lee: None. **N. Hammer:** None. **B. Fischer:** None. **S. Stojanovic:** None. **J. Roeper:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.15

Topic: E.03. Basal Ganglia

Support: NIA AG065682
G-RISE T32GM136499

Title: Striatal Sonic Hedgehog Promotes Behavioral Flexibility Via Cholinergic Modulation

Authors: *S. URIBE-CANO[1], A. H. KOTTMANN[2];
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Abstract: The dorsolateral (DL) striatum supports stimulus-action associations to streamline skilled behavior. Distorted pre- and post- synaptic dopaminergic (DA) mechanisms in this region also seem to produce rigid and compulsive behavior. Midbrain Dopamine neurons (DAN) signal downstream targets via numerous signaling factors including DA, Glutamate, GABA and peptides, the functional relevance of which is not fully understood. We previously observed that DAN express the signaling peptide Sonic Hedgehog (Shh) throughout life. In the striatum, we find the highest density of Shh pathway activity in DL regions. Among neural targets of DAN, Shh can be received selectively by Cholinergic (CIN) and Fast Spiking Interneurons of the striatum which express Smoothened (Smo), the GPCR effector downstream of Shh signaling. CIN are of particular interest in the striatum given they are the major source of striatal Acetylcholine (ACh) and are linked to the interruption and switching of actions. To clarify the behavioral significance of DAN signaling to CIN via Shh, we examined how genetic manipulations of the Shh pathway impacted learning efficiency on a rotarod task and behavioral rigidity across instrumental lever pressing tasks employing Random Interval and Progressive Ratio schedules. By observing changes after either DL-localized AAV-Cre mediated ablation of Smo in adult mice or CIN-specific ChATCre ablation of Smo (Smo_{CIN}-/-), we are able to isolate features of behavior mediated by Shh signaling onto CIN in the adult DL striatum. We find that adult DL-specific ablation of Smo produces deficits in motor learning, decreased sensitivity to devaluation of instrumental lever pressing, and increased persistence of lever pressing in a progressive ratio task. Similar results were obtained in Smo_{CIN}-/- mice with ablation of Smo restricted to Cholinergic neurons. These findings are complemented by initial observation that adult expression of SmoM2, a constitutively active form of Smo, in the DL striatum produces an opposite phenotype with accelerated motor learning and increased sensitivity to instrumental lever pressing devaluation. Finally, to probe the functional mechanism by which Shh onto CIN affects striatal function, we employ fiber photometry alongside Dopamine (DA) and ACh fluorescent sensors to examine how manipulation of Smo on CIN affects ACh in the striatum. We examine changes to the profile of ACh activity across genetic and pharmacological manipulations of the Shh pathway. In the aggregate, these results begin to suggest that changes in Shh signaling strength onto DL CIN impacts the balance between persistence and switching of action due to Smo modulation of CIN.

Disclosures: S. Uribe-Cano: None. **A.H. Kottmann:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.16

Topic: E.03. Basal Ganglia

Support: 2021 CUNY Interdisciplinary Research Grant

Title: Sars-cov-2 spike protein alters striatal ace2 activity resulting in parkinsonian disturbances

Authors: *A. R. WALLS[1], A. H. KOTTMANN[2];
[1]City Univ. of New York, New York, NY; [2]Molecular, Cell. and Biomed. Sci., CUNY Sch. of Med., New York, NY

Abstract: First emerging in late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has developed into a global pandemic. As of May 2022, over a million Americans have died from infection and 10-30% of recovered patients experience Long COVID symptoms. While most neurological symptoms of Long COVID are mild, 5 to 8 in 100,000 infections result in signs of basal ganglia (BG) dysfunction and dementia reminiscent of Parkinsonian Disease with prefrontal dementia (PD-FTD). Interestingly, spike protein binding to its cellular receptor ACE2 acts as an allosteric modulator of ACE2's peptidase activity and substrate specificity. Besides cleaving peptides of the renin angiotensin system (RAS), ACE2 is also capable of processing numerous cell-signaling peptides present in the brain including apelins, neurotensins, and endo-opioids, all of which have been implicated in neurological disorders. We thus hypothesize that the binding of spike protein, or autoantibodies of similar structure, to ACE2 alters its catalytic activity resulting in changes to the relative strength of multiple signaling systems in the BG, a set of nuclei centrally implicated in age-related neurodegenerative diseases, psychosis, and dementia. However, whether there is functionally relevant ACE2 activity in the BG is currently hotly debated. Using stringent immunohistochemistry analyses, we have identified ACE2 and RAS receptor expression among striatal neurons, including cholinergic interneurons (CINs). Further, preliminary results derived from perfusion of ACE2 inhibitors adjacent to a fiber photometry wire implanted in the dorsal striatum indicate that striatal ACE2 modulates the levels of extracellular acetylcholine. We are also conducting experiments to identify peptides formed by ACE2 activity in the striatum by MALDI mass spectroscopy. We are currently assessing the effect of RAS signaling on striatal neurotransmission by locally injecting related peptides and inhibitors and measuring the relative levels of dopamine and acetylcholine by fiber photometry. We will extend these experiments to the injection of ACE2-binding spike protein variant fragments. Finally, we will investigate the effects of conditional ablation of ACE2 from CINs on cellular physiology, neurotransmitter levels, and behavior. These results begin to suggest a potential mechanism by which spike protein or infection elicited autoantibody interactions with ACE2 could cause PD-like disturbances in the BG.

Disclosures: A.R. Walls: None. **A.H. Kottmann:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.17

Topic: E.03. Basal Ganglia

Support: NIH Grant RO1DA041705

Title: Computational modeling of induction of plateau bursting via simulated application of blockade of M-type potassium channels.

Authors: *C. KNOWLTON[1], T. ZIOUZIOU[2], J. ROEPER[3], C. C. CANAVIER[4];
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Abstract: Dopamine neurons in the ventral tegmental area (VTA-DA) exhibit projection-specific electrophysiological phenotypes with distinct levels of dynamic range, post-inhibitory rebound, and intrinsic variability. Previously, we implemented computational models that incorporate known differences in electrophysiology. These models capture differences in response to depolarizing current ramps and hyperpolarizing pulses consistent with in vitro recordings of VTA-DA cells with identified projection targets. In-vivo recordings from the Roeper lab identified a novel bursting mechanism consisting of plateau bursts, which are discharges of 2-4 rapid (20-75 Hz) spikes riding a single slower depolarizing wave such as the one that often underlies a single spike in a repetitive pace-making mode. Application of muscarinic agonists to identified retrobead/TH+ VTA DA cells were found to induce intrinsic plateau bursting in a subset (n=13/37) of cells that project to the medial shell of the nucleus accumbens (mNAcc), but not in any (n=0/18) cells that projected to the lateral shell (lNAcc) during in-vitro perforated patch and on-cell recordings.
Our previously developed models of lNAcc and mNAcc projecting VTA-DA neurons incorporate known differences between these populations, including less SK channel activation, less long-term inactivation of NaV1.2, weaker fast spiking currents and slower recovery and inactivation of Kv4 for mNAcc projecting VTA-DA neurons . Only the lower level of SK channel activation contributed to the greater tendency of medial projecting cells to emit plateau bursts in vitro. In order to model ACh modulation, we added the M-type potassium channel and ICAN mediated by TRM4 to the model, and allowed for the modification existing channels (NaV1.2, SK) that are known to be sensitive to muscarinic activation in other neuronal populations. We demonstrate that the blockade of M-type potassium channels is sufficient to produce high frequency plateau bursts in both simulated in-vivo balanced states and in-vitro environments but only in the canonical mNAcc-projecting model. We demonstrate that the tight coupling between SK and high-threshold calcium channels found in the lNAcc, but not mNAcc projecting cells can explain the lack of plateau bursts in that population. We experimentally verified model predictions via the presence of plateau bursts under a specific blocker of KM in mNAcc but not lNacc projecting cells.

Disclosures: C. Knowlton: None. **T. Ziouziou:** None. **J. Roeper:** None. **C.C. Canavier:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.18

Topic: E.03. Basal Ganglia

Title: An in vivo patch-clamp and modelling study of K-ATP Channels in midbrain dopamine neurons

Authors: *R. EGGER[1], C. J. KNOWLTON[2], C. C. CANAVIER[2], J. ROEPER[1];
[1]Inst. of Neurophysiol., Goethe-University Frankfurt, Frankfurt am Main, Germany; [2]Louisiana State Univ. Hlth. Sci. Ctr., Hlth. Sci. Ctr., New Orleans, LA

Abstract: We have recently established deep in vivo patch-clamp recordings of dopamine (DA) midbrain neurons in mice (Otomo et al. 2020). We now apply this approach to study the functional role of ATP-sensitive potassium (K-ATP) channels. We have previously demonstrated that the expression of K-ATP channels in DA neurons in the medial substantia nigra (SN) are required for in vivo burst firing and in turn for novelty-induced exploratory behavior (Schiemann et al. 2012). However, the moment-to-moment contribution of K-ATP channels to ongoing in vivo activity of DA neurons has not yet been explored. To address this question, we added 100 µM of the K-ATP channel blocker tolbutamide to the internal pipette solution to inhibit these channels selectively in the target cell in vivo. Previous control experiments comparing electrical in vivo activity in on-cell and whole-cell mode demonstrated stable firing pattern and gave no evidence that in vivo whole-cell patching *per se* altered intrinsic K-ATP channel activity (Otomo et al. 2020). When dialyzing tolbutamide into DA SN neurons the minimal voltage of the interspike intervals (ISIs) significantly depolarized after 3 min of wash-in compared to the first minute of recording (n = 21). In n = 5 cells oscillatory rebound firing was significantly altered by KATP-blockade resulting in less deep hyperpolarization-events compared to the first minute of recording and control, consistent with previous modeling of medial SN DA neurons (Knowlton et al. 2018). In addition, the smaller spikes and tendency to enter depolarization block in tolbutamide are predicted by our Markov models of NaV1.2 (Knowlton et al. 2021). This preliminary data set suggests that in SN as well as VTA DA neurons K-ATP channels are continuously open and shape ongoing electrical activity. Similar to previously reported for pancreatic alpha-cells (Göpel et al. 2000) open K-ATP channels in some DA neurons might be necessary for action potential firing.

References:
Göpel et al. (2000) J. Physiol 528:509-20.Knowlton et al. 2018. J Neurophysiol. 119(1):84-95Knowlton et al. 2021 PLoS CB 17(9): e1009371Otomo et al. (2020) Nature Communications 11:6286 Schiemann et al. (2012) Nature Neuroscience 15:1272-80

Disclosures: R. Egger: None. **C.J. Knowlton:** None. **C.C. Canavier:** None. **J. Roeper:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.19

Topic: E.03. Basal Ganglia

Support: Eagles Autism Foundation
Tourette Association of America
Intellectual and Developmental Disabilities Research Center

Title: Regulation of striatal circuit formation by the nuclear-localized protein Zswim6

Authors: *N. T. HENDERSON[1], K. CHOI[1], D. TISCHFIELD[2], S. A. ANDERSON[4], E. KORB[3], M. V. FUCCILLO[1];
[1]Dept. of Neurosci., [2]Neurosci. graduate group, [3]Dept. of Genet., Univ. of Pennsylvania, Philadelphia, PA; [4]Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: The striatum integrates synaptic inputs from multiple brain regions and is crucial for many motor and cognitive processes. Despite these central functions and its association with brain disease, relatively little is known about the genetic and molecular mechanisms governing striatal circuit development and maintenance. Zswim6 (Zs6) is a striatally expressed gene that is implicated in Schizophrenia and intellectual disability. Notably, two recurrent, de novo point mutations result in a complex disorder involving intellectual disability and autistic features. The function of Zs6 is unknown, but the presence of SWIM and sin3-like domains suggest a role in gene regulation. To begin testing this, we expressed Zs6 in primary neuronal cultures, and observed robust nuclear localization. Further suggesting a role in transcriptional regulation, tagged Zs6 expressed in HEK293 cells biochemically associated with Brg1, a component of the SWI/SNF remodeling complex. We next tested the functional effects of Zs6 deletion on chromatin architecture and gene expression. Consistent with the known role of sin3 domains in transcriptional repression, we found that conditional knockout (cKO) of Zs6 in striatal GABAergic progenitors increases chromatin accessibility, as assessed by ATAC-seq. Using single nucleus RNA-seq, we show that deletion of Zs6 increases the proportion of neurogenic progenitors in the developing striatum, while reducing the expression of genes involved in synaptic transmission and membrane excitability. Together, these data suggest that Zs6 may regulate the transition of GABAergic progenitors to post-mitotic SPNs. To further assess the function of Zs6 in the development of striatal circuits, we utilized SPN-subtype specific Zs6 cKO mice together with acute slice synaptic physiology and morphological analyses. Conditional deletion of Zs6 in SPNs did not affect cell morphology, but impacted synaptic function. Zs6 deletion in either direct pathway or indirect pathway SPNs caused an increase in paired-pulse ratio, resulting from reduced desensitization of AMPARs. AMPA/NMDA ratios and mEPSC amplitudes were also reduced, further suggesting widespread dysregulation of AMPAR signaling. Finally, deletion of Zs6 in adulthood via injection of a Cre-expressing AAV recapitulated these synaptic phenotypes, indicating that continued expression of Zs6 in adulthood is required for maintaining synaptic function. Future experiments will involve identifying genes directly regulated by Zs6 using ChIP-seq, and examining circuit-level and behavioral consequences of synaptic dysfunction resulting from Zs6 loss-of-function.

Disclosures: **N.T. Henderson:** None. **K. Choi:** None. **D. Tischfield:** None. **S.A. Anderson:** None. **E. Korb:** None. **M.V. Fuccillo:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.20

Topic: E.03. Basal Ganglia

Support: NSF IOS-1845355
NIH R01NS094450
NIH F31 NS124343-01

Title: Differential Innervation of Dorsal Striatal Spiny Projection Neurons and Fast-Spiking Interneurons by Primary Sensory and Motor Cortex

Authors: *B. SANABRIA[1], S. BASKAR[2], C. R. LEE[3], D. J. MARGOLIS[4];
[1]Rutgers Univ. New Brunswick, Piscataway, NJ; [2]Cell Biol. and Neurosci., Rutgers, The State Univ. of New Brunswick, Piscataway, NJ; [4]Cell Biol. and Neurosci., [3]Rutgers Univ., Piscataway, NJ

Abstract: The striatum, a key input structure of the basal ganglia, contributes to sensorimotor learning by sorting information about our surroundings, actions, and rewards. Part of the complexity of the striatum derives from the functional and anatomical organization of its neuronal circuitry. In mice, during texture-discrimination, optogenetic stimulation of corticostriatal synapses from the primary sensory cortex (S1) preferentially excites striatal parvalbumin-expressing fast-spiking interneurons (FSIs) and reduces behavioral responses. In contrast, optogenetic stimulation of corticostriatal synapses from the primary motor cortex (M1) equally excites striatal spiny projection neurons (SPNs) and FSIs, and promotes behavioral responses. The mechanism underlying the integration of M1 and S1 by SPNs and FSIs remains unclear. Striatal activity is produced by the combination of inputs they receive from local and distant neurons. Thus, we hypothesized that there are distinct differences in the number and distribution of S1 and M1 projections onto SPNs and FSIs. AAVs expressing Ruby2 or GFP spaghetti monster fluorescent proteins (sm.FP) were injected into both M1 and S1 to label corticostriatal inputs. Ex vivo whole cell current clamp recordings of striatal neurons with biocytin was used to label single striatal neurons. Confocal z-stacks images were acquired, and 3D reconstructions of M1 and S1 projections innervating our biocytin filled neuron were created using Imaris software. Corticostriatal projections from S1 and M1 were observed to course through the striatum and terminate as puncta. Puncta making close approximations (<0.5µm) to edge of our filled neurons were quantified as putative synapses. The number of synapses as well as their distribution along the entirety of the neuron was calculated. Our results strongly indicate that there is a significantly greater number synaptic contacts originating from M1 than from S1 onto striatal SPNs. In contrast, no significant differences between the average number of contacts

from M1 and S1 were found in FSIs. Furthermore, the S1 synapse was highly likely to colocalize near an M1 synapse on SPNs but in FSIs these synapses were more spread out. These results suggest that the mechanism underlying the stronger functional innervation of SPNs by M1 than S1 is the increased density of synaptic inputs from M1. The close proximity of S1 and M1 suggest that they are integrated by SPNs through coincidence detection. Our findings will have fundamental implications for how sensorimotor integration is performed in the striatum.

Disclosures: **B. Sanabria:** None. **S. Baskar:** None. **C.R. Lee:** None. **D.J. Margolis:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.21

Topic: E.03. Basal Ganglia

Support: Swedish Medical Research Council (VR-M-2020-01652)
EU/Horizon 2020, no.945539 (HBP SGA3)
Swedish e-science Research Center
Digital Futures

Title: Striatal mechanisms for entrainment to high frequency components - an in silico study

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Abstract: Oscillatory features are seen across various brain regions, both during physiological and pathological states. Such oscillatory activity is suggested to be important for coordinating signaling across different brain regions, for learning, memory, attention, motor behavior, etc. For instance, oscillatory components seen in the cortico-basal ganglia-thalamic network are correlated to ongoing motions. Active motor states are associated with higher oscillatory frequencies (> 35 Hz). However, the neurophysiological mechanisms are still not well understood, neither with regard to what are the sources for generating these oscillations, nor how the local network utilizes these oscillatory features. Here we explore in silico, using a large-scale microcircuit model of the mouse dorsolateral striatum [1], how high frequency oscillations are conveyed and read out in the striatum. Striatum, the input stage of the basal ganglia, receives convergent glutamatergic inputs from cortex, thalamus, pedunculopontine nucleus, etc. The model consists of direct- and indirect pathway striatal projection neurons (SPN), fast-spiking interneurons (FS), low-threshold spiking interneurons, and cholinergic interneurons. Each neuron is activated by simulated synaptic inputs. Preliminary simulations suggest that high frequency components are most easily conveyed via the FS neurons, even when spiking asynchronously [2]. The FS population, however, forms a gap junction coupled network. Gap junctions between

FS give rise to only a low degree of spike synchronization for experimentally estimated gap junction conductances, unless the inputs to the FS neurons are highly correlated [3]. We hypothesize that striatal high frequency entrainment leads to more synchronized activation of the FS network, thus the FS population could possibly more efficiently shape the activity of the SPNs and the local network.
References:
[1] Hjorth, et al (2020) Proc. Natl. Acad. Sci. U. S. A. 117, 9554-9565; [2] Belić, et al (2017) PLoS ONE 12(4): e0175135; [3] Hjorth, et al (2009) Journal of Neuroscience 29 (16), 5276-5286

Disclosures: **K. Pajo:** None. **J.J.J. Hjorth:** None. **J. Frost Nylén:** None. **I. Carannante:** None. **A. Kozlov:** None. **S. Grillner:** None. **J. Hellgren Kotaleski:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.22

Topic: E.03. Basal Ganglia

Support: National Institute of Neurological Disorders and Stroke Grant 6R35NS097185
National Institute of Neurological Disorders and Stroke Grant 1F31NS127499

Title: Predicting spiking responses to local network inhibition in external globus pallidus neurons

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Abstract: The external globus pallidus (GPe) is an inhibitory synaptic network of autonomously active neurons. In the absence of synaptic input, GPe neurons spike regularly. GPe neurons provide one another with ongoing periodic GABAergic synaptic currents, measurable in slice preparations. Anatomical data suggest GPe neurons may receive as few as 5 unitary local connections in vivo, and 1-2 intact connections from local presynaptic neurons can be identified in the spontaneous inhibitory synaptic potentials (IPSPs) of GPe neurons in slices. To determine the effect of local network activity on the spiking activity of GPe neurons, we obtained perforated-patch, current-clamp recordings of Parvalbumin+ and Npas1+ GPe neurons in coronal slice preparations of the GPe from male and female mice. We recorded spontaneous IPSPs produced by unitary local connections and measured their effects on the spontaneous firing of GPe neurons. The firing pattern effect of network activity was blocked by GABAergic antagonists and recreated by applying inhibitory postsynaptic conductance (IPSG) trains simulating 1-5 active presynaptic neurons using dynamic clamp. Both real and simulated local network inhibition produced large effects on the regularity of spiking, while causing only moderate effects on rate that adapted slowly over time. These results suggest that ongoing local

network inhibition from autonomously active GPe neurons contributes substantially to the irregular firing of GPe neurons in vivo. GPe neurons can be conceptualized as oscillators. The spike-time response of an oscillating neuron to an input depends on the oscillation phase when the input arrives and can be represented by the neuron's phase-resetting curve (PRC). We measured PRCs of PV+ and Npas1+ GPe neurons, which exhibited a range of PRC shapes. GPe neurons of both types also showed slow spike frequency adaptation to prolonged inputs. To predict the spiking responses of GPe neurons to unitary IPSG trains, we used a phase model of GPe neurons consisting of their rate, PRC, and an adaptation variable. A phase model with adaptation accurately predicted the effect of 1-5 unitary IPSGs on the rate and regularity of GPe neurons. These results suggest that a simple phase model can predict the spiking responses of GPe neurons to realistic synaptic input.

Disclosures: J.A. Jones: None. **C.J. Wilson:** None.

Poster

690. Cell Type Dysregulation in Disease

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 690.23

Topic: E.03. Basal Ganglia

Support: CRSNG #31160126

Title: Unexpected role for AKT signaling during motor skill learning in mice

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Abstract: Motor memory is responsible for the memorization allowing the execution of daily tasks. People perform various complex motor tasks automatically every day. Despite the importance of these skills, research on the molecular mechanisms underlying motor learning is still at its infancy. We previously demonstrated in mice that the mechanistic target of rapamycin (mTOR) plays a critical role in the learning of a complex motor skill. Protein kinase B (Akt) family (Akt1, Akt2 and Akt3) is a protein closely associated with mTOR signaling that is known to play a role in specific functions of the nervous system. Remarkably, Akt1 and Akt3 have the ability to regulate synaptic plasticity. To assess the role of Akt during motor learning, we use the accelerating rotarod allowing the distinction of the two known phases of learning, namely the faster and slower phases. C57BL/6 mice, aged 10 to 12 weeks old, were trained on the accelerating rotarod (0 to 40 rpm in 300 seconds, 10 trials/day) and sacrificed at either training day 1, 2, 3 or 8 (n=4 mice/group). Western-blot and densitometric analysis were performed on striatal, hippocampal, cortex and cerebellum brain tissues with a pan-Akt antibody phosphorylated at Serine 473 and Akt1, Akt2 and Akt3 total antibodies. At the behavioral levels, we observed a fast improvement of mice performance during the first day whereas moderate

gains in performance occurred at day 2 and 3. No further ameliorations were observed between day 3 and 8 meaning that mice had fully learned the task. After each training days, we observed that the levels of total Akt1, Akt2 and Akt3 were not altered in the striatum, hippocampus, cortex or cerebellum. In addition, no statistical difference in the levels of p-Akt1 was distinguished between groups in any brain regions. On the other hand, levels of p-Akt3 were increased gradually from rotarod training day 1 to day 8 in every brain region. However, it is noteworthy that the increased p-Akt3 levels did not followed the same pattern of changes among brain regions. For instance, in the striatum, the increased p-Akt3 levels were statistically significant at day 3 and 8 when compared to training days 1 and 2. However in the hippocampus, cortex and cerebellum, p-Akt3 levels were increased to statistical significance on training days 1 to 8 when compared to untrained mice. Our data revealed that activation of Akt3 was differentially modulated in the striatum in comparison to other brain regions during the learning phases of a complex motor skill. These data were at a preliminary stage. Nevertheless, they raised the interesting possibility that Akt3 kinases play a critical role in the molecular processes of motor memory encoding.

Disclosures: **K. Lagueux:** None. **M. Cyr:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.01

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: MOST 111-2113-M-001-021-
AS-CDA-110-L08

Title: Development of subtype-selective photoswitchable agonists for $GABA_A$ receptors

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Abstract: Photopharmacology, an emerging approach that uses a photoswitchable drug to bi-directionally modulate a biomolecule with high spatiotemporal precision, offers unique opportunities for mechanistic studies or therapeutic targeting of the nervous system. We aim to develop photopharmacology agents for type-A γ-aminobutyric acid receptors ($GABA_ARs$), the main mediators of inhibitory neurotransmission. Specifically, we seek to discover photoswitchable agonists that allow a selective and reversible manipulation of tonically active δ-subunit-containing $GABA_ARs$ (δ-$GABA_ARs$). δ-$GABA_ARs$ exhibit distinct pharmacology from other $GABA_AR$ subtypes and are attractive therapeutic targets for neurological and psychiatric disorders. Optical manipulation of δ-$GABA_ARs$ in the nervous system would advance the discovery of their unique roles in health and diseases. Because δ-$GABA_ARs$ can be selectively activated by THIP (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol; gaboxadol), we created a

series of azobenzene-containing THIP analogues as the candidates of their photoswitchable agonist. We identified several compounds that can robustly and reversibly activate α4β3δ (an "extrasynaptic" type) but not α1β2γ2 (a "synaptic" type) $GABA_A$Rs in human embryonic kidney (HEK) cells when light triggers *trans-to-cis* azobenzene isomerization. Interestingly, they also cause a weak photo-activation of α4β3 receptors but do not trigger α4β2δ responses in either *trans* or *cis* configuration, suggesting that these agonists are selective for β3-containing $GABA_A$Rs. When tethered at the β3+/α4- interface, these compounds drive receptor photo-activation, indicating that they are capable of targeting the putative GABA-binding pocket. A "red-shifted" photoswitchable agonist, DMAAI, has been tested on cultured hippocampal neurons and enabled 460-nm light to rapidly and reversibly silence action potential firing at 10 μM. Together, our results suggest a novel class of photoswitchable $GABA_A$R agonists for precisely manipulating neuronal inhibition in diverse applications.

Disclosures: **W. Lin:** None. **J. Lee:** None. **S.M.M. Lopez:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.02

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Medical Research Council (MRC) grant MC-UP-1201/1 (to T.B.)
Sainsbury Wellcome Centre Core grant from the Gatsby Charitable Foundation (GAT3755 to T.B.)
Wellcome Senior Research Fellowship (219627/Z/19/Z to T.B.)
Biotechnology and Biological Sciences Research Council (BBSRC) grant BB/S00310X/1 (to K.S. and T.B.)

Title: Control of AGRP neuron firing and body weight by synaptic GABAA receptor α3 subunits

Authors: A. V. STEMPEL[1], Y. NISHIMURA[2], A. TOZER[1], P. IORDANIDOU[1], L. JIN[3], *T. BRANCO[1], **K. STARAS**[2];
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Abstract: Activation of AGRP (Agouti-related protein) neurons in the arcuate nucleus of hypothalamus elicits feeding behavior and acts as a negative valence signal for learning food-seeking behaviors. AGRP neuron activity is rapidly suppressed upon exposure to food-related sensory cues and food consumption, suggesting that inhibitory control of AGRP neurons is important for regulation of feeding behavior. Here we report that in the mouse, synaptic inhibition mediated via GABA-A receptors (GABAARs) is sufficient to generate prolonged inhibition of AGRP neuron spiking within milliseconds. Whole-cell patch clamp recordings in

acute brain slices show that AGRP neurons receive fast and strong synaptic GABAAR inputs that are markedly biphasic, showing distinct fast and slow components. Using an *in vivo* RNA knock-down approach we dissect the contributions that specific GABAAR alpha subunits make to this inhibitory waveform. We show that knock-down of *Gabra3* expression selectively disrupts the slow component and causes a significant increase in body weight. Taken together, our findings suggest that GABAAR α3 subunits play a key role in the regulation of feeding behavior through the generation of long-lasting inhibitory synaptic currents.

Disclosures: A.V. Stempel: None. **Y. Nishimura:** None. **A. Tozer:** None. **P. Iordanidou:** None. **L. Jin:** None. **T. Branco:** None. **K. Staras:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.03

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH Grant R01MH114908
NIH Training Grant T32GM133332

Title: Investigating mechanisms of γ2-$GABA_A$R plasticity underlying benzodiazepine tolerance

Authors: *C. CHAPMAN[1], J. M. LORENZ-GUERTIN[1], S. DAS[1], N. POVYSHEVA[2], T. C. JACOB[1];
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Abstract: Benzodiazepines (BZDs), including Valium (diazepam; DZP), are frequently prescribed anxiolytic and anticonvulsant drugs which positively modulate inhibitory heteropentameric GABA type A receptors ($GABA_A$Rs) by binding at the interface of α1-3 or α5 subunits with the γ2 subunit. Use of these key clinical drugs is limited by the development of tolerance, but the underlying molecular mechanisms are unknown. We previously showed acute 24-hour DZP treatment increases phosphorylation and destabilization of the inhibitory postsynaptic scaffolding protein gephyrin, decreasing synaptic retention of receptors and enhancing lysosomal-mediated degradation of γ2-$GABA_A$Rs. Our current overall goal is to understand γ2-$GABA_A$R plasticity induced by long-term (7 day; 7d) DZP treatment. We hypothesize that adaptive mechanisms during sustained BZD treatment generate a cellular hyperexcitable state that impairs BZD sensitivity of canonical synaptic αβγ2 $GABA_A$R via phospho-dependent mechanisms, while additional mechanisms promote the assembly and synaptic accumulation of BZD-insensitive $GABA_A$R. Membrane fractionation biochemical results from 7d DZP vs vehicle treated mice show an increase in synaptic receptors that are BZD-insensitive along with a reduction of extrasynaptic $GABA_A$R without any loss of γ2-$GABA_A$R. This occurs concurrent with a functional reduction in DZP sensitivity and tonic

inhibition. Preliminary γ2-$GABA_AR$ co-immunoprecipitation mass spectrometry in cortical neurons support enhanced formation of BZD-insensitive receptors with 7d DZP. We also found no change in surface expression or synaptic localization of γ2-$GABA_AR$ following 7d DZP in cortical neurons by measurements from both endogenous γ2-$GABA_ARs$ and receptors containing pH-sensitive GFP and fluorogen-activating peptide (FAP) tagged γ2 subunit ($\gamma2^{pH}FAP$). Phospho-dependent γ2 regulation is also implicated in BZD tolerance, with our *in vivo* mass spectrometry analysis of 7d DZP treated mice indicating an overall upregulation of kinase expression. However, prior work has generated opposing data on γ2 phosphorylation sites S327 and S343 with BZD treatment, prompting our further investigation of γ2 phospho-regulation both generally and with 7d DZP by $\gamma2^{pH}FAP$ phospho-mutant analysis. Ongoing studies are dissecting the effects of 7d DZP on γ2-$GABA_AR$ plasticity, including receptor composition, trafficking, and phospho-dependent regulation. Uncovering the DZP-induced GABAergic neuroadaptations defining tolerance will provide a foundation for approaches promoting the development of safer prescription drugs without long-term risks to patients.

Disclosures: C. Chapman: None. **J.M. Lorenz-Guertin:** None. **S. Das:** None. **N. Povysheva:** None. **T.C. Jacob:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.04

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Title: Desensitizing properties of GABRB3 variants exacerbate the severity of gain-of-function developmental and epileptic encephalopathies

Authors: *S. LIN[1], V. LIAO[1], P. AHRING[1], M. CHEBIB[1], N. ABSALOM[2];
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Abstract: Developmental and epileptic encephalopathies (DEE) are a group of severe disorders characterised by seizures, a very young age of onset and comorbidities including severe intellectual disability, behavioural and movement disorders. Often, patients are resistant to treatment, and some experience severe side effects resulting in cessation of the pharmacological agent. *De novo* genetic variants in the *GABRB3* gene encoding the γ-aminobutyric acid type A ($GABA_A$) receptor are known to be associated with DEE. An exhaustive genotype/phenotype correlation demonstrated that increased GABA sensitivity, or gain-of-function variants, presented with a distinct and more severe clinical phenotype with a younger age of onset. We sought to determine if the desensitization properties of the receptor variants also influenced the clinical severity.
Method: Concatenated receptors containing 19 different gain-of-function single variants were expressed in *Xenopus* oocytes where current decay rates, maximum open probability and steady-state currents were quantified with two-voltage clamp electrophysiology. Values were compared

with non-parametric ANOVA and Dunn's post-hoc test, where comparisons were restricted to variants measured on a single day. The biophysical characteristics were then compared to the age of onset as a proxy of clinical severity, and the receptor maximum open probability and its association with clinical presentation.
Result: Gain-of-function variants could be separated into variants with faster current decay rates with increasing desensitization properties, or variants with a higher steady-state current at equilibrium and thus reduced desensitization. Variants in similar structural motifs often had similar changes in their biophysical properties, and a simple linear kinetic model indicated that several variants in the second transmembrane region lining the pore directly altered the desensitizing equilibrium constant. Reduced desensitization correlated with a younger age of onset, albeit more weakly than the correlation with GABA sensitivity.
Conclusion: These results indicate that along with the change in GABA sensitivity, the age of onset for patients with DEE is also influenced by desensitization. Variants in the M1 and M2 domain that increase steady-state currents have a younger age of onset than variants in the other regions. Therefore, $GABA_A$-receptor associated DEEs can be a consequence of either a loss or gain in $GABA_A$ receptor activity and the greater the increase in currents via changes in GABA sensitivity or desensitization properties, the more severe the clinical outcomes.

Disclosures: S. Lin: None. **V. Liao:** None. **P. Ahring:** None. **M. Chebib:** None. **N. Absalom:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.05

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH/NINDS Intramural Support

Title: Shisa7 regulates synaptic and extrasynaptic $GABA_AR$ trafficking which impacts neurodevelopmental behaviors

Authors: K. WU, R. SHEPARD, D. CASTELLANO, W. HAN, ***S. PANDEY**, Q. TIAN, Y. LI, D. LIJIN, W. LU;
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Abstract: GABA-A receptors ($GABA_ARs$) are ligand-gated ion channels that mediate the majority of fast inhibitory neurotransmission in the central nervous system (CNS). $GABA_ARs$ can be classified as mediating either phasic or tonic inhibition. Phasic inhibition is mediated by synaptically localized $GABA_ARs$ that respond to presynaptic GABA release, whereas tonic inhibition is mediated by $GABA_ARs$ localized either extrasynaptically or perisynaptically that respond to low ambient levels of GABA. Due to their ubiquity across the CNS, it is not surprising that impaired $GABA_AR$-mediated signaling is associated with a broad range of

neurological and psychiatric disorders. Therefore, defining mechanisms that regulate $GABA_AR$ activity and determining how perturbation of these processes are involved in pathophysiological conditions continue to be of high importance. We recently identified a $GABA_AR$ auxiliary subunit, Shisa7, which is a single-pass transmembrane protein that interacts with either α1- or α2-$GABA_ARs$ and thereby regulates phasic inhibition. However, it is unknown whether Shisa7 regulates tonic inhibition. In this study, we report that Shisa7 is critical for the regulation of tonic inhibition in hippocampal neurons. In Shisa7 knockout (KO) neurons, α5-$GABA_AR$ mediated tonic currents are significantly reduced. Mechanistically, Shisa7 is crucial for α5-$GABA_AR$ exocytosis. Additionally, Shisa7 regulation of tonic inhibition requires PKA that phosphorylates Shisa7 S405. Subsequently, we generate a Shisa7 S405A knock-in (KI) mouse line that is phospho-deficient at S405. These mice display reduced surface expression of $GABA_ARs$ in hippocampal neurons. Importantly, both synaptic and tonic inhibition are decreased in KI mice. Moreover, chemically induced inhibitory long-term potentiation is impaired, highlighting a critical role of Shisa7 S405 in GABAergic synaptic plasticity. Lastly, KI mice exhibit locomotor hyperactivity, increased grooming and impaired sleep homeostasis associated with neurodevelopmental disorders. Collectively, this study expands on our previous studies further elucidating the importance of Shisa7 in regulating tonic inhibition and reveals a phosphorylation site critical for Shisa7-dependent trafficking of synaptic and extrasynaptic $GABA_ARs$ which contributes to behavioral endophenotypes displayed in neurodevelopmental disorders.

Disclosures: **K. Wu:** None. **R. shepard:** None. **D. Castellano:** None. **W. han:** None. **S. Pandey:** None. **Q. Tian:** None. **Y. Li:** None. **D. Lijin:** None. **W. Lu:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.06

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH/NINDS R01NS115800
The Iowa Neuroscience Institute

Title: Enhancing delta-subunit containing $GABA_A$receptors reduces seizure-like activity in neonates and adults

Authors: *G. LIDDIARD[1,2], J. GLYKYS[3,4,5];
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Abstract: Phenobarbital modulates inhibition by enhancing $GABA_A$ receptors and is the main anticonvulsant used to treat neonatal seizures. However, roughly 50% of neonatal seizures do not respond to this anticonvulsant. A reason for phenobarbital's inefficacy is that $GABA_A$ receptor-mediated neurotransmission is mainly excitatory in the neonatal period. Also, traditional

GABAergic anticonvulsants, including phenobarbital, target synaptic receptors. It is unknown if targeting $GABA_A$ extrasynaptic receptors would aid in controlling neonatal seizures or worsen them due to the excitatory actions of $GABA_A$ receptor activation at this early age. We evaluated the effect of different concentrations of THIP, a delta-subunit $GABA_A$ receptor agonist, on seizure-like activity in the hippocampal CA1 region and the pre-hippocampal neocortex using acute brain slices from C57BL/6J mice across development (post-natal day 5-45). Field electrodes recorded seizure-like activity induced by either a potassium channel blocker (4-Aminopyridine, 4-AP) or Low-$MgCl_2$ containing artificial cerebrospinal fluid. We used 4-AP as a model for recurrent seizures and the Low-$MgCl_2$ solution as a model for late-stage pharmaco-resistant seizures. In the 4-AP model, THIP 1 µM did not reduce seizure-like activity at any age. THIP 10 µM showed a significant reduction in seizure-like activity in the neonatal neocortex but not the neonatal hippocampus. In contrast, THIP 10 µM showed a significant decrease in seizure-like activity in both adult regions. Finally, THIP 50 µM significantly reduced seizure-like activity in both areas and ages recorded. In the Low-$MgCl_2$ model, THIP 50 µM significantly reduced seizure-like activity in both regions and ages recorded. Our results indicate that enhancing extrasynaptic $GABA_A$ delta-containing receptors reduces seizure-like activity in neonates and adults. We conclude that THIP, and other delta-subunit-specific agonists, could serve as novel treatments for neonatal seizures.

Disclosures: G. Liddiard: None. **J. Glykys:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.07

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: University of Pittsburgh School of Medicine Research Funds NINDS grant T32 NS086749

Title: The impact of chronic α5 $GABA_A$ receptor negative allosteric modulation on hippocampal GABAergic and glutamatergic plasticity

Authors: *J. L. NUWER[1], N. V. POVYSHEVA[2], T. C. JACOB[1];
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Abstract: In the central nervous system, GABA type A receptors ($GABA_ARs$) generate fast inhibitory signals to dampen and control neuronal activity at the network and cellular levels, thus contributing to the balance between excitation and inhibition (E/I balance). α5 subunit containing $GABA_ARs$ are of particular interest due to their enriched hippocampal expression and critical roles in development, synaptic plasticity, cognition, and memory. Negative allosteric modulators that target α5 $GABA_ARs$ (α5 NAMs) enhance cognition and have shown promise in preclinical

studies to mitigate cognitive impairment in Down syndrome, schizophrenia, and post-anesthesia - conditions characterized by excess GABAergic inhibition. Despite *in vivo* efficacy in both rodents and humans, no study has examined the effects of chronic α5 NAM treatment on inhibitory and excitatory synapse plasticity to identify mechanisms of action. We previously showed that 2-day treatment in mature primary hippocampal neurons with L-655,708 (L6), an imidazobenzodiazepine that acts as a weak but highly selective α5 NAM, modulates NMDA receptor subtype synaptic surface localization by enhancing the synaptic GluN2A/B ratio. Additionally, 2-day L6 treatment does not modify surface α5 $GABA_AR$ expression, inhibitory synapse function, or responsiveness to L6, suggesting that α5 NAMs may have sustained efficacy with reduced tolerance liability unlike other $GABA_AR$-targeting drugs that act at the benzodiazepine binding site. Based on these results, we hypothesized that 7-day L6 treatment would lead to increased Ca^{2+} dynamics via increased synaptic GluN2A subunit expression while maintaining GABAergic inhibition and L6 efficacy. We treated primary hippocampal neurons for 7 days with L6 or vehicle and measured the effects of chronic α5 NAM exposure on glutamatergic and GABAergic synapses at DIV21-22 using confocal microscopy, biochemical, and functional techniques. Surprisingly, 7-day L6 treatment increased the synaptic surface levels of α5 $GABA_AR$ and decreased the overall surface levels of both GluN2A and GluN2B, as shown by confocal imaging experiments. In agreement with these findings, preliminary Ca^{2+} imaging data reveal reduced activity-evoked Ca^{2+} influx in L6-treated neurons. Additional studies are ongoing to evaluate α5 NAM effects *in vivo* and determine the impact of chronic α5 NAM treatment on hippocampal E/I balance. Combined with a better understanding of the regulatory mechanisms governing α5 $GABA_ARs$ and α5 NAM-induced plasticity, the results of these studies will be invaluable in determining therapeutic application of α5 $GABA_AR$-preferring drugs.

Disclosures: **J.L. Nuwer:** None. **N.V. Povysheva:** None. **T.C. Jacob:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.08

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH Grant R01NS112534

Title: General anesthetics counteract cholesterol in protecting γ-aminobutyric acid type A ($GABA_A$) receptors surface expression to induce anesthesia

Authors: *Z. YUAN, M. PAVEL, S. HANSEN;
The Scripps Res. Inst., Jupiter, FL

Abstract: General anesthetics have been shown to disrupt the clustering of the palmitoylated phospholipase D2 (PLD2) with ganglioside GM1 lipids and translocate the liberated PLD2 to

phosphatidyl inositol 4,5-bisphosphate (PIP_2) clusters to activate TREK-1 to induce anesthesia (Pavel et. al., 2020). Rapid synaptic inhibition in the mammalian central nervous system is largely mediated by γ-aminobutyric acid (GABA) type A receptors ($GABA_AR$) (Jacob et. al., 2012). The $\gamma2$ subunit is palmitoylated (Keller et. al., 2004) and the $\alpha1$ subunit has a PIP_2 binding site reported from cryo-EM (Laverty et. al., 2019), providing a structural basis for $GABA_AR$ anchoring to GM1 clusters and translocating to PIP_2 regions when left out of GM1 clusters, being similar to PLD2. $GABA_AR$ opening probability has been shown to be regulated by cholesterol level (Sogaard et. al., 2006). The cholesterol-rich GM1 clusters also serve as an entry point for endocytosis. PIP_2 clusters separate from the typical endocytic pathway in GM1 clusters. Endocytosis decreases membrane expression to inactive channels and propofol has been reported in regulating $GABA_AR$ surface expression by inhibiting endocytosis (Li et. al., 2015). First, we performed dSTORM super-resolution imaging on primary neurons with and without propofol treatment. Propofol significantly decreased GM1 cluster number and size, suggesting propofol disrupted GM1 clusters into less and smaller clusters which could no longer serve as an endocytic point. Next, we combined dSTORM imaging on permeabilized and non-permeabilized cells and confocal imaging to study the effect of propofol, a general anesthetic, on endocytosis. We found that propofol significantly inhibited endocytosis by direct inhibition and accumulated $GABA_AR$ on GM1 clusters by translocating the receptors out of PIP_2 clusters. Cholesterol is synthesized by astrocytes delivered through apolipoprotein E (ApoE) to the neurons in the brain. To test the role of cholesterol in recruiting $GABA_AR$ to GM1 clusters, we performed dSTORM imaging on brain slices and primary cortical culture of animals with astrocyte-specific cholesterol depletion. Lowering cholesterol exhibited a similar trend as propofol treatment. We also loaded cholesterol to primary neurons with ApoE. We found that increased cholesterol level induced endocytosis and propofol treatment reversed the effect. We also performed electrophysiology on WSS-1 cells with overexpression of $GABA_AR$ to show the effect of propofol and cholesterol modulation on $GABA_AR$ function. In conclusion, general anesthetics (i.e., propofol) counteract cholesterol in inducing anesthesia through modulating GABAAR surface expression.

Disclosures: **Z. Yuan:** None. **M. Pavel:** None. **S. Hansen:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.09

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH/NINDS R21 NS111945-02

Title: Possible interactions between O-GlcNAcylation and Phosphorylation in modulating hippocampal GABAergic Transmission

Authors: *S. PHILLIPS[1,2], L. L. MCMAHON[2];
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Abstract: Crosstalk between O-GlcNAcylation and phosphorylation affects the regulation of various proteins involved in cellular function such as transcription, translation, and transportation. Separately, serine phosphorylation and O-GlcNAcylation modulate GABA-gated currents, yet no studies have examined how the interplay between both serine modifications affect $GABA_AR$ function and the strength of GABAergic transmission. Phosphorylation of Ser 409 on the β1 subunit by protein kinase A (PKA) decreases $GABA_AR$ currents, while PKA-dependent phosphorylation of Ser 408 and Ser 409 on the β3 subunit increases $GABA_AR$ currents in HEK293 cells. Studies from our lab have recently shown that an acute increase in O-GlcNAcylation significantly decreases the amplitude of synaptic inhibitory postsynaptic currents in CA1 pyramidal cells. While it is unknown which serines undergo O-GlcNAcylation on $GABA_AR$ β subunits, it is possible that phosphorylation and O-GlcNAcylation occur on the same serines thereby competing with one another, or may occur on separate serines, which may or may not interact in a functional manner. Because phosphorylation and O-GlcNAcylation have potent effects on $GABA_AR$ function, it is important to determine how O-GlcNAcylation effects $GABA_AR$ function simultaneously with serine phosphorylation, and if prior phosphorylation prevents or augments the effect of O-GlcNAcylation. To test this, we used whole-cell recordings of evoked IPSCs from CA1 pyramidal cells in acute slices from 3-5 week old male and female rats and bath applied the PKA activator, forskolin (50μM), either before (n= 6) or after (n=7) bath application of glucosamine and the OGA inhibitor, thiamet-G to increase O-GlcNAcylation. The data show a possible interaction such that a prior increase in O-GlcNAcylation, which depresses evoked IPSC amplitude, elicits a forskolin-dependent increase in IPSC amplitude. On the other hand, forskolin elicits a depression of the IPSC amplitude in the absence of a prior increase in O-GlcNAcylation. These data suggest the polarity of a PKA-dependent modulation of $GABA_AR$ function is dictated by the presence or absence of a co-occurring O-GlcNAc modification. Whether serine phosphorylation and O-GlcNAcylation are competing for the same site or different sites, and how these post-translational modifications are interacting at the level of the GABAAR requires additional investigation.

Disclosures: S. Phillips: None. **L.L. McMahon:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.10

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH Grant F30MH126548
NIH Grant R01MH123748
NIH Grant R01MH123748

Title: Sleep spindle abnormalities associated with slow $GABA_A$ inhibition in parvalbumin positive interneurons

Authors: *P. M. LAMBERT, S. V. SALVATORE, A. M. BENZ, H.-J. SHU, S. J. MENNERICK;
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Abstract: $GABA_A$ receptors ($GABA_AR$) are the primary fast inhibitory neurotransmitter receptor in the CNS but can also mediate slow forms of inhibition. $GABA_ARs$ are heteropentameric chloride channels which subunits influence both physiological and pharmacological properties of receptor function. $GABA_ARs$ containing the δ subunit, encoded by the *Gabrd* gene, are typically localized to extrasynaptic sites of certain neuron types, where they participate in tonic inhibition. By contrast, other subunit combinations mediate fast, phasic inhibition, considered the dominant influence in most cells. In the mouse cortex, δ subunit containing $GABA_AR$ receptors are expressed on the surface of some pyramidal cells as well as parvalbumin positive (PV+) interneurons. The coordinated activity of PV+ interneurons synapsing onto pyramidal neurons supports gamma frequency oscillations in the extracellular field which can be measured by EEG, however it remains unclear what role tonic inhibitory tone, mediated by δ $GABA_ARs$, onto PV+ interneurons may play in shaping this or other oscillatory activity. Using PV-Cre mice crossed with *Gabrd*$^{fl/fl}$ mice (PV-δcKO), we assessed the effects of ablating δ-mediated inhibition of PV+ interneurons on network oscillatory activity through EEG/EMG recordings of freely behaving PV-δcKO mice and their WT ($Cre^{-/-}$) littermates. To capture multiple behavioral states and state transitions, recordings were performed for 12 hours during the light phase. PV-δcKO mice exhibited elevated EEG power in beta and low gamma frequency ranges (12- 55 Hz) during active wake, non-REM (NREM), and REM sleep, within expected frequencies dependent on PV+ interneuron activity. Mice also showed preserved theta rhythms during both active wake and REM. Surprisingly, PV-δcKO mice showed elevated sigma frequency (10-15 Hz) power during NREM, as well as a larger increase in sigma power at NREM to REM transitions, two common indicators of sleep spindle activity. Using a previously validated algorithm for the automated detection of sleep spindles in rodent EEG, we found that PV-δcKO mice indeed had altered spindle event amplitudes and durations. Together this suggests an important role for the δ inhibitory tone onto PV+ interneurons in regulating coordinated network activity, including sleep-related spindle oscillations not previously linked to inhibition onto PV+ interneurons.

Disclosures: P.M. Lambert: None. **S.V. Salvatore:** None. **A.M. Benz:** None. **H. Shu:** None. **S.J. Mennerick:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.11

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

Support: ARUK-NC2020-UCL
MRC-GO501263

Title: Positive allosteric modulation of extrasynaptic delta $GABA_A$ receptors alleviates anxiety in an APP knock-in mouse model of Alzheimer's disease

Authors: *A. ALHAMDI, **W. ZHANG**, A. ISLAM, A. B. ALI;
Sch. of Pharm., Univ. college London, London, United Kingdom

Abstract: Alzheimer's disease (AD) is a common neurodegenerative disease that is associated with gradual memory loss and neuropsychiatric symptoms (NPS) such as agitation and anxiety that affects ~40% of AD patients. AD-associated toxic amyloid-beta accumulation, synaptic dysfunction and hyperexcitability were shown to be correlated with dysfunction of selective interneurons. We hypothesize that the extrasynaptic δ-subunit containing $GABA_A$ receptors (δ-$GABA_A$Rs), found on selective interneurons, known to have an emerging role in mood disorders, are altered during AD pathogenesis that manifests in the AD-associated memory loss and NPS. To investigate our hypothesis, we combined neuroanatomy with behavioural studies using a physiologically relevant familial mouse model of AD that recapitulates the condition as in humans, age-matched (12-16 months) to wild-type control mice. Confocal microscopy analysis revealed that the overall expression of δ-$GABA_A$Rs was significantly reduced in $APP^{NL\text{-}F/NL\text{-}F}$ mice, and in post-mortem brain tissue of AD patients compared to age-matched control counterparts. Interestingly, the δ-$GABA_A$Rs were selectively expressed in parvalbumin (PV)- and neuropeptide Y(NPY)-, but not in calretinin(CR)-expressing interneurons in the CA1 and dentate gyrus (DG) regions of the hippocampus of both genotypes. Furthermore, this selective expression in PV and NPY cells was significantly reduced and consistent with decline of these interneurons in the $APP^{NL\text{-}F/NL\text{-}F}$ AD model compared to the wild-type mice. In vivo positive allosteric modulation of the δ-$GABA_A$Rs using a delta-selective-compound 2 (DS2, 2 mg/kg) showed a significant reduction in the anxiety expressed by $APP^{NL\text{-}F/NL\text{-}F}$ mice compared to the vehicle-treated groups shown by two behavioural experimental paradigms; the open arena and light dark chamber tests. Furthermore, the drug treated $APP^{NL\text{-}F/NL\text{-}F}$ mice showed "recovery" of the downregulated δ-$GABA_A$Rs in CA1 and DG. Our data suggest that δ-$GABA_A$Rs, located in discreet neuronal circuitry of the hippocampus, are downregulated during AD, and modulation of this subunit using a δ-subunit selective agonist could be a targeted therapy to alleviate anxiety, and ultimately halt cognitive decline which would greatly improve the quality of life of AD patients and caregivers.

Disclosures: **A. Alhamdi:** None. **W. Zhang:** None. **A. Islam:** None. **A.B. Ali:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.12

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH 1R01MH117149-01

Title: WWC2 normalizes inhibitory synaptic transmission via regulation of $GABA_AR$ expression

Authors: *T. L. DUNHAM, J. WILKERSON, K. M. HUBER, L. J. VOLK;
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Abstract: WWC2 (WW and C2 domain-containing protein 2) is a signaling scaffold enriched in the hippocampus and implicated in schizophrenia and autism spectrum disorders. WWC2 is a homolog of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) trafficking regulator KIBRA (KIdney/BRAin protein, aka WWC1), however the function of WWC2 in the brain is unknown. We immunoprecipitated WWC2 from wild-type mouse brain tissue and found that WWC2 interacts with the inhibitory synaptic scaffold gephyrin, but not the excitatory synaptic scaffold PSD-95. We then generated a forebrain selective knockout (KO) of WWC2 by crossing *WWC2* floxed mice (*WWC2 f/f*; wild-type control, WT) with *Emx1-cre* mice. We collected hippocampi from p28-32 animals of both sexes and fractionated the tissue to purify the cytosolic, membrane, and postsynaptic density fractions. KO hippocampal tissue exhibited a near total loss of WWC2 and increased membrane expression of γ-amino butyric acid receptor type-A ($GABA_AR$) subunits β2, β3, and γ2, with no changes in AMPAR subunit expression compared to WT littermates (n=5-10/group). We corroborated the increase in membrane $GABA_AR$β2/3 content via surface biotinylation and streptavidin pulldown in acute hippocampal slices from similarly aged WT and KO animals (n=4/group). To examine the functional implications of increased membrane $GABA_AR$ expression, we examined inhibitory and excitatory synapse function in hippocampal slice cultures from p6 *WWC2 f/f* pups biolistically transfected with mCherry-cre. Paired whole cell recordings of cre-negative (WT) and cre-positive (cKO) CA1 pyramidal cells revealed changes to mIPSCs (n=21 pairs) and mEPSCs (n=22 pairs) in the cKO neurons. When compared to their paired WT cell, cKO neurons exhibited a bimodal shift in mIPSC distribution and amplitude, while mEPSCs were larger on average. cKO cells also had decreased capacitance, increased input resistance (IR), and a 2 mV hyperpolarization of the resting membrane potential (n=42 or 43 pooled pairs). To examine whether any of the changes to passive properties are due to structural differences in neurons lacking WWC2, we cultured hippocampal cells from P0 *WWC2 f/f* pups and transfected them on DIV3 with AAV-GFP or AAV-GFP-cre. When subjected to Sholl analysis on DIV18, cre-positive neurons exhibited deficits in dendritic branching (GFP n=23, cre n=30). This is consistent with the decreased capacitance in the recorded cKO neurons. Here, we provide the first data on the function of WWC2 in the mouse hippocampus, where we show that it has a novel role in regulating inhibitory receptor expression, baseline inhibitory transmission, and neuronal morphology.

Disclosures: T.L. Dunham: None. **J. Wilkerson:** None. **K.M. Huber:** None. **L.J. Volk:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.13

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

Support: NIH/NINDS Intramural Research Program

Title: Shisa7-dependent regulation of $GABA_A$ receptor single-channel gating kinetics

Authors: *D. CASTELLANO[1], K. WU[1], A. KERAMIDAS[2], W. LU[1];
[1]NINDS, NIH, Bethesda, MD; [2]Inst. for Mol. Biosci., Univ. of Queensland, Brisbane, Australia

Abstract: In the brain, $GABA_A$ receptors are the primary mediators of fast inhibitory synaptic transmission. Although it is widely known that their pore-forming subunits are critical towards determining channel function, it remains unclear whether their receptor properties are also modulated by $GABA_A$R-associated transmembrane proteins. We previously identified Shisa7 as a $GABA_A$R auxiliary subunit that modulates the trafficking, pharmacology, and deactivation properties of these receptors. However, whether Shisa7 also regulates $GABA_A$R single-channel properties has yet to be determined. Here, we performed single-channel recordings of α2β3γ2L $GABA_A$Rs transfected in HEK293T cells and found that while Shisa7 does not change channel slope conductance (i_{GABA}), it reduced the frequency of openings. Importantly, Shisa7 modulates $GABA_A$R gating kinetics by decreasing the duration and open probability (P_o) within bursts. Through kinetic analysis of dwell time components, activation modeling, and macroscopic simulations, we demonstrate that Shisa7 accelerates $GABA_A$R deactivation by governing the time spent between close and open states during gating. Together, our data provide a mechanistic basis for how Shisa7 controls $GABA_A$R gating and reveal for the first time that $GABA_A$R single-channel properties can be modulated by an auxiliary subunit. These findings shed light on processes that shape the temporal dynamics of GABAergic transmission.

Disclosures: D. Castellano: None. **K. Wu:** None. **A. Keramidas:** None. **W. Lu:** None.

Poster

691. Subcellular and Subunit: Selective Actions of the GABA-A Receptor

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 691.14

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant 1RF1MH117055-01
CBTE Fellowship
NUS Development Grant

Title: Subcellular bidirectional $GABA_A$R pharmacology

Authors: *S. S. X. LIM[1], H. YAN[2], S. C. BURWELL[2], B. C. SHIELDS[1], A. CHOUDHURY[1], S. SINGH[1], D. KOO[1], M. R. TADROSS[1];
[1]Dept. of Biomed. Engin., [2]Dept. of Neurobio., Duke Univ., Durham, NC

Abstract: The $GABA_A$ receptor ($GABA_AR$) is a neurotransmitter-gated Cl^- channel, expressed in virtually every neuron in the brain. While canonically a postsynaptic receptor, $GABA_ARs$ have been found in all neuronal compartments, each thought to have a distinct impact on how a neuron transforms inputs to outputs. $GABA_ARs$ on distal dendrites are thought to modulate *inputs*, providing an inhibitory counterbalance to synaptic excitation. Somatic $GABA_ARs$, downstream of dendritic processing, are thought to have veto power over action potential *output*. Finally, $GABA_ARs$ in the axon may decouple transmitter release from action potential firing, with potential to individually tune collaterals. Beyond these biophysically inspired roles, several striking experimental observations are consistent with subcellular specialization of the $GABA_AR$. For example, GABA-releasing neurons exhibit subcellular precision in their anatomical wiring; parvalbumin-expressing (PV) interneurons preferentially innervate the soma, whereas somatostatin (SST) and spiny projection neurons (SPN) target the distal dendrite of recipient neurons. Moreover, divergent regulation has been seen in Parkinson's disease, wherein *opposite* changes in $GABA_A$ synapses that target the *soma* vs *distal dendrites* of the same neuron have been observed. Nevertheless, it has not been possible to manipulate $GABA_A$ receptors with subcellular precision. To address this gap, we have developed technologies for subcellular targeting with DART (Drugs Acutely Restricted by Tethering). DART genetically programs neurons to express a protein, which covalently captures and concentrates drugs, to produce a localized cell-specific pharmaceutical effect. Here, we describe novel subcellular refinements of the technology. First, we describe a method to deliver DART pharmaceuticals to axon projections without diffusion into somatodendritic compartments, enabling axon-specific pharmacology. Second, we present a novel soma-targeted version of the DART protein, validated in neurons from multiple brain regions. Finally, we pair these genetic reagents with antagonist and positive-allosteric-modulator DART pharmaceuticals for the $GABA_AR$ to enable subcellular, bi-directional interrogation. The tools are compatible with use in freely behaving mice, and should provide a modular foundation for subcellular targeting of virtually any drug.

Disclosures: S.S.X. Lim: None. **H. Yan:** None. **S.C. Burwell:** None. **B.C. Shields:** None. **A. Choudhury:** None. **S. Singh:** None. **D. Koo:** None. **M.R. Tadross:** None.

Poster

692. Modulatory GPCR Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 692.01

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Title: Role of nuclear β1-adrenergic receptors in norepinephrine-induced regulation of astrocyte gene expression

Authors: *J. MAGLASANG, M. SZYMANSKI, S. HERGENROTHER, K. BENTON, D. LOBNER, P. GASSER;
Marquette Univ., Milwaukee, WI

Abstract: Norepinephrine (NE) exerts powerful influences on metabolic, neuroprotective and immunoregulatory functions of astrocytes. These effects, mediated by G-protein-coupled α- and β-adrenergic receptors, include both rapid changes in enzyme activity and delayed changes in gene expression. For example, NE induces rapid activation of cytosolic glycogen phosphorylase, leading to increases in glycogen breakdown, and gradual increases in the expression of genes that allow adaptive re-synthesis of glycogen. Until recently, all effects of NE were believed to be mediated by receptors localized exclusively to the plasma membrane, but recent studies in cardiomyocytes have demonstrated that adrenergic receptors can also signal from intracellular membranes, including the nuclear membrane. We have recently identified β1-adrenergic receptors (β1-ARs) localized to the inner nuclear membrane in astrocytes and have demonstrated that NE accesses and activates nuclear β1-ARs via transporter-mediated uptake. These findings raise the hypothesis that NE-induced regulation of astrocyte gene expression is mediated in part by nuclear β1-ARs. To begin to test this hypothesis, we examined the effects of NE on astrocyte expression of mRNA for PPP1R3C (Protein Targeting to Glycogen (PTG)), a gene previously shown to be upregulated by NE. Astrocytes were treated for 15 minutes with 1uM NE, followed by washing, incubation for two hours, and extraction of total RNA. PTG expression was measured using qPCR. Astrocytes responded to a brief pulse of norepinephrine with significant increases in PTG mRNA. The effect of NE was inhibited by pretreatment with the β1-selective antagonist CGP 20712, but not the β2-selective antagonist ICI 118, 551. To test the hypothesis that the effects of NE are mediated by nuclear, but not plasma membrane β1-ARs, astrocytes were pretreated with either the membrane-permeable β-AR antagonist propranolol, or the membrane-impermeable β-AR antagonist sotalol, followed by treatment with NE. Pre-treatment of astrocytes with propranolol completely blocked NE-induced increases in PTG mRNA, while pretreatment with sotalol had no effect. These data are consistent with the hypothesis that NE-induced increases in PTG expression are mediated by nuclear β1ARs and suggest that integrated cellular responses to NE involve activation of both plasma membrane and intracellular adrenergic receptors.

Disclosures: J. Maglasang: None. **M. Szymanski:** None. **S. Hergenrother:** None. **K. Benton:** None. **D. Lobner:** None. **P. Gasser:** None.

Poster

692. Modulatory GPCR Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 692.02

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Title: Detection of histamine H4 receptor mRNA expression in the nervous system at the cellular level by in situ hybridization

Authors: *C. JIN[1], K. KARLSTEDT[2], P. PANULA[1];
[1]Medicum/Anatomy, [2]Medicum/Physiology, Helsinki Univ., Helsinki, Finland

Abstract: Histamine is widely distributed in peripheral mammalian tissues and in tuberomamillary neurons in the posterior hypothalamus. Histamine exerts its functions via G protein-coupled H1, H2, H3 and H4 receptors. The roles of the first three receptors in the brain are well understood, but the expression and possible functions of the fourth receptor in the brain are poorly known. In order to detect histamine H4 receptor (Hrh4) mRNA expression in the mouse nervous system, *in situ* hybridization assays with several DIG-labeled antisense riboprobes or RNAscope probes were performed on PFA-fixed-paraffin-embedded tissue sections. RNAscope Hrh4 probes were applied together with neuronal marker elavl3 probes. We detected Hrh4 mRNA expression in neurons of mouse dorsal root ganglion and trigeminal ganglion coexpressed with neuronal marker elavl3. In the brain, specific expression of Hrh4 was found in several layers of olfactory bulb and in habenula. In addition, weaker positive signals were seen in various cortical areas (frontal, temporal, auditory, parahippocampal, retrosplenial, and piriform areas), locus coeruleus, and vestibular nuclei. Quantitative analysis using qRT-PCR showed that Hrh4 expression in most brain areas was very low or nearly undetectable, with olfactory bulb as an exception. Even in the olfactory bulb, expression of Hrh1, Hrh2 and Hrh3 was higher than that of Hrh4. In agreement with earlier *in vitro* findings, endothelial cells in different brain areas expressed Hrh4. Expression was also found in choroid plexus. The results suggest that Hrh4 may play roles in sensory functions, regulation of brain endothelium and formation of CSF or its flow. It remains to be shown whether Hrh4 mRNA is translated and functional in brain neurons.

Disclosures: C. Jin: None. **K. Karlstedt:** None. **P. Panula:** None.

Poster

692. Modulatory GPCR Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 692.03

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: VA BLR&D 2 I01 BX002745-06A2
NIH/NINDS K08NS114170

Title: Suppression of in vitro epileptiform activity by vigabatrin: dependence on GABA-B receptors and GABA transporter type 1 (GAT1)

Authors: G. HOLMES-LEON[1], N. LI[1], R. P. BOYLE[1], J. ALBRECHT[1], A. NOLAN[2], ***C. B. RANSOM**[1,3];
[1]Epilepsy Ctr. of Excellence, VA Puget Sound, Seattle, WA; [2]Lab. Med. and Pathology, [3]Neurol., Univ. of Washington, Seattle, WA

Abstract: Several antiepileptic drugs modulate GABAergic signaling, either by actions on ionotropic GABA-A receptors or elevation of extracellular GABA concentrations. Metabotropic GABA-B receptors also affect neuronal excitability, but are not recognized as targets of

antiepileptic drugs. We investigated effects of the antiepileptic drug vigabatrin and GABA-B receptor activation on spontaneous, epileptiform discharges induced by 4-aminopyridine (4AP) in hippocampal brain slices from mice. As previously reported, the GABA-B receptor agonist baclofen caused a dose-dependent reduction in frequency of 4AP-induced epileptiform discharges, but did not affect the amplitude or duration of individual discharges. Suppression of *in vitro* epileptiform activity by baclofen was blocked by the GABA-B receptor antagonist CGP55845 (10 μM, CGP) and the K^+ channel blocker Ba^{2+} (100 μM), indicating that baclofen was acting on postsynaptic $GABA_B$ receptors and activating GIRK channels. The antiepileptic drug vigabatrin is a GABA transaminase inhibitor that increases extracellular GABA concentrations. Pre-treatment of brain slices with vigabatrin (150 μM, 2 h) caused a marked suppression of 4AP-induced spontaneous activity, significantly prolonging the latency to onset of spontaneous activity or preventing activity altogether. Inhibition of GABA-A receptors with SR95531 (1 μM) did not reverse effects of vigabatrin. The GABA-B antagonist CGP and the GIRK channel blocker Ba^{2+} significantly shortened the latency to onset of spontaneous activity and increased the frequency of 4AP-induced activity in vigabatrin-treated slices. CGP alone did affect 4AP-induced activity in untreated slices from wild-type mice or GABA transporter type 1 knockout mice (GAT1KO). Vigabatrin treatment had no effect on 4AP-induced activity in slices from GAT1KO mice. Our results indicate for the first time that vigabatrin suppresses *in vitro* epileptiform activity via activation of GABA-B receptors and GIRK channels. This effect of vigabatrin was absent in GAT1KO mice, suggesting that vigabatrin effects are dependent on GAT1 function for either transport of vigabatrin into intracellular compartments (location of GABA transaminase) or for subsequent release of GABA and elevation of ambient GABA levels sufficient to activate GABA-B receptors.

Disclosures: G. Holmes-Leon: None. **N. Li:** None. **R.P. Boyle:** None. **J. Albrecht:** None. **A. Nolan:** None. **C.B. Ransom:** None.

Poster

692. Modulatory GPCR Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 692.04

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: FRM

Title: Autocrine and paracrine action of somatostatin released by O-LM interneurons on the CA1 feedback circuit

Authors: *M. MUSELLA[1], D. DEBANNE[1], S. INCONTRO[2];
[1]Inserm UMR_S 1072, [2]Aix-Marseille University, UMR_1072, Marseille, France

Abstract: Somatostatin (SST) is a neuropeptide whose expression characterises a subpopulation of inhibitoryGABAergic interneurons located in the brain. SST is of great interest in the

pathophysiologicalcontext as a deficit of SST is observed in many neurological and psychiatric diseases such as epilepsy,depression, or schizophrenia. SST exerts its physiological role through different receptors (SSTR1 to5) coupled to a G protein. In the hippocampus, the effects of SST on the principal cells are wellknown. It inhibits excitatory synaptic transmission by decreasing glutamate release from pyramidalneurons and reduces their intrinsic excitability. This decrease in excitability is achieved by facilitatingcurrents carried by Kv7 channels. Within the hippocampus, O-LM interneurons contain SST andexpress Kv7.2/3 channels. However, there is no data on the presence of SST auto-receptors on O-LMinterneurons, on its mode of release and on the effect it might have on the intrinsic excitability ofthese interneurons as well as on the synaptic transmission they have with neighbouring pyramidalneurons. Furthermore, the role of SST modulation of the CA1 feedback circuit remains mostlyunexplored. We therefore studied how SST is released by O-LM interneurons in the hippocampalCA1 and defined its potential inhibitory action by autocrine (on O-LM) and paracrine (on otherpyramidal neurons) pathways. To achieve these objectives, we made single O-LM interneuronsrecordings and dual cell recordings of O-LM interneurons and CA1 pyramidal cells; in order torelease SST endogenously we applied a repeated stimulation protocol at difference frequenciessimulating the known acetylcholine induced non epileptic repetitive discharge. The preliminaryresults obtained suggest that SST transiently decreases the excitability of O-LM interneurons as wellas the synaptic transmission that takes place between the pyramidal cells and the latter and that thereis indeed an autocrine and a paracrine effect of SST that the O-LM interneurons release only followingstimulation at a frequency > 20 Hz. In conclusion, the SST neuropeptide modulates CA1 neuronalactivity by controlling O-LM synaptic excitation as well as O-LM interneurons and CA1 pyramidalcells excitability, thus giving an important contribution in maintaining hippocampal CA1 activitybelow the seizure-triggering threshold.

Disclosures: **M. Musella:** None. **D. Debanne:** None. **S. Incontro:** None.

Poster

692. Modulatory GPCR Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 692.05

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Whitehall Foundation 2021-08-077
Presbyterian Health Foundation

Title: Regulation of oxytocin receptor signaling in neurons

Authors: H. T. M. HOANG, E. TROYANO-RODRIGUEZ, R. Y. NAGARAJA, M.-P. AGBAGA, ***M. AHMAD**;
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Abstract: Social deficits are a prominent feature of autism spectrum disorder and many other neuropsychiatric diseases. Since there are currently no drugs available to treat these debilitating symptoms, it is critical to decipher the neuronal mechanisms underlying social behavior and their impairments in mental illnesses. Oxytocin, first discovered as a hormone that strengthens contractions during labor and facilitates lactation, has subsequently been found to have a critical role as a neuromodulator regulating social behavior. Recent work has begun to clarify how oxytocin acts on neuronal circuits to modify inter-neuronal communication and circuit properties. However, there is a large gap in the understanding of the intracellular signaling pathways that are activated by oxytocin acting on its receptor in neurons. In particular, the regulatory mechanisms that control oxytocin receptor (OXTR) signaling in neurons remain unexplored. We have identified robust and rapid-onset desensitization of OXTR response in multiple regions of the mouse brain. Sequential application of OXTR agonists reveals that spiking of neurons in acute brain slices in response to the second application of the agonist is smaller than the first response, indicating OXTR desensitization. The intracellular mobilization of calcium in response to OXTR activation in primary neuronal cultures also undergoes desensitization. Recordings in β-arrestin 1 and 2 knockout mice reveal that these β-arrestin isoforms are individually redundant for neuronal OXTR desensitization. Further experiments will test whether deletion of both isoforms has an effect on this process. In order to identify the molecular motifs within OXTR that are required for desensitization, we have generated a series of mutations in the C-terminal tail that impair specific forms of post-translational modifications. Systematic testing of these mutants shows that agonist-dependent phosphorylation and palmitoylation play an important role. Finally, we have used proximity labeling technique utilizing biotin ligase miniTurbo to label OXTR-associated proteome in primary cultured cortical neurons, which elucidates the proteins that associate with neuronal OXTR to affect its regulation in the brain. Our work provides insights into the regulatory mechanisms governing an important G protein-coupled receptor in the brain and may uncover novel targets for the future development of therapeutic agents that alleviate social deficits in neuropsychiatric disorders.

Disclosures: **H.T.M. Hoang:** None. **E. Troyano-Rodriguez:** None. **R.Y. Nagaraja:** None. **M. Agbaga:** None. **M. Ahmad:** None.

Poster

692. Modulatory GPCR Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 692.06

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: VR 2018-03320
VR 2018-05501
VR 2018-03988
SSF RIF14-0078
SSF ICA16-0010

Title: Thermal proteome profiling for characterization of melanocortin receptor activation with endogenous neuropeptides

Authors: F. A. SANDBAUMHÜTER, M. NEZHYVA, P. E. ANDRÉN, ***E. T. JANSSON**; Pharmaceut. Biosci., Uppsala Univ., Uppsala, Sweden

Abstract: G-protein coupled receptors are largely responsible for cell-to-cell signaling as receivers of messages mediated by neurotransmitters and neuropeptides. The involvement of melanocortin receptors in several diseases related to energy homeostasis such as obesity and anorexia make this family of melanocortin receptors a potential target to alleviate these disease states.
We have established a workflow based on thermal proteome profiling to investigate indirect interactions in the biochemical pathways downstream of the melanocortin 3 receptor and three of its endogenous peptides: alpha-MSH, gamma-MSH and ACTH. Since proteins bound to ligands are thermally stabilized, these will during a heat ramp stay more resistant to denaturation and not aggregate. Similarly, proteins unbound from a ligand get thermally destabilized and will be more prone to denaturation. Analysis of the soluble fraction of cell lysates in a temperature range and in presence of a ligand reveals the proteins that interact with named ligand. When performed on whole HEK-293 overexpressing MC3R, this method further extends to provide information about proteins affected downstream in the pathway.
Our preliminary data show that for each of the three endogenous ligands, i.e., ACTH, alpha-MSH and gamma-MSH we observed ~100 proteins that were thermally stabilized or destabilized. Some of these proteins belong to reaction pathways related to RHO GTPases, MAPK kinases and gene transcription. These pathways are expected to be affected downstream of melanocortin receptor activation. Interestingly, some of the affected proteins are involved in carbohydrate metabolism as well as NMDA receptor activation. Further, for proteins found to be thermally stabilized or destabilized after stimulation with a ligand, we estimate the EC50 for each protein to assess similarities or differences between the three different ligands. We also investigate to what extent protein expression is affected by ligand stimulation using our model system. Dose dependent up/down regulation is measured with label-free quantitative proteomics and is correlated to the ligand-protein interaction observed with thermal proteome profiling.
We show how neuropeptides from a common prohormone (proopiomelanocortin) appear to affect similar biochemical pathways, but in distinguished ways.

Disclosures: F.A. Sandbaumhüter: None. **M. Nezhyva:** None. **P.E. Andrén:** None. **E.T. Jansson:** None.

Poster

692. Modulatory GPCR Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 692.07

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: RO1MH118258

Title: Neuromedin B excites neurons of the basolateral amygdala through inhibition of Kir channels and activation of non-selective cation channels

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Abstract: The bombesin (BB) family of peptides includes the mammalian members neuromedin B (NMB) and gastrin-releasing peptide that interact with two G-protein coupled BB receptors, BB1Rs and BB2R, respectively, and have been implicated in neuropsychiatric disorders including anxiety. BB1Rs and BB2Rs signal through a pertussis toxin insensitive G-protein resulting in the activation of phospholipase C (PLC) that hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) generating the secondary messengers inositol 1,4,5-trisphosphate (IP_3) leading to release of intracellular Ca^{2+}, and diacylglycerol activating protein kinase C (PKC). Whereas high densities of BB1Rs are expressed in the basolateral amygdala (BLA), an area involved in fear and anxiety-like responses, the function of BB1Rs in this nucleus have not yet been fully determined. Using whole cell patch clamp electrophysiology, we found that activation of BB1Rs by its endogenous ligand, NMB, excited BLA principal neurons in brain slices collected from male and female SD rats. NMB-mediated excitation of BLA neurons was mediated by inhibition of inwardly rectifying potassium channels and the activation of non-selective cation channels. With targeted pharmacology and knockout mice, we determined that BB1R activation excited BLA neurons via the inhibition of a G protein-coupled inwardly rectifying K^+ (GIRK) channels and activating a transient receptor potential (TRP) channel. Preliminary data suggests NMB activates TRPV1 channels. The effects of NMB on excitability required activity of PLC, PKC, and intracellular Ca^{2+} release. As membrane PIP_2 is known to regulate ion channel activity, we further demonstrated that NMB-elicited excitation involves phosphoinositide dynamics as modulation of membrane PIP_2 content significantly affected BLA neuronal excitability. These data may explain a signaling and ionic mechanism whereby BB1R activation modulates fear and anxiety-like responses.

Disclosures: C. Boyle: None. **S. Lei:** None.

Poster

692. Modulatory GPCR Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 692.08

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: National Science Centre, Poland (2016/20/S/NZ7/00424)

Title: Gpr39 knockout mice do not differ from wild-type mice in terms of total zinc content of the hippocampus

Authors: *U. DOBOSZEWSKA[1], A. SAJNÓG[2], D. BARAŁKIEWICZ[2], P. WLAź[3];
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[3]Maria Curie Sklodowska Univ., Lublin, Poland

Abstract: Motivation: Zinc homeostasis is important in diseases of the central nervous system which are characterized by a defective balance between excitation and inhibition, such as epilepsy. The role of extracellular zinc signaling via the G-protein coupled receptor 39 (GPR39) in inhibitory neurotransmission was proposed by Chorin et al. (2011). Moreover, GPR39 was suggested as a novel drug target for dampening seizures by Gilad et al. (2015). We further explored the phenotype of GPR39 knockout (KO) and wild-type (WT) mice in terms of the seizure threshold or epileptogenesis. The genotype did not influence the seizure threshold in response to maximal electroshock. Also, it did not affect epileptogenesis induced by pentylenetetrazole (PTZ)-kindling. However, we observed decreased total serum zinc concentration in GPR39 KO mice subjected to the PTZ-kindling model, compared to WT that underwent this procedure. Since zinc may be an agonist of GPR39 receptor, we examined whether the changes in serum zinc in GPR39 KO mice are accompanied by alteration in zinc content of the hippocampus, a brain region important for epileptogenesis.Methods: GRP39 KO mouse model was generated by the Mouse Genome Engineering Facility (crisprmice.eu) in mixed genetic background (C57BL6/Tar x CBA/Tar). A deletion of 44 bp causing p.Lys38fs*57X frameshift mutation was introduced. GPR39 KO and WT mice were subjected to the PTZ-kindling model of epilepsy (approval number 72/2019 of the Local Ethical Committee in Lublin). GPR39 KO and WT mice received GPR39 agonist, compound TC-G 1008 (10 mg/kg i.p.) or vehicle 30 min before each dose of PTZ (25 mg/kg) (dose and pre-treatment time based on previous studies). The model consisted of 13 injections of PTZ. 24 h after the completion of the kindling paradigm, the brains of mice were dissected. 12 µm hippocampal coronal sections were prepared. Total zinc content was analyzed in hippocampal sections using Laser Ablation Inductively Coupled Plasma Mass Spectrometry (LA-ICP-MS). 4 brains per group were analyzed in 3 replicates.**Results**: The LA-ICP-MS method did not reveal differences in total zinc level in the hippocampus between GPR39 KO and WT mice subjected to the PTZ-kindling model, that received either vehicle or TC-G 1008.**Conclusions**: The lack of differences was shown by a method which detects total level of an element, i.e., the form bound to proteins and the ionic form. The results thus suggest lack of interference of the genotype with zinc-binding proteins. The lack of differences in zinc level in the hippocampal tissue may be due to homeostatic mechanisms tightly controlling the brain levels.

Disclosures: U. Doboszewska: None. **A. Sajnóg:** None. **D. Barałkiewicz:** None. **P. Wlaź:** None.

Poster

692. Modulatory GPCR Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 692.09

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: MH123757
MH120212

Title: Gpr88 ciliary enrichment is regulated by its third intracellular loop and CT and tulp3

Authors: *A. T. EHRLICH[1], B. L. KIEFFER[2], M. VON ZASTROW[3];
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Abstract: GPR88 is an orphan G protein-coupled receptor (GPCR) that critically modulates dopamine-dependent behaviors making it an attractive therapeutic target for the treatment of neuropsychiatric illness. GPR88 is an unusual GPCR because it localizes to the primary cilium of some neurons (striatal) but not others (cortical). The primary cilium has been shown to be a specialized signaling compartment. Here, we are investigating how GPR88 directs its actions on medium spiny neurons (MSNs) and to what extent does its localization to cilia influence its cellular response. We first asked whether GPR88 is essential for ciliogenesis? Cilia density and length were measured in the striatum and found to be similar in GPR88-WT and GPR88-KO animals with no significant differences between males and females. We next looked for structural determinants for ciliary targeting of GPR88 in IMCD3 cells and identified the third intracellular loop and C-terminus as regions involved in ciliary enrichment of GPR88. Further, using siRNA knockdown and CRISPR/Cas9 gene editing, we found that GPR88 ciliary enrichment is dependent on ciliary machinery including Tulp3 but not Rab23. Our preliminary results using transiently expressed Flag-GPR88 in MSNs shows that it localizes to plasma membrane, endosomes and is enriched in ciliary compartments. Finally, we have recently begun interrogating the role of GPR88 in MSNs using genetically encoded cAMP and PKA biosensors. Our preliminary findings in both overexpression and endogenous receptor expression systems suggest that, using a synthetic agonist, GPR88 activation can weakly inhibit dopamine D1 induced cAMP production. Manipulations of GPR88 ciliary localization are underway to delineate the signaling function of ciliary GPR88 further. Taken together, GPR88 ciliary enrichment depends on its third intracellular loop, C-terminus as well as the ciliary adaptor protein, Tulp3.

Disclosures: A.T. Ehrlich: None. **B.L. Kieffer:** None. **M. Von Zastrow:** None.

Poster

692. Modulatory GPCR Signaling

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 692.10

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Brain & Behavior Research Foundation

Title: The role of GPR171 in anxiety and depression in female mice

Authors: *M. C. RADDATZ[1], M. MATTOON[2], E. N. BOBECK[1];
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Abstract: Depression is a major crisis that affects approximately 15 million people in the United States. Of those affected, the majority are female. Despite the prevalence of depression, the therapeutic treatments are limited due to side effects, potential hormonal interactions, or restricted efficacy. One of the most promising sources of pharmaceutical targets includes G-protein coupled receptors (GPCR). Of particular interest is a novel recently de-orphanized GPCR, GPR171. Previously, we have shown that agonism of the receptor alleviates chronic pain. However, due to the novel nature of the receptor, no study has looked at the receptor's role in anxiety and depression in female mice. Given that the agonist relieves chronic pain with repeated use, we set out to determine if this treatment leads to negative sides effects in depression and anxiety. Female C57BL/6 mice were injected with either a GPR171 agonist or vehicle for 6 days. On day 7 mice were subjected to the open field test (OFT), elevated plus maze (EPM), and forced swim test (FST) to assess anxiety and depression. Time spent in the center vs. the outer edge of the OFT and time spent in the open arms vs. closed arms in the EPM was automatically recorded using ANYmaze software. Immobility in the forced swim was recorded by two independent scorers blind to the drug treatment. Results indicate that while activation of the receptor does not have any major effects on anxiety in the OFT or EPM, the agonist decreased immobility time in the FST representing a reduction in depression-like behaviors when compared to vehicle-treated mice. These effects are unlikely to be attributed to any differences in movement seeing as agonist-treated mice and vehicle-treated mice did not differ significantly in total distance traveled in the EPM or OFT. These effects also hold regardless of the estrus stage the mice were in, though further testing will elucidate on the interaction between the receptor and estrogen levels. Together, these findings identify a GPR171 agonist as a potential pharmaceutical target for depression in female mice and further support its use in treatment of chronic pain.

Disclosures: M.C. Raddatz: None. **M. Mattoon:** None. **E.N. Bobeck:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.01

Topic: B.05. Synaptic Plasticity

Support: NIH R01 NS062736
NIH T32 GM099608
NIH F99 NS125772
ARCS Fellowship

Title: Prior potentiation initiates a synapse-specific refractory period for plasticity at individual dendritic spines

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Abstract: Learning is crucial for survival. One intriguing aspect of learning in humans is that the efficiency of learning can be improved when there are breaks between episodes of learning. One area of the brain important for formation of long-term memories is the hippocampus. In hippocampal circuits, it has been shown that long-term potentiation (LTP) of synaptic strength, a cellular mechanism proposed to underlie learning, is more effective when repeated stimuli are temporally spaced. Excitatory synaptic connections in the hippocampus occur at small protrusions on dendrites called dendritic spines, which increase in size as synaptic strengths are increased during learning. We propose that the spaced timing requirement for learning is the result of a synapse-specific temporary refractory period induced by prior LTP at individual dendritic spines. Here, we use 2-photon glutamate uncaging and time-lapse imaging to show that individual dendritic spines, which exhibit long-term growth and AMPAR insertion in response to LTP-inducing glutamatergic stimuli, are unable to exhibit further plasticity in response to the same stimulus 30 minutes later. Notably, size-matched spines on the same cell undergo normal plasticity, supporting that the refractory period is restricted to stimulated spines. Interestingly, if the interval between stimuli is increased to 60 minutes, plasticity is recovered, indicating that the required molecular signaling pathways have returned to baseline in this time frame. We began to explore the signaling mechanisms responsible for this refractory period by probing the activation of CaMKII, a kinase critical for LTP and learning. Using 2-photon fluorescence lifetime imaging (2p-FLIM) of a genetically-encoded CaMKII FRET probe, we found that 30 minutes after plasticity induction at single spines, CaMKII activation in response to glutamatergic stimulation was significantly reduced. Importantly, size-matched control spines did not exhibit reduced CaMKII 2p-FLIM signals and there was no correlation between spine size and CaMKII sensor activity in response to glutamatergic stimulation. We are currently investigating the mechanisms that lead to this plasticity-induced reduction in CaMKII signaling. This work will further our understanding of the signaling mechanisms that underlie learning.

Disclosures: J. Flores: None. **K. Zito:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.02

Topic: B.05. Synaptic Plasticity

Support: R01 NS091010
R21 NS112750
R21 NS109722
R01 DC014690
R01 EY025349

P30 EY022589
F32 NS103267

Title: Local functional interactions determine eligibility for synapse elimination during learning

Authors: *N. HEDRICK[1], Z. LU[2], E. A. BUSHONG[5], Y. MAGAÑA[3], S. JILANI[3], B. LIM[4], M. H. ELLISMAN[6], T. KOMIYAMA[7];
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Abstract: Synaptic connections in the brain are dynamic, and show turnover during learning. During motor learning, neurons in the primary motor cortex (M1) show both outgrowth of new synapses and elimination of pre-existing ones. However, what types of functional information are selected or removed at the synaptic level - and how such selection occurs - remain unclear. We recently demonstrated that new synapses formed in M1 during motor learning display clustered encoding of learned behaviors with neighboring synapses on the same dendrite, pointing to the structuring of local correlations as a central “goal” of synapse turnover. We therefore hypothesized that the elimination of pre-existing synapses would also subserve the structuring of local correlations. To this end, we performed longitudinal *in vivo* 2-photon imaging of glutamatergic inputs on dendritic spines in M1 during motor learning. We found no evidence that the functional properties of individual spines taken in isolation predict their own future elimination. For example, the frequency of activity was not different between eliminated and stable spines, ruling out the possibility that elimination occurs due to disuse. Eliminated spines also showed activity levels comparable to maintained spines during rewarded movements, illustrating that task engagement alone is insufficient to explain elimination. Instead, we found that local correlations are a critical component of determining the elimination of pre-existing spines. Specifically, spines that are eventually eliminated showed lower co-activity with nearby spines on the same dendrite earlier in learning. Furthermore, movement kinematic encoding of pre-existing spines had a predictive power for spine elimination and formation; that is, spine elimination was less likely, and formation was more likely, in the vicinity of pre-existing spines that are active during movements with the learned kinematic pattern. Thus, a single spine’s activity taken in isolation is a poor predictor of its survival. Instead, local correlation patterns - and the associated movement encoding features - predict synaptic longevity during learning. Despite these features that affect the likelihood of spine eliminations, we find no evidence that elimination is differentially likely to occur nearby other structural plasticity events. This is in contrast to spine formation, which is known to cluster nearby enlargement and other new spines Elimination therefore appears to occur sparsely, and does not facilitate further expression of similar plasticity mechanisms, illustrating a distinct strategy for the removal of information streams from a neuron’s input repertoire.

Disclosures: **N. Hedrick:** None. **Z. Lu:** None. **E.A. Bushong:** None. **Y. Magaña:** None. **S. Jilani:** None. **B. Lim:** None. **M.H. Ellisman:** None. **T. Komiyama:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.03

Title: WITHDRAWN

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.04

Topic: B.05. Synaptic Plasticity

Support: NIH R01 MH123212
NIH R21 AG063193
Kavli Neuroscience Discovery Institute
Schmidt Science Foundation Nascent Innovation Grant

Title: Imaging millions of synapses and tracking plasticity in behaving mice

Authors: *A. R. GRAVES[1,2], G. COSTE[1], T. XU[1], D. BERGLES[1], J. SULAM[2], A. CHARLES[2], R. HUGANIR[1];
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Abstract: Synaptic plasticity is a widely studied model of learning and memory that directly links molecular changes at synapses—the sites of neurotransmission and communication between neurons—to changes in the strength of neural circuits. Potentiation of excitatory synapses is observed during many forms of learning, while synaptic degradation is observed in neurological diseases. Unfortunately, due to their small size and high density, synapses are extremely difficult to observe in vivo, and even harder to track over time. Thus, our ability to directly relate synaptic plasticity with behavior is severely limited. To address this crucial limitation, we have genetically labeled endogenous AMPA-type glutamate receptors (AMPARs), allowing direct visualization of millions of excitatory synapses in behaving animals using in vivo two photon microscopy. Further, we have developed, validated, and implemented a first-in-class machine learning algorithm capable of detecting millions of individual synapses and tracking how they change over time. Applied to in vivo images from transgenic mice with fluorescently labeled AMPARs, this restoration algorithm super-resolves diffraction-limited synapses, enabling longitudinal tracking of synaptic plasticity in vivo and direct visualization of fundamental mechanisms of learning with unprecedented spatial resolution.

Disclosures: A.R. Graves: None. **G. Coste:** None. **T. Xu:** None. **D. Bergles:** None. **J. Sulam:** None. **A. Charles:** None. **R. Huganir:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.05

Topic: B.05. Synaptic Plasticity

Support: NIH Grant NS094499
Harold and Leila Y. Mathers Charitable Foundation
Discovery Innovation Fund in Basic Biomedical Sciences from Stanford University

Title: The synapses outside the basket: Exploring the distal synapses of parvalbumin basket cells

Authors: *K. D. MICHEVA, M. M. PEREZ, D. V. MADISON;
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Abstract: Parvalbumin-containing baskets cells in mammalian cortex are best known for the "baskets" of synapses by which they cover the somata and proximal dendrites of pyramidal neurons providing powerful inhibition. However, these interneurons also target distal dendrites by synapses that likely have different functions compared to perisomatic synapses. Here we focus on the less explored distal parvalbumin (PV) synapses by combining analysis of synaptic connection maps of PV interneuron to pyramidal neuron pairs previously generated by us using immunofluorescence array tomography (IF AT), together with two publicly available datasets of serial section transmission electron microscopy (ssTEM, Bock et al. 2011, Lee et al. 2016), and conjugate immunofluorescence - scanning electron microscopy array tomography (IF-SEM AT, Collman et al. 2015) from adult mouse cortex. Analysis of the synaptic connection maps of PV to pyramidal neuron pairs reveals that individual PV neurons use different axonal paths to preferentially contact perisomatic vs. more distal locations of the same postsynaptic neuron. PV axonal paths that synapsed onto the soma or proximal dendrites (within 25 µm from soma), had only 15% of their synapses targeting more distal locations of that neuron, compared to an average of 43% distal synapses. Among the distal PV synapses, those targeting dendritic spines are of particular interest. Inhibitory synapses on spines are known to be highly plastic and almost always share the spine with an excitatory synapse, the origin of which is still disputed. We used the ssTEM datasets where PV axons could be reliably identified by the formation of symmetric synapses (ultrastructural hallmark of inhibitory synapses), and the presence of myelin sheath (characteristic of PV interneurons). More than 25% of PV synapses in l2/3 of adult mouse visual cortex were on dendritic spines, the great majority of which also received an excitatory synapse. The excitatory synapses on these spines showed variable morphologies, in many cases resembling synapses of pyramidal neurons, contrary to previous reports that these are thalamocortical synapses. Indeed, conjugate IF-SEM of mouse cortex showed that the excitatory synapses on dually innervated spines are often VGluT1-immunopositive and therefore likely of intracortical origin. We conclude that PV neurons exhibit selective axonal targeting that could enable nuanced control of the postsynaptic neuron, either via perisomatic synapses to hyperpolarize the neuronal soma and prevent action potential firing, or via distal synapses to inhibit specific intracortical or subcortical input to the neuron.

Disclosures: **K.D. Micheva:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KDM has founder's equity interests in Aratome, LLC (Menlo Park, CA), an enterprise that produces array tomography materials and services.. **M.M. Perez:** None. **D.V. Madison:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.06

Topic: B.05. Synaptic Plasticity

Title: The benzodiazepine diazepam alters microglial synaptic engulfment via translocator protein (18 kDa)

Authors: *J. HERMS[1,3,4], M. CUI[1,3,2], G. RAMMES[5], Y. SHI[1,3,4];
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Abstract: Benzodiazepines are widely prescribed drugs to treat insomnia and anxiety and have been long suspected of causing cognitive impairment by various mechanisms, including elimination of synapses. On both physiological and pathological conditions, microglia have emerged as one of the major contributors to synaptic elimination. However, whether benzodiazepines affect synaptic elimination by microglia remains elusive. To explore the impact of benzodiazepines on microglial synaptic engulfment, we gave wild-type mice a daily administration of the commonly used benzodiazepine diazepam, for one week (5 mg/kg), and observed increased complexity and volume of microglia. Then we employed the *CX3CR1-eGFP : Thy1-YFP-H* mice, in which microglia and post synaptic compartments (dendritic spines) are respectively labelled with green and yellow fluorescent proteins. Using the 2 photon *in vivo* imaging, the frequency of microglia-dendritic spine contact rises after diazepam treatment accompanied by a decreased survival rate of microglia-contacted dendritic spines by the end of the one-week diazepam administration. To investigate the mechanism underlying the diazepam-induced microglial alterations, we subsequently blocked binding sites of diazepam in the central nervous system. We first employed the *TSPO knockout* (*TSPO* $^{-/-}$) mice, in which one of the major binding sites of diazepam – the 18 kDa translocator protein (TSPO) is genetically depleted. In *TSPO* $^{-/-}$ mice, we observed that diazepam administration alters neither microglia morphology nor their engulfment of synaptic materials. While blocking another major binding site of diazepam – $GABA_A$ receptors ($GABA_AR$) in transgenic mice with quadruple (H-R) point mutation of $GABA_AR$, in which a1, a2, a3 and a5 subunits lack the histidine residue necessary for diazepam binding, failed to prevent alterations of microglia. These results collectively demonstrated that diazepam alters microglia morphology, microglial-synapse interaction and subsequent synaptic engulfment in a TSPO dependent manner. Our results identify TSPO as a

potential target for interfering microglial synaptic elimination not only in physiological condition, but also in various neurodegenerative diseases, in which TSPO expression elevates aberrantly, such as Alzheimer's disease.

Disclosures: **J. Herms:** None. **M. Cui:** None. **G. Rammes:** None. **Y. Shi:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.07

Topic: B.05. Synaptic Plasticity

Support: T32GM007635
F32 AG071073
R35NS116879
UF1NS107710
NS110383
T32NS099042
NIMH R01MH124778

Title: Dually innervated dendritic spines develop in the absence of excitatory input and resist structural plasticity

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Abstract: Dendritic spines, the primary sites of excitatory synaptic connectivity in the central nervous system, can be contacted by both an excitatory and an inhibitory presynaptic terminal resulting in nanometer-scale proximity of opposing synaptic functions. Dually innervated spines (DiSs) have been observed on principal neurons throughout the neocortex where they represent up to 25-30% of spine synapses and account for approximately one third of total dendritic inhibitory inputs. While DiSs are widely observed, how or whether they are functionally distinct from neighboring, singly innervated spines (SiSs) is unclear. In addition, the developmental timeline and functional properties of DiSs remain uncharacterized. Here we used a combination of serial section electron microscopy, live imaging and local synapse activity manipulations to investigate DiSs in hippocampus. Dual innervation occurred early in development, even on spines where the excitatory input was locally silenced with tetanus neurotoxin. Synaptic NMDA receptor currents were selectively reduced at DiSs through tonic GABAB receptor signaling. Accordingly, spine enlargement normally associated with long-term potentiation on SiSs did not

occur at DiSs. Silencing somatostatin interneurons or pharmacologically blocking GABABRs restored NMDA receptor function and structural plasticity to levels comparable to neighboring SiSs. Thus, hippocampal DiSs are stable structures where function and plasticity are potently regulated by tonic, nanometer-scale GABAergic signaling.

Disclosures: **M.S. Kleinjan:** None. **W.C. Butcha:** None. **R.A. Ogelman:** None. **I. Hwang:** None. **M. Kuwajima:** None. **D. Hubbard:** None. **D.J. Kareemo:** None. **O. Prikhodko:** None. **W.C. Abraham:** None. **S.J. Franco:** None. **K.M. Harris:** None. **W. Oh:** None. **M.J. Kennedy:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.08

Topic: B.05. Synaptic Plasticity

Support: Vetenskapsrådet
Hjärnfonden

Title: Regulation of Nogo receptor 1 protein by chemical long term potentiation

Authors: *A. T. BRODIN, J. SPIELBAUER, K. WELLFELT, L. OLSON, T. E. KARLSSON; Neurosci., Karolinska Inst., Solna, Sweden

Abstract: The formation of lasting memories requires structural alterations of the neuropil. Nogo receptor 1 (NgR1) is a potent negative regulator of plasticity that is strongly expressed in the hippocampus. It is thus an important question how this inhibition can be overcome to allow for the formation of lasting memories. One hypothesis is that certain types of neural activity can regulate the expression of inhibitory molecules including NgR1, but this has yet to be shown conclusively. We utilize quantitative immunohistochemistry on primary hippocampal cell cultures to assess levels of NgR1 protein in different cellular compartments after chemical long-term potentiation (LTP) or long-term depression (LTD). We find that chemical LTP induces a rapid (~15-30 min) and lasting (>3h) significant downregulation of NgR1 protein throughout the neuron. We also detect a trend towards increased NgR1 levels in the same time frame after a chemical LTD protocol. Further we present data on the synaptic localisation of NgR1 during these processes. These results implicate NgR1 downregulation as a possible early event in memory formation.

Disclosures: **A.T. Brodin:** None. **J. Spielbauer:** None. **K. Wellfelt:** None. **L. Olson:** None. **T.E. Karlsson:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.09

Topic: B.05. Synaptic Plasticity

Support: Takeda Pharmaceutical Company Limited

Title: Establishment of an in vitro assay system of neuronal cell death to investigate the risk and mechanism of seizure inducing activities of GluN2A positive allosteric modulators

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Abstract: *N*-methyl-$_D$-aspartate (NMDA) receptors play important roles in a variety of neural activities in the central nervous system, including excitatory synaptic transmission, synaptic plasticity, neurodevelopment, and neurodegeneration, and are closely linked to neuronal survival. Drugs that modulate the function of NMDA receptors would improve cognitive function such as learning and memory, and have potential to treat psychiatric disorders such as depression. On the other hand, excessive NMDA receptor activation has been reported to cause neuronal cell death triggered by a drastic response of intracellular Ca^{2+} influx and to induce abnormal electrical excitation of neurons, resulting in the induction of seizure such as epilepsy. Therefore, it is important to estimate the risk of seizure induction by drug candidates at the early stage of drug discovery research of NMDA receptor activators. However, in vivo experiments are generally more expensive and time consuming than in vitro experiments and the results of in vivo studies are often affected by the brain penetrability of test compounds. In this study, we established an in vitro neuronal cell death assay to estimate the risk of seizure induction using primary cultured neurons from Sprague-Dawley rats, and evaluated positive allosteric modulators (PAMs) of GluN2A, an NMDA receptor subtype, in this assay system. A total of 21 known and newly generated compounds were tested with the in vitro neuronal cell death assay using intracellular ATP content as a readout and followed by observation study to evaluate the seizuregenicity of compounds with brain penetration in male Institute of Cancer Research (ICR) mice. The results showed that correlation between unbound compound concentrations in the brain in which seizure was observed and in vitro cell death-inducing effects was confirmed in ICR mice, suggesting the in vitro neuronal cell death assay would be useful to evaluate the risk of seizure induction. In addition, to examine the contribution of GluN2A to the neuronal cell death by test compounds, we evaluated the cell death-inducing activity using primary cultured neurons from wild-type (WT) and GluN2A knockout (KO) rats. We found that the newly synthesized compounds induced cell death in primary cultured neurons from KO rats in a dose dependent manner as well as in ones from WT rats, suggesting a contribution of GluN2A to the neural toxicity by compounds tested was low. In summary, our in vitro neuronal cell death assay would be applicable to evaluate the risk of seizuregenicity of compounds and be useful to further analyze the mechanism of seizuregenicity.

Disclosures: **T. Hirakawa:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **K. Nakashima:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **Y. Yamamoto:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **E. Sunahara:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **N. Narita:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **T. Hasui:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **A. Nakatani:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **K. Suzuki:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **H. Iwashita:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.10

Topic: B.05. Synaptic Plasticity

Support: NIH-NINDS (R35 NS127232)
Nomis foundation (FP)

Title: Srgap2a and its human-specific paralog srgap2c regulate structural forms of synaptic plasticity in the adult cortex

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Abstract: The cellular, molecular and genetic mechanisms underlying human brain evolution are still poorly understood. More specifically, the molecular basis underlying human-specific features of synaptic development or synaptic plasticity is largely unknown. Our lab identified a human-specific gene duplication called SRGAP2C which, by inhibiting all known functions of the post-synaptic protein SRGAP2A, leads to slower rates of excitatory (E) and inhibitory (I) synaptic maturation and increased synaptic density (Charrier et al. 2012; Fossatti et al. 2016). We have recently shown that this increased density of E synapses in cortical layer 2/3 pyramidal neurons (PNs) originates from increased cortico-cortical connections and leads to changes in the coding properties of these neurons in vivo as well as improved behavioral performance in a sensory discrimination task (Schmidt et al. 2021). Since both SRGAP2A and SRGAP2C are still expressed in adult cortical PNs, we tested if they play a role in synaptic plasticity. A model system to induce structural forms of synaptic plasticity (whisker trimming) leads to striking increase in dendritic spine turnover in juvenile mice but not in wild-type adult mice. Using first a constitutive SRGAP2A knockout mouse model, we found that whisker trimming in adult (>P90) $SRGAP2A^{+/-}$ mice induce striking increase in spine density 3-5 days post-trimming which is due to higher rates of spine formation than the accompanied increase in spine elimination. As

expected based on previously published studies, whisker trimming in adult wild-type littermates did not induce any significant changes in spine density or dynamics. Since SRGAP2A and SRGAP2C are not only expressed in cortical PNs but also in microglial cells which play a critical role in synaptic plasticity, we tested whether cortical PNs-specific SRGAP2A deletion (or humanization of SRGAP2C expression) is required for this form of structural plasticity in adult cortex. We used a conditional SRGAP2A knockout mouse and performed sparse, Cre-mediated deletion, in layer 2/3 PNs which revealed a significant but lower magnitude increase in dendritic spine increase than in the constitutive SRGAP2A$^{+/-}$ mice, hinting at the possibility that expression of SRGAP2A/C in microglial cells participates to this form of structural plasticity in adult cortical circuits. We are testing this using microglial specific SRGAP2A deletion.Altogether, our data suggest (1) that SRGAP2A exerts a novel role in limiting structural forms of synaptic plasticity and (2) that in the human cortex, synapses might still be able to undergo structural forms of plasticity past the critical period.

Disclosures: S. Bernal Garcia: None. **J. Tsai:** None. **A. Losonczy:** None. **F. Polleux:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.11

Topic: B.05. Synaptic Plasticity

Support: 1R01NS116051-01A1

Title: Differential roles of NSG1 and NSG2 on synaptic function, anxiety, learning and memory

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Abstract: Members of the neuron-specific gene family (NSG1-3) are small endolysosomal proteins that have been implicated in the trafficking and processing of multiple receptors and signaling proteins specifically in neurons. Critically, NSG3 levels are altered in brains of Schizophrenic patients while NSG1 and NSG2 have been shown to interact with proteins associated with Alzheimer's Disease. However, all NSG proteins are best characterized for their diverse roles in the regulation of synaptic strength via modulation of AMPAR trafficking. Previous work shows that NSG1 promotes recycling of AMPARs to the plasma membrane during long-term potentiation while NSG2 promotes heightened synaptic strength during basal activity. Additionally, our lab has shown that NSGs occupy only a minority of synapses when assessed in fixed samples. This suggests that either NSGs traffic between synapses to affect function or are selectively targeted to a unique subset of synapses. We first show that NSG2 was found more often co-localized with PSD95 (~30%) compared to NSG1 (~15%). Furthermore,

using time-lapse imaging of mNG-NSG1/NSG2 we show that both NSG1 and NSG2 appear to be selectively targeted to a subset of synapses rather than being trafficked between dendritic spines. Lastly, we found that individual KO of NSG1 or NSG2 in C57Bl/6 mice affects behavior in largely divergent ways. It is likely that differences in protein-protein interactions sub serve these different spatial and functional properties. Our data suggests that NSGs are involved in plasticity and therefore in synaptic function. Thus, our future work aims to determine the protein interactome of NSG family members at the plasma membrane using novel proximity-based biotin labeling to find novel protein interactions.

Disclosures: A. Serrano Rodriguez: None. **A. Zimmerman:** None. **P. Chander:** None. **S. Wilson:** None. **J.P. Weick:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.12

Topic: B.05. Synaptic Plasticity

Support: AHA-Allen Initiative in Brain Health and Cognitive Impairment award made jointly through the American Heart Association and The Paul G. Allen Frontiers Group: 19PABH134610000AHA
NIH Grant 1R21AG068967-01
Larry L. Hillblom Foundation
Don and Lorraine Freeberg Foundation
Fiona and Sanjay Jha Chair in Neuroscience

Title: Lost scaling between subsynaptic components in the dorsolateral prefrontal cortex may underlie aging-related working memory impairment in the common marmoset (Callithrix jacchus)

Authors: *C. GLAVIS-BLOOM[1], C. R. VANDERLIP[1], S. WEISER NOVAK[1], M. KUWAJIMA[2], L. M. KIRK[2], K. M. HARRIS[2], U. MANOR[1], J. H. REYNOLDS[1];
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Abstract: Subsynaptic components such as boutons, synapses, and mitochondria are highly correlated in their sizes and are anatomical indicators of synaptic efficacy. To investigate how these correlations change with age and cognitive impairment, we quantified morphological characteristics of subsynaptic components in the common marmoset. The marmoset shares key, primate-specific neuroanatomical features, cognitive capacities, and aging phenotypes with humans, and their short lifespan enables longitudinal studies of aging. We measured working memory capacity in a cohort of aging marmosets and found age-related impairment. We also found a remarkable degree of heterogeneity in cognitive aging trajectories. We focus here on the dorsolateral prefrontal cortex (dlPFC) because it is critical for working memory and undergoes

morphological and functional changes early in the aging process. Using electron microscopy, we visualized ultrastructure in layer III of the dlPFC from three marmosets: a young adult, an aged cognitively unimpaired animal, and an aged cognitively impaired animal. Through unbiased stereological methods, we segmented boutons, synaptic mitochondria, and synapses, and reconstructed them in three dimensions to quantify morphology. This approach revealed both age-related differences and differences between the cognitively unimpaired from the cognitively impaired marmoset. Consistent with prior observations in macaques, we find that aged marmosets have fewer synapses than young marmosets, and the remaining synapses have an increased surface area. In addition, we find that synapse size is even larger in the aged marmoset with cognitive impairment, as compared to the unimpaired aged marmoset. Bouton size was also increased with age but did not vary significantly across impaired and unimpaired aged marmosets. To assess synaptic efficacy, we measured whether subsynaptic ultrastructure changes were proportionately scaled. We found that the ratio of synapse to bouton size was maintained in the young adult and aged unimpaired marmosets, whereas in the aged impaired marmoset, the ratio was significantly larger. Since mitochondria provide energy to fuel synaptic transmission, and their size is correlated with energy production, we assessed the ratio of synapse to mitochondria size. We found that, in the aged impaired marmoset, mitochondria were disproportionately smaller than expected for the size of the synapse with which they were associated. Together, these results demonstrate a loss of scaling between subsynaptic components that is specific to age-related cognitive impairment.

Disclosures: C. Glavis-Bloom: None. **C.R. Vanderlip:** None. **S. Weiser Novak:** None. **M. Kuwajima:** None. **L.M. Kirk:** None. **K.M. Harris:** None. **U. Manor:** None. **J.H. Reynolds:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.13

Topic: B.05. Synaptic Plasticity

Support: Supported by NIH grant NS047718, the Craig H. Neilson Foundation, and generous donations from Cure Medical, Research for Cure
J. Yonan was the recipient of a predoctoral fellowship from NIH 5T32 NS045540 and a diversity supplemental under NIH R01 NS108189 (OS)

Title: De novo growth of mature dentate gyrus granule cells following PTEN deletion is dependent on sustained mTOR activation and triggers new synapse formation by input pathways with intact PTEN expression

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Abstract: Previous studies have documented that conditional genetic deletion of phosphatase and tensin homolog (PTEN) in adult neurons initiates new growth of cell bodies and dendrites. It is currently unknown, however, how dendritic growth affects input pathways, and especially whether dendritic growth triggers new synapse formation by input pathways with intact PTEN expression. Here, we explore consequences of PTEN deletion in mature dentate gyrus granule cells via unilateral intra-dentate injections of AAV-Cre into adult male and female $PTEN^{f/f}$;$Rosa^{tdTomato}$ and control $Rosa^{tdTomato}$ mice. In $PTEN^{f/f}$;$Rosa^{tdTomato}$ mice, Cre expression deletes PTEN in transduced cells while simultaneously activating expression of tdTomato leaving PTEN expression intact in input and target neurons. In $Rosa^{tdTomato}$ control mice, Cre results in expression of tdTomato only. Mice received unilateral injections of AAV-Cre at 2 months of age and survived for 2 weeks, 1-, 2-, 4- and 6-months post-injection (n=4-6 mice per timepoint). Cell body size of PTEN deleted granule cells increased gradually by 2 months post deletion to about 2.4-fold larger than control which was accompanied by 1.9-fold increases in molecular layer thickness by 4 months after AAV-Cre injection. Prolonged rapamycin administration to inhibit mTOR activation during the acute (0-2 months) period after PTEN deletion prevented *de novo* growth of cell bodies, while delayed (2-4 months) rapamycin administration prevented dendritic growth and reversed increases in soma size. Quantitative assessment of Golgi-stained granule cells at 6 months post deletion revealed 1.4-fold increases in dendritic length, 1.8-fold increases in dendrite caliber and 1.5-fold increases in spine densities in the inner, middle, and outer molecular layers. Despite dramatic dendritic growth, BDA tract tracing of perforant path and commissural inputs to PTEN deleted granule cells at delayed timepoints after deletion revealed that the laminated pattern of input to the inner and middle molecular layers was maintained. Our results indicate that PTEN deletion triggers *de novo* growth of mature granule cells, that postsynaptic dendritic growth in PTEN deleted granule cells is sufficient to induce new synaptic connections by input pathways in which PTEN expression is intact, and that *de novo* growth of fully mature dentate granule cells requires sustained mTOR activation.

Disclosures: J.M. Yonan: None. **O. Steward:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); OS is a co-founder and holds economic interests in the company “Axonis”, which holds a license on patents relating to PTEN deletion and axon regeneration.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.14

Topic: B.05. Synaptic Plasticity

Support: NIH/NINDS Grant R01NS089578

Title: Trafficking of AMPA receptor subunits in Par1c/MARK1 knockout mice

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[1]Neurosci. and Cell Biol., Rutgers Robert Wood Johnson Med. Sch., Piscataway, NJ; [2]Neurosci. and Cell Biol., Rutgers Wood Johnson Med. Sch., Piscataway, NJ

Abstract: Dendritic spines are sites of postsynaptic excitatory input that are critical for learning and memory. Dysfunction and malformations of dendritic spines have been linked to neurodevelopmental disorders such as autism spectrum disorder (ASD). Our laboratory has recently generated a forebrain-specific conditional knockout (cKO) of partitioning defective 1 c (Par1c), also known as microtubule affinity regulating kinase 1 (MARK1), which is a serine/threonine kinase linked to ASD and bipolar disorder. We found that Par1c cKO mice show dendritic spine and behavioral abnormalities *in vivo*. To examine how loss of Par1c affects the postsynaptic receptors and scaffolding proteins, we performed Western blot analysis of synaptosomes. Interestingly, we found a significant increase in synaptic levels of the AMPA receptor subunit GluR2. To probe for the underlying mechanisms, we performed phosphoproteomic analysis of WT and Par1c cKO hippocampi. We discovered a significant decrease in the phosphorylation of S843 of RalGAPα1 in Par1c cKO hippocampi, which is a site that matches the Par1 phosphorylation consensus sequence.
RalGAPα1 has been appreciated for its role in neurodevelopmental disorders with haploinsufficiency of RalGAPα1 leading to brain developmental delays. In addition, RalGAPα1 is known to regulate membrane trafficking. Thus, our current experiments are aimed at establishing RalGAPα1 as a Par1c substrate, and to determine whether RalGAPα1 regulates GluR2 trafficking downstream of Par1.

Disclosures: R. Shear: None. **H. Zhang:** None. **E. Kelly-Castro:** None. **M. Sun:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.15

Topic: B.05. Synaptic Plasticity

Support: NCN Grant Maestro 2017/26/A/NZ3/00379
NAWA Iwanowska Programme PPN/IWA/2019/1/00109
Max Planck Florida Institute

Title: Mmp-9 contributes to individual dendritic spine plasticity through ntfs signaling

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Abstract: Understanding the complex network of molecular interactions which underlie morphological and functional synaptic plasticity is a major research challenge. The matrix metalloproteinase-9 (MMP-9) has repeatedly been implicated in plasticity of excitatory synapses,

however the exact mechanistic insight into its function is missing. To address this issue, we measured the effects of MMP-9 inhibition in plasticity of dendritic spines of CA1 pyramidal neurons in organotypic hippocampal slices. We have used glutamate uncaging (uLTP) to elicit long-term structural plasticity to stimulate individual apical spines a protocol of 30 laser pulses (0.5 Hz). We measured spine volume change after uLTP in either presence of MMP-9 inhibitors or MMP-9 KO. uLTP protocol resulted in a marked spine growth (up to 3-fold initial increase, followed by a 50% sustained increase lasting for at least 20 min.). The increase in spine volume was taken as a measure of a structural LTP of the spines. Treatment with MMP-9 inhibitors (Inhibitor I or GM 6001) significantly impaired the spine growth both during its transient and sustained phase. Similarly, uLTP protocol induced significantly smaller spine growth in neurons derived from the MMP-9 KO mice in comparison to their WT littermates. This structural plasticity impairment was reversed by overexpression of MMP-9 in KO neuronal slices. Given our results indicating postsynaptic MMP-9 is required for synaptic plasticity, we hypothesized that it acts through processing neuropeptides. To test this, we recorded the activity of Tropomyosin receptor kinase B (TrkB) and Insulin-like growth factor I receptor (IGFIR) using FRET/FLIM sensors. In the control neurons, we observed activation of these receptors during glutamate uncaging for the time course of 20 minutes. However, in neurons where MMP-9 signaling is inhibited, activation of TrkB and IGF1R was attenuated. Our results imply that MMP-9 has a role in dendritic spines plasticity at the onset of the LTP induction and suggest a fundamental role of MMP-9 involvement in activation of neurotrophic factors receptors on dendritic spines.

Disclosures: **D. Legutko:** None. **X. Tu:** None. **P. Michaluk:** None. **R. Yasuda:** None. **L. Kaczmarek:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.16

Topic: B.05. Synaptic Plasticity

Support: PRIN Project 2017 HPTFFC from Italian Ministry of University and Research

Title: Towards circuit-specific mapping of synaptic potentiation

Authors: *F. LATINI[1], A. JACOB[1], M. DI CAPRIO[2], M. MAINARDI[3], A. CATTANEO[1]; [2]Neurosci., [1]Scuola Normale Superiore, Pisa, Italy; [3]Scuola Normale Superiore, CNR, Pisa, Italy

Abstract: The storage and recall of new information rely on the recruitment of specific neuronal ensembles, named cellular engrams, whose activation is necessary and sufficient for, e.g., reactivating the behavior associated with a given associative learning task. Nevertheless, the neuronal cell body receives input from dendrites, which collect the activity of excitatory synapses primarily hosted on dendritic spines. Indeed, interfering with learning-induced

structural long-term potentiation (sLTP) of dendritic spine subsets impinges on the acquisition of a novel behavioral task. A step towards studying the physical substrates of memory at a synaptic resolution is represented by SynActive (SA). This approach allows the expression of a protein of interest specifically at synapses subjected to activity- or learning-dependent potentiation involving local protein translation. Here, we combined SA with GFP Reconstitution Across Synaptic Partners obtaining SA-GRASP: such that the post synaptic moiety of split GFP is under the control of SA-regulatory elements, conferring GFP reconstitution only at potentiated synapses. After extensive validation of SA-GRASP in cultured neurons, we used SA-GRASP to map synaptic potentiation at specific monosynaptic circuits. We employed two pairs of AAVs, encoding: (a1) tetracyclin-responsive element (TRE3g)-controlled presynaptic half of GRASP; (a2) presynaptic label (mTurquoise-2 blue fluorescent protein) and the reverse tetracyclin-responsive transactivator (rtTA); (b1) TRE3g- and SynActive-controlled postsynaptic half of GRASP; (b2) postsynaptic label (tdTomato) and rtTA. The "TetON" system allowed control over the temporal window for SA-GRASP transcription. We performed stereotaxic injections in mice hippocampi, delivering AAVs a1-a2 to the CA3, b1-b2 to the CA1. Mice were then challenged with the encoding phase of the contextual fear conditioning associative learning protocol. To handle the data generated, we have designed a semi-automated pipeline for image analysis of CA1 apical dendrites, allowing us to the determine the spatial distribution of learning-associated CA3-CA1 potentiated synapses expressing reconstituted GFP. Our analysis indicates a spatially nonuniform and clustered pattern, lending support to the notion that specific memories are encoded in neurons through the recruitment of specific subsets of dendritic spines. Moreover, we employed this technique in transgenic models of Alzheimer's disease revealing a variation in the topography of synaptic potentiation thus proposing an underlying adaptation in the recruitment of dendritic subsets under neurodegenerative conditions.

Disclosures: F. Latini: None. **A. Jacob:** None. **M. Di Caprio:** None. **M. Mainardi:** None. **A. Cattaneo:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.17

Topic: B.05. Synaptic Plasticity

Support: CIHR awarded to N.S. File #178355

Title: Sex differences in hippocampal perineuronal net expression across aging

Authors: *M. RAMLJAK, G. M. RURAK, S. SIMARD, S. SIDDIQI, A. AGUILAR-VALLES, N. SALMASO;
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Abstract: Normal aging is characterized by a general decline in cognitive function and neuroplasticity, both of which show sex differences on a number of measures in humans and in rodent models. Perineuronal nets (PNNs) are specialized extracellular matrix structures found primarily surrounding interneurons of the hippocampus, cortex, and amygdala. In development, PNN formation marks the closure of critical periods and mature PNNs stabilize synapses and inhibit plasticity in interneuron populations, including somatostatin and parvalbumin (PV) interneurons. PNNs also show sex differences in expression patterns in juveniles, however, it is unknown whether similar sex differences exist over the lifespan. To investigate this, we employed a rodent model to assess hippocampal PNN/PV expression, as well as cognitive and anxiety behaviors in juveniles (postnatal day (P)35), young adults (P90), and in aged adults (1 year) of both males and females. We found that the overall density of PNNs in the hippocampus increases from P35 to 1 year in males, but not females, which show relatively higher and stable expression across the lifespan. We also found that PV interneuron density does not change from P35 to P90 but increases from P90 to 1 year in both males and females, with females showing higher PV density than males. As expected, the proportion of PV cells surrounded by PNNs increases with age, reaching approximately 45% co-expression at peak levels, however, females reach these levels by P90, whereas males only reach this proportion at 1 year. Interestingly, similar patterns by age and sex were observed in anxiety levels on the elevated plus maze (EPM), and a significant negative correlation was noted between EPM measures of anxiety and PV/PNNs. Taken together, these data suggest that important sex differences in hippocampal PNN expression exist over later development. These sex differences warrant further study as to their functional significance on the capacity for hippocampal plasticity and related behaviors.

Disclosures: M. Ramljak: None. **G.M. Rurak:** None. **S. Simard:** None. **S. Siddiqi:** None. **A. Aguilar-Valles:** None. **N. Salmaso:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.18

Topic: B.05. Synaptic Plasticity

Support: NIH-NIDA DA32444
NIH-NIDA DA15014

Title: Effect of the chemokine CXCL12 on dendritic spine maturation, turnover, and clustering

Authors: *C. HO[1,2], E. IROLLO[1,2], A. SACAN[3], O. MEUCCI[1,2,4];
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Abstract: Dendritic spine loss and synaptic pruning are thought to contribute to cognitive decline in several disorders, including HIV-associated neurocognitive disorders (HAND). Our previous work in a rat model of HAND, the HIV-transgenic rat (HIV-Tg), showed that both spine deficits and cognitive impairment can be rescued by treatment with the chemokine CXCL12. These effects require engagement of the Rac1/PAK intracellular pathway, a major regulator of actin polymerization in dendritic spines. However, it is not known if CXCL12 also regulates spine dynamics (maturation, turnover, and clustering), which also correlates with cognitive performance in behavioral tasks. In order to address these questions, we examined how CXCL12 altered the expression and distribution of postsynaptic proteins typically present in mature excitatory synapses, such as postsynaptic density protein 95 (PSD-95) and the AMPA receptor subunit GluA1. In primary rat cortical neurons treated with CXCL12 (20nM, 3h), we observed a consistent and significant increase in the number and percentage of PSD-95^{+} thin spines and overall spines. At this same time point, we observed a similar trend for spines containing phospho-PSD-95^{Ser295} and GluA1, coupled with a small but significant increase in the overall spine head diameter. These results suggest that CXCL12 may promote spine maturation. In parallel, we analyzed if CXCL12 regulated spine clustering, another form of maturation involving multiple spines, in medial prefrontal cortex (mPFC) pyramidal neurons of wild-type and HIV-Tg rats. We assessed clustering among spines using the nearest neighbor (NN) index, which quantifies the deviation of the observed interspine distances from those expected in a random distribution. In mPFC neurons of CXCL12-treated HIV-Tg rats, we found a significantly shorter interspine distance and decreased NN index. Similarly, we found a decreased NN index for thin spines in CXCL12-treated primary cortical cultures. These results suggest that CXCL12 may induce dendritic spine clustering, rendering spines closer and more functionally mature. Finally, ongoing live-cell imaging studies in primary neurons infected with AAV1-hSyn EGFP suggest that CXCL12 may increase spine turnover and formation. This preliminary conclusion will be further investigated in additional studies using brain slices from both wild-type and HIV-Tg rats. The long-term goal is to advance our understanding of how CXCL12 regulates dendritic turnover and how this can be exploited for therapeutic use.

Disclosures: C. Ho: None. **E. Irollo:** None. **A. Sacan:** None. **O. Meucci:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.19

Topic: B.05. Synaptic Plasticity

Support: Whitehall Foundation

Title: Trans-synaptic adhesion mediated by C1QL3

Authors: *K. CARO[1], M. STICCO[1], T. RELIGA[1], S. RESSL[2], **D. MARTINELLI**[1]; [1]Neurosci., Univ. of Connecticut Hlth. Ctr., Farmington, CT; [2]Neurosci., The Univ. of Texas at Austin, Austin, TX

Abstract: Chemical synapses allow for information transfer between neurons of the brain and their dynamic properties are crucial for proper brain function. Synaptic plasticity and homeostasis (formation and pruning) are implicated in learning and post-natal brain development. Synaptic adhesion molecules (SAMs) make a specialized cell-cell junction across the synaptic cleft, and various complexes have been shown to control synapse formation, dendritic spine morphology, and synaptic plasticity. Dysfunction of SAMs have been implicated in neuropsychiatric disorders such as autism and schizophrenia. Complement component 1, Q subcomponent-like 3 (C1QL3) is a novel potential SAM that has been shown to bind to a post-synaptic receptor adhesion G protein-coupled receptor B3 (ADGRB3). *C1ql3* is expressed in many regions of the brain including the suprachiasmatic nucleus, cerebral cortex, and limbic system. *C1ql3* knock out (KO) in the basolateral amygdala leads to loss of excitatory synapses projecting to the prefrontal cortex and a subsequent deficit in fear conditioning consistent with a role of C1QL3 in promoting synapse maintenance. We demonstrate that C1QL3 is able to promote cell-cell adhesion in heterologous cells expressing ADGRB3 and neuronal pentraxins, and bind to each with physiologically relevant binding affinities *in vitro*, consistent with the role of a SAM. We aim to support the presence of this trans-synaptic adhesion complex at synapses with stimulated emission depletion super-resolution microscopy *in vitro* and *in vivo,* and demonstrate that colocalization of the pre- and post-synaptic binding partners is lost after *C1ql3* KO. This may elucidate a molecular mechanism underlying C1QL3's role in synaptic maintenance.

Disclosures: K. Caro: None. **M. Sticco:** None. **T. Religa:** None. **S. Ressl:** None. **D. Martinelli:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.20

Topic: B.05. Synaptic Plasticity

Support: UNAM PAPIIT IA201915
CONACyT 254878
CONACYT CVU-778825

Title: The haploinsufficiency of Shank3 alters the synaptic plasticity in individual dendritic spines

Authors: *G. PERERA-MURCIA, Y. RAMIRO-CORTES, L. TENORIO-HERNÁNDEZ;
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Abstract: It has been reported a correlation between neurodevelopment disorders andmorphological alterations of dendritic spines. Reports indicate that autism spectrumdisorders (ASD) are associated with mutations in a host of genes that are criticalregulators of synaptic structure and function. For instance, the Phelan-McDermidsyndrome (PMS) is considered an ASD. PMS is caused by a loss in the telomericportion of chromosome 22, where the only involved gene in synaptic function is*Shank3*. This deletion is likely responsible for some of the neurological features ofthe PMS. SHANK3 is a scaffold protein of the postsynaptic density of glutamatergicneurons; it interacts indirectly with NMDA and mGluR, and directly with AMPA all ofthese receptors are involved in the synaptic plasticity response. It is unknown howthe haploinsufficiency of Shank3 impacts the synaptic response and its structuralcorrelates. To address this, we used heterozygous Shank3 mice ($Shank3^{+/-}$) andtwo-photon uncaging glutamate in organotypic hippocampal slice cultures toexamine the structural correlates of synaptic plasticity at the individual dendriticspines from $Shank3^{+/-}$ mice. Our data show that spines from $Shank3^{+/-}$ mice did notshrink in response to the uncaging mGluR-LTD protocol as in spines from wild-typemice, instead, we found a potentiation in the stimulated spines. Whereas the long-term synaptic depression was elicited by uncaging NMDA-LTD protocol in dendriticspines from $Shank3^{+/-}$ mice, in spines from wild-type mice this protocol inducedonly short-term depression. Regarding synaptic potentiation, dendritic spines from$Shank3^{+/-}$ mice did not potentiate in response to uncaging LTP protocol as spinesfrom wild-type mice.These data show for the first time that the haploinsufficiency of*Shank3* disrupts the synaptic plasticity response and its structural correlates thatmay be responsible for the neuronal alterations reported in PMS.Keywords: synaptic plasticity, dendritic spines, Shank3, Phelan-McDermidsyndrome

Disclosures: G. Perera-Murcia: None. **Y. Ramiro-Cortes:** None. **L. Tenorio-Hernández:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.21

Topic: B.05. Synaptic Plasticity

Support: NIH Grant 1ZIANS003140-08

Title: Novel mutation in dimerization domain of NLGN4X in ASD patients

Authors: *E. HONG, K. W. ROCHE;
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Abstract: Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by impaired social interactions, communication deficiency, and repetitive behaviors. There are many genes have been identified as being associated with ASD from both human genetics and etiological evidence links Neuroligins (NLGNs) to ASD. NLGNs are postsynaptic cell adhesion molecules that bind to presynaptic neurexins and play a pivotal role in neuronal development, synaptic transmission, and synaptic plasticity. NLNG4X, one of the NLGN family members, is poorly conserved between humans and rodents showing the low sequence homology (~ 51 %). The largest number of ASD-associated variants are in NLGN4X among the NLGN members. Among the ASD-associated rare variants, most of the mutations are located in the esterase homology domain and it has been identified that those mutations showed deficits in surface trafficking and impaired neuronal function. Here, we report a novel NLGN4X variant located in the dimerization domain identified in ASD patients. NLGNs can form both homodimer and heterodimer followed by binding with neurexin, and dimerization may play a critical role in their function in neural networks suggesting its implication on ASD although there are only a few studies focusing on this mutation. With a biochemical approach, we find that the rare variant impairs formation of heterodimers with NLGN3, while increased interactions with Neurexin.

Disclosures: E. Hong: None. **K.W. Roche:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.22

Topic: B.05. Synaptic Plasticity

Support: National Honor Scientist Program (NRF-2012R1A3A1050385)

Title: Synaptic connections in the lateral amygdala encode auditory fear memory

Authors: *H. LEE, D. CHOI, J. KIM, J.-I. KIM, Y. SUNG, J. CHOI, S. JAYAKUMAR VENKAT, P. PARK, H. JUNG, B.-K. KAANG;
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Abstract: Adaptation to an environment guarantees survival by acquiring appropriate behavioral response to a specific stimulus by encoding related memory in the brain. This memory formation and recall require activation of engram cells and synaptic potentiation among engram ensembles. How synaptic connection between engram cells encoding memory is modulated during memory formation and extinction remained unknown, due to the lack of appropriate molecular tool to directly examine specific synapses between engram cells. Applying a previously established synapse-labeling technique, dual-eGRASP (enhanced Green Fluorescent Protein Reconstitution Across Synaptic Partners), we found that synapses between engram cells in auditory cortex (AC) and lateral amygdala (LA) during auditory fear conditioning showed structural plasticity,

observed as enlarged spine morphology of engram-engram spine in the LA. This enlargement of synaptic engram spines after fear memory formation was significantly reduced after fear extinction, while re-conditioning with the same tone and shock after extinction restored the morphology of the engram spines. Our results show spine-structural evidence of unlearning mechanism during extinction in the auditory fear memory circuit and propose synaptic connection between engram cells as synaptic engram, which demonstrates a functional unit encoding memory.

Disclosures: **H. Lee:** None. **D. Choi:** None. **J. Kim:** None. **J. Kim:** None. **Y. Sung:** None. **J. Choi:** None. **S. Jayakumar Venkat:** None. **P. Park:** None. **H. Jung:** None. **B. Kaang:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.23

Topic: B.05. Synaptic Plasticity

Support: NIH Grant F31NS127511-01

Title: Examining the role of BDNF/Astrocytic TrkB.T1 signaling on perisynaptic astrocyte process plasticity at the synapse.

Authors: *B. C. PINKSTON[1], J. L. BROWNING[1], L. M. HOLT[2], M. L. OLSEN[1];
[1]Virginia Polytechnic Inst. and State Univ., Virginia Polytechnic Inst. and State Univ., Blacksburg, VA; [2]Mt Sinai, Mount Sinai Sch. of Med., New York, NY

Abstract: Perisynaptic astrocyte processes (PAPs) are fine terminal structures located on the distal processes of astrocytes that contain numerous neurotransmitter receptors, ion channels, cell-adhesion molecules, and the ability to release synaptogenic molecules. PAPs enable astrocytes to contribute to synapse homeostasis, development, and stabilization, but despite decades of research indicating their synaptic roles, there is little known regarding the molecular signals that recruit PAPs to synapses or induce structural plasticity in response to neuronal signaling. Our recent published work demonstrates that astrocytes express high levels of TrkB, the receptor for brain derived neurotrophic factor (BDNF). We identified that truncated TrkB, TrkB.T1, is the predominant TrkB receptor identified in cortex and is predominantly expressed in astrocytes relative to other CNS cell populations. Both global and conditional deletion of TrkB.T1 in astrocytes is sufficient to reduce astrocyte morphological maturation *in vitro* and *in vivo*, alters mature astrocyte gene expression *in vivo*, and reduces excitatory synapse formation *in vitro.* Using neuron-astrocyte co-cultures, our preliminary data indicate that TrkB.T1 knockout (KO) astrocytes fail to develop PAPs around glutamatergic synapses *in vitro*. *In vivo*, conditional deletion of TrkB.T1 in astrocytes alters PAP-related gene expression in cortex. Further, using conditional TrkB.T1 KO mice, we have examined the role of BDNF signaling onto astrocyte TrkB.T1 in the mouse whisker barrel cortex. Our data indicate aberrant astrocyte structural

plasticity and excitatory synapse formation following chronic whisker stimulation. Ongoing studies using astrocyte-neuron co-cultures and experience-dependent plasticity in the whisker barrel cortex *in vivo* are aimed at examining BDNF/TrkB.T1 signaling as a mechanism underlying PAP arrival and plasticity at developing synapses. This work details a novel molecular mechanism by which astrocyte structural plasticity occurs at excitatory synapses.

Disclosures: B.C. Pinkston: None. **J.L. Browning:** None. **L.M. Holt:** None. **M.L. Olsen:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.24

Topic: B.05. Synaptic Plasticity

Support: NIMH R21MH125227

Title: Altered neuronal autophagy as a contributor to prefrontal cortical dendritic spine destabilization in female schizophrenia subjects

Authors: *K. J. BJORNSON, A. M. VANDERPLOW, M. E. CAHILL;
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Abstract: Male and female schizophrenia patients differ with regards to age of onset, disease course, and symptomology. Recent evidence from our laboratory suggests that the activity level of prefrontal cortical signal transduction pathways largely differ between male and female subjects afflicted with the same neuropsychiatric disorder. Such findings highlight the need to consider sex as a critical variable in identifying common pathways that are disrupted in these conditions. Schizophrenia is characterized by disordered perceptions of reality and thought, altered affect, and cognitive impairment. A consistent pathological hallmark of schizophrenia is the reduced stability of dendritic spines on pyramidal neurons in the dorsolateral prefrontal cortex (DLPFC), which is theorized to contribute the reduced engagement of this region during cognitive processing in schizophrenia subjects. Decreased dendritic spine stability and the concomitant reduction in spine density in pyramidal neurons can occur via several distinct mechanisms, including increased neuronal autophagy. Neuronal autophagy is among the primary means by which pyramidal neurons can self-regulate the density of dendritic spines, such that increased activity of neuronal autophagy pathways can cause pruning and removal of dendritic spines. Based on pathological findings in schizophrenia, we theorized that increased autophagy could be a mechanism by which the reduction in dendritic spine density occurs in DLPFC pyramidal neurons in schizophrenia subjects. To this end, we examined the activity and expression profile of proteins in autophagy pathways in a large cohort of schizophrenia, bipolar disorder, and unaffected control subject DLPFC homogenates. Our findings identified increased activity of the AMP-activated protein kinase (AMPK)-Beclin1 autophagy pathway in the DLPFC

of female schizophrenia subjects with no alteration in other diagnostic groups, including male schizophrenia subjects. Utilizing super resolution imaging, we show that Beclin1 is enriched in dendritic spines; however, the precise mechanisms by which it regulates spine pruning is not yet known. Using a reverse-translational approach in mice, our ongoing studies are utilizing viral mediated gene transfer to investigate the function of Beclin1 within prefrontal cortical pyramidal neurons and any associated effects on cognitive abilities. Taken together, these data suggests alterations in AMPK-Beclin1 mediated autophagy is a potential mechanism contributing to the disruption of synaptic stability in female schizophrenia patients.

Disclosures: K.J. Bjornson: None. **A.M. Vanderplow:** None. **M.E. Cahill:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.25

Topic: B.05. Synaptic Plasticity

Support: NIA T32AG000279
NINDS R35NS116879
NINDS NS110383
NIA NS110383
NIMH NS110383

Title: Alzheimer's disease protein amyloid-beta preferentially binds excitatory, not inhibitory, hippocampal neurons with perisynaptic distribution, and impairs plasticity in a synapse-specific manner

Authors: *H. S. ACTOR-ENGEL, S. L. SCHWARTZ, K. C. CROSBY, B. S. SINNEN, J. N. BOURNE, C. S. WINBORN, K. R. SMITH, M. J. KENNEDY;
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Abstract: The ability of synapses in the brain to strengthen and weaken in response to experience is called synaptic plasticity, and it is critical for learning and memory. Widely recognized as a causative agent for Alzheimer’s disease (AD), soluble amyloid beta oligomers (Aβo) perturb critical forms of synaptic plasticity, trigger synapse loss and eventually lead to neuronal death. While a large body of work has described how Aβo disrupts synaptic function, a number of basic questions remain. How quickly does Aβo associate with the neuronal surface? What part of the synapse is Aβo binding? Are Aβo-bound synapses selectively impaired? What accounts for cell-type specific pathology in AD? Using live-cell confocal imaging of dye-labeled Aβo in mixed-sex primary rat hippocampal cultures, we show Aβo rapidly associates with hippocampal neurons within seconds to minutes. We used a combination of super resolution light microscopy and immunogold EM labeling to assess precisely where Aβo binds to neurons. Surprisingly, Aβo does not bind directly at the synaptic cleft; but localizes immediately adjacent

to the postsynaptic density and active zone on both sides of the synaptic cleft. Aβo associates with a subset of excitatory synapses (64±6.8%), with Aβo-bound spines selectively impaired for morphological plasticity. Lastly, we find that acutely applied Aβo binds selectively to a subset of excitatory, but not inhibitory hippocampal neurons. We observed similar results following chronic Aβo exposure in mixed sex 5xFAD mice. To determine the identity of neurons that bind Aβo, we are using fluorescence activated cell sorting (FACS) to purify Aβo-binding cell populations and performing single cell RNA sequencing (scRNA-seq). Taken together, this body of work describes the precise location of Aβo association from the cellular to the nanoscale. This information will be critical for identifying therapeutic targets for the prevention of Aβo-induced synaptic deficits and other AD-related pathologies.

Disclosures: H.S. Actor-Engel: None. **S.L. Schwartz:** None. **K.C. Crosby:** None. **B.S. Sinnen:** None. **J.N. Bourne:** None. **C.S. Winborn:** None. **K.R. Smith:** None. **M.J. Kennedy:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.26

Topic: B.05. Synaptic Plasticity

Support: NSF GRFP 2020294366
Simmons Foundation SFARI grant #385188
NIH R01 #1RF1AG068063-01A1

Title: Acute sleep deprivation drives distinct changes in the synapse and behavior of developing and mature mice

Authors: *S. GAY[1], E. CHARTAMPILA[1], C. BROWN[1], N. BARKER[2], A. PREVATTE[2], J. SIMON[3], L. HERRING[2], G. H. DIERING[4];
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Abstract: Sleep is essential for proper cognitive function and brain maturation. The importance of sleep in brain development is suggested by the comorbidity of sleep disruptions in numerous neurodevelopmental disorders. Recent studies have shown that chronic sleep loss early in life can have long lasting effects on adult social behavior. However, it is unclear how developing mammals respond to sleep loss and if sleep loss differently affects developing and mature mammals. To address this, we systematically analyzed the behavioral and molecular response to acute 4-hour sleep deprivation (SD4) in juvenile (postnatal, p21), adolescent (p42-45), and adult (p90+) mice of both sexes. Utilizing a non-invasive home-cage recording system, PiezoSleep, we measured sleep rebound behavior in response to SD4. Adult mice compensated for SD4 by an

increase in sleep amount in the subsequent active period, called sleep rebound, completely recovering the lost sleep within 24hrs. Juvenile mice did not engage any measured sleep rebound behavior and did not make up for lost sleep, whereas adolescent mice showed a partial recovery, suggesting that developing mice do not quickly recover lost sleep. Using qPCR, we show that SD4 drives a clear induction in the expression of immediate early genes (IEGs) Arc and Homer1a in adults, as previously reported. Similar to sleep rebound behavior, juvenile and adolescent mice showed a severely blunted IEG induction response to SD4. The lack of sleep rebound behavior and IEG induction in response to SD4 in juveniles raises the question of how developing mice are affected by SD. The synapse is remodeled during sleep, impacted by sleep deprivation, and many neurodevelopmental disorders are considered synaptopathies, or diseases of the synapse, making it a locality of interest to determine the effects of SD in developing mice. We used sub-cellular fractionation to isolate synapse fractions from mouse forebrain and analyzed the samples using quantitative proteomics and phosphoproteomics. Following SD4, the juvenile and adolescent synaptic proteome was profoundly and uniquely affected by sleep deprivation, showing changes in hundreds of synaptic proteins and phosphorlyations. Adult mice showed fewer changes in response to sleep deprivation, suggesting that mice gain resilience to sleep loss with maturation. Our study shows that developing mice are sensitive to the effects of sleep loss, which suggests how early life sleep loss could contribute to neurodevelopmental disorders.

Disclosures: S. Gay: None. **E. Chartampila:** None. **C. Brown:** None. **N. Barker:** None. **A. Prevatte:** None. **J. Simon:** None. **L. Herring:** None. **G.H. Diering:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.27

Topic: B.05. Synaptic Plasticity

Title: Altered synaptic plasticity and neuronal morphology in human model of EPM1

Authors: *A. PIZZELLA[1], N. ABATE[1], L. CANAFOGLIA[2], S. CAPPELLO[3], M. CRISPINO[1], R. DI GIAIMO[1,3];
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Abstract: Progressive myoclonic epilepsy 1 (EPM1) is a rare neurodegenerative disease characterized by mutation of CSTB gene, which encodes for a small protein inhibitor of the Cathepsin proteases. Low levels of functional CSTB impact cell proliferation, differentiation and interneuron recruitment during neurogenesis. Moreover, CSTB contributes to synaptic plasticity. The aim of my project is to investigate the molecular mechanisms that are impaired in the pathology, with special attention to the possible alteration of synaptic plasticity. We used two different experimental models: i) synaptosomes obtained from Human Cerebral Organoids

(hCOs) as *in vitro* model for studying human synaptic terminals; ii) neurons generated in vitro from Neuronal Progenitor Cells (NPCs). Synaptosomes were obtained by mild homogenization of hCOs, followed by subcellular fractionation of the homogenate. We confirmed, by Western blot analyses (WB), that the synaptosomal fraction is enriched in synaptic proteins, and we detected, in the same fraction, the presence of well-known extracellular vesicles markers, as CD81, CD9 and CD82. The expression profile of these proteins depends on the maturation of the organoids, and more interestingly, is changing in synaptosomes obtained from EPM1 hCOs. Indeed, in EPM1 synaptosomes we observed, by WB, a reduction of synaptic markers, particularly evident at early stages, as confirmed by immunostaining on hCOs slices. Interestingly, we also observed in EPM1 synaptosomes a relevant decrease in the expression level of the eukaryotic initiation factor EiF4G2, suggesting the impairment of local system of protein synthesis in the synaptic areas of EPM1 hCOs. In addition, we detected decreased level of extracellular vesicles proteins, by mass spectrometry analysis and WB, suggesting the involvement of altered secretion mechanisms in the EPM1 pathogenesis. We also performed a morphological analysis of 8-week-old neurons differentiated from EPM1-patient and control NPCs, using Neurolucida analyser. Interestingly, EPM1 neurons show longer, thinner and more branched neurites compared to control ones, suggesting that a more complex neuronal morphology, and presumably altered connectivity, is associated to the pathology. Altogether, our data revealed alteration of synaptic plasticity and neuronal morphology in human model of EPM1, opening the way to future investigation aimed to understand in details the molecular mechanisms underlying the physiopathology of EPM1.

Disclosures: **A. Pizzella:** None. **N. Abate:** None. **L. Canafoglia:** None. **S. Cappello:** None. **M. Crispino:** None. **R. Di Giaimo:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.28

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01NS089578

Title: Neurodegeneration in Par1b knockout mice

Authors: *H. CAIOLA, Q. WU, S. SONI, H. ZHANG;
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Abstract: Neurodegenerative diseases such as Alzheimer's disease (AD) are a major cause of death and disability in older populations. Currently, about 1 in 9 Americans (65+) are living with AD and as of 2019, AD is the sixth-leading cause of death in the USA. Hallmarks of AD pathology include amyloid beta (Aß) and tau accumulation. It has been posited that Aß accumulation results in hyperphosphorylation of tau and production of neurofibrillary tangles

(NFTs) leading to transcriptional changes, synapse loss, and ultimately neuronal death. Many clinical trials have attempted to target parts of the Aß and tau pathway but have unfortunately failed. This suggests a need for further examination of the Aß cascade to identify other potential therapeutic targets. The Par1 family of serine/threonine kinases, also known as microtubule affinity regulating kinase (MARK), have been proposed as druggable targets for AD therapies. Par1 has been shown to trigger the tau hyperphosphorylation cascade which directly phosphorylates tau on Ser262 and Ser356. Additionally, Par1b/MARK2 and Par1d/MARK4 have been genetically linked to AD. Interestingly, we found that Par1b has decreased expression in the medial temporal lobes of post-mortem human AD patients, which is contrary to expectation. Given this finding and the link between Par1 and AD, we hypothesized that loss of Par1b may contribute to the neurodegeneration seen in AD. We employed behavioral, and histological techniques in a Par1b knockout (KO) mouse model to characterize the role of Par1b in neurodegeneration. Through behavioral assays, we found that Par1b KO mice exhibit deficits in learning and social behavior. Furthermore, we found that Par1b KO mice have fewer mature dendritic spines and excitatory synapses, and reduced mEPSC frequency. In addition to these cognitive and synaptic deficits, Par1b KO mice exhibit age-dependent hippocampal neurodegeneration at 6-8 months of age as evidenced by decreased hippocampal size and increased ventricle size. Altogether, these data support a model in which Par1b is important for learning and normal brain aging. Current and future efforts will focus on establishing a direct link between loss of Par1b and AD by crossing Par1b KO mice with AD transgenic mice. Moreover, further investigation into the neurodegeneration seen in these animals will provide insight into the molecular mechanisms underlying neurodegeneration and AD with the goal of identifying druggable targets to use in therapeutics.

Disclosures: **H. Caiola:** None. **Q. Wu:** None. **S. Soni:** None. **H. Zhang:** None.

Poster

693. Structural Plasticity: Synapses

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 693.29

Topic: B.05. Synaptic Plasticity

Support: Grant: APVV-200331.
Grant: LM2018129 and

Title: Disruption of extracellular matrix after oral treatment of rats with 4-methylumbelliferone decreases brain diffusivity.

Authors: *E. M. SYKOVA[1], I. VORISEK[2], Z. STARCUK, Jr.[3], J. KRATOCHVILA[3], S. KUBINOVA[4], J. C. F. KWOK[5], J. SYKA[6], J. SVOBODOVA BURIANOVA[7], T. SMOLEK[1], N. ZILKA[1];
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Abstract: Extracellular space (ECS) contains the interstitial fluid with various ions and with a mesh-like structure called extracellular matrix (ECM). ECM is a network of macromolecules, glycosaminoglycans, proteoglycans and glycoproteins, secreted by neurons and glia. We do not know how changes in the ECM structure influence occurrence and progression of brain disorders. However, it has been found previously that changes of the ECM influence ECS diffusion parameters (ECS volume and geometry) during various brain pathologies or in ECM knock-out animals (Sykova and Nicholson, 2008). In this study we investigated the effect of oral treatment of adult rats with 4-methylumbelliferone (4-MU), an inhibitor of hyaluronan synthesis, on ECM composition and ECS diffusivity. We measured the level of hyaluronan (using hyaluronan binding protein) and chondroitin sulfates (using CS56 antibody) by densitometry measurement on brain sections. We found that 2 months of 4-MU diet resulted in 42.3% ± 11.2% and 38.7% ± 9.1% reduction of hyaluronan and chondroitin sulfates in ECS, respectively. There was also a significant down-regulation of perineuronal nets (PNN) on the neuronal surface, labelled by *Wisteria floribunda* agglutinin. To study changes in the ECS diffusivity we used *in vivo* diffusion-weighted magnetic resonance imaging (DW-MRI). Exposure to 4-MU diet resulted in the somatosensory cortex, auditory cortex, thalamus, hippocampus and pallidum in a significant decrease of the apparent diffusion coefficient of water from 967 ± 8 to 903 ± 12 $\mu m^2/s$, the fractional anisotropy (FA) from 0.21 ± 0.02 to 0.16 ± 0.01 and perfusion detected by arterial spin labelling from 82 ± 9 to 52 ± 4 ml/100g/min (data from cortex). We have not found changes in brain metabolites as measured by MR proton spectroscopy. After the animals were fed again with a standard diet, the parameters returned to control values. The possible explanation for decreased diffusivity and of FA could be a decrease in the ECS volume, due to collapse of ECM structure. We suggest that DW-MRI can be used for non-invasive detection of the dynamic changes in molecules of ECM. Oral treatment with 4-MU results in ECM remodeling which can affect extrasynaptic transmission, synaptic plasticity, neurodegeneration, neural regeneration and may explain some observed functional effects of the 4-MU.

Disclosures: **E.M. Sykova:** None. **I. Vorisek:** None. **Z. Starcuk:** None. **J. Kratochvila:** None. **S. Kubinova:** None. **J.C.F. Kwok:** None. **J. Syka:** None. **J. Svobodova Burianova:** None. **T. Smolek:** None. **N. Zilka:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.01

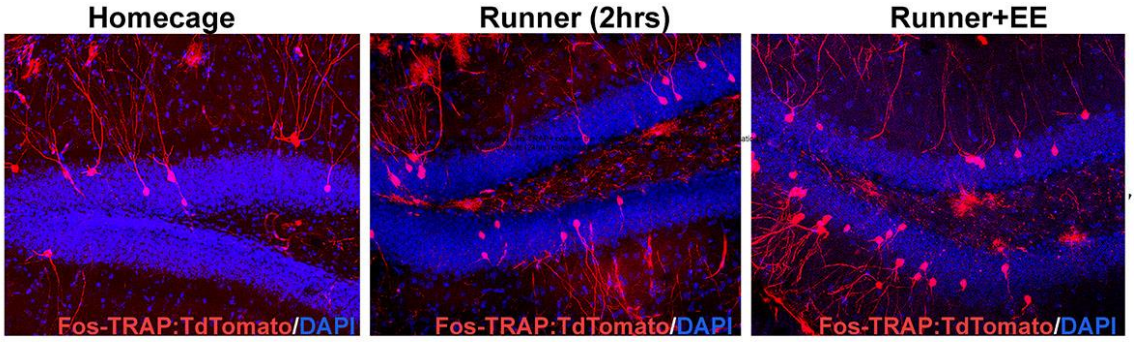
Topic: B.05. Synaptic Plasticity

Support: NS117371 (GLW)
Collins Medical Trust (CC)

Title: Fos-trap activation of dentate granule cells by pairing brief environmental enrichment with exercise.

Authors: A. VESHAGH, A. SIMMONDS, C. CHATZI, *G. WESTBROOK;
Vollum Inst., Portland, OR

Abstract: The benefits of physical exercise for learning and memory are largely based on sustained periods of exercise, but can be apparent within 24 hours. Our previous experiments demonstrated an increase in synaptic function and dendritic spines in the outer molecular layer of the dentate gyrus in young adult female and male mice following 2 hours of exercise. The increase peaked at 3 days post-exercise in Fos-TRAP activated dentate granule cells. We hypothesize that exercise-activated granule cells are preconditioned for salient stimuli to enhance structural plasticity. To test this idea, we paired exercise with a 2nd bout of exercise 1 or 4 days later; and compared that to exercise paired with brief environmental enrichment (EE, 6 hours - 3 days). Arc and Fos immunolabeled cells overlapped in exercise-activated granule cells, suggesting similar cohorts. Single bouts of exercise resulted in a 3-fold increase in Fos+ cells. EE alone (6 hrs) produced no increase in Fos+ cells whereas 24 hrs of EE doubled c-Fos+ cells. When two exercise periods were separated by 24 hr, 12.5 ± 5.6%, of exercise-TRAPed cells were re-activated as identified by Fos immunolabeling, whereas with a 4-day separation only 1.3 ± 0.3 overlapped, suggesting that each exposure activated independent cohorts. We then asked whether dentate granule cells activated by exercise were more likely to be activated by a related, but perhaps more complex stimulus - EE. Running (2hrs) paired with EE (24hrs) increased Fos-TRAPed cells compared to running only. We are directly testing the preconditioning hypothesis by introducing running wheels for 2 hours on day 0, followed by EE on days 2,3 & 4. Our data suggest that, similar to data from humans, even brief period of environmental enrichment may enhance neuronal plasticity.
Acknowledgements. We thank the OHSU Light Microscopy Core for assistance with imaging and data analysis. Supported by NS117371 (GLW) and Collins Medical Trust (CC).



Brief exercise (2hrs) increased Fos-TRAP+ cells in the dentate gyrus (left and middle). Combination of exercise with enriched environment (24hrs) enhanced the increase in Fos-TRAP+ cells.

Disclosures: A. Veshagh: None. **A. Simmonds:** None. **C. Chatzi:** None. **G. Westbrook:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.02

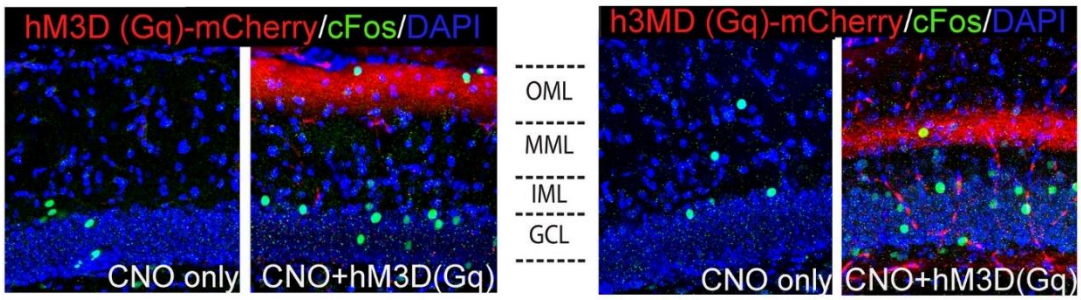
Topic: B.05. Synaptic Plasticity

Support: NS117371 (GLW)
Collins Memorial Trust (CC)

Title: Laminar-specific activation of mouse dentate granule cells by acute exercise.

Authors: A. SIMMONDS, A. VESHAGH, *C. CHATZI, G. L. WESTBROOK;
Vollum Inst., Portland, OR

Abstract: Hippocampal dentate granule cells receive sensory information from two major cortical pathways in a laminated and functionally segregated manner. The medial entorhinal cortex conveys spatial information via the medial perforant path (MPP), and the lateral entorhinal cortex, codes for contextual and time cues via the lateral perforant path (LPP), which provides for pattern separation of incoming sensory and motor information. We used conditional Fos-TRAP female and male mice to permanently mark exercise-activated dentate granule cells. We previously reported that single bouts of voluntary exercise in these mice (2 hrs) resulted in transient increases in EPSCs and dendritic spines for inputs from the lateral, but not the medial entorhinal cortex. We examined several underlying mechanisms for the laminar-specific activation here. Preferential activation following exercise could not be attributed to newly-generated granule cells which also receive LPP input. Selective stimulation of either LEC or MEC by DREADDs showed an increase in dendritic spines in the OML and MML, respectively. This result suggests that preferential activation following exercise may reflect the pattern of inputs activated by locomotion onto dentate granule cells. To examine the perforant path inputs to exercise-activated neurons we used an activity-dependent retrograde AAV expressed in exercise-activated granule cells (Fos-TRAP+ cells). There was a preponderance of axons projecting from LEC. Our results indicate that the preferential activation of the OML by exercise reflects the drive of locomotor-related inputs from the LEC rather than selective molecular mechanisms in the granule cell dendrites. How exercise affects other salient stimuli involving contextual or spatial cues may underlie the benefits of exercise on learning and memory.
Acknowledgements. We thank the OHSU Light Microscopy Core for assistance with imaging and data analysis. Supported by NS117371 (GLW) and Collins Memorial Trust (CC).



Chemogenetic activation increases granule cell activity. OML (left) and MML (right) labeling in CNO and CNO+ excitatory DREADD-mCherry (red band) with DREADD-induced increase in cFos+ (green) granule cells.

Disclosures: **A. Simmonds:** None. **A. Veshagh:** None. **C. Chatzi:** None. **G.L. Westbrook:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.03

Topic: B.05. Synaptic Plasticity

Support: KAKENHI 18H05213
KAKENHI 19H04994

Title: Calcium-based learning rules for the rapid detection of temporal communities in synaptic input

Authors: *G. SIVORI, T. FUKAI;
Okinawa Inst. of Sci. and Technol., Onna-son, Japan

Abstract: The brain is thought to statistically model the external world to predict its continually changing features. In the predictive coding hypothesis, cortical pyramidal cells (PCs) in higher-order networks indicate activity patterns from lower-order networks to extract the characteristic statistical features of bottom-up information streams. However, how predictions and errors are computed and propagated at the cellular level remains elusive. Aiming to explore these computations, we propose a biologically realistic Hebbian plasticity rule. In our model, somatic spikes backpropagating to the dendrites transiently increase the intracellular Ca2+ concentration. The transient Ca2+ dynamics mimic the internal error signal derived previously in a machine-learning-based learning rule between somatic spiking activity and stimulus-driven dendritic activities. The intracellular error signal serves for learning at the dendritic compartments, enabling the PCs to selectively respond to the communities of coincidently and repeatedly activated presynaptic neurons. Our model predicts that a transient increase of somatodendritic coupling conductances during spiking significantly accelerates the temporal community

detection. Numerical simulations suggested that just a few stimulus presentations are sufficient for the detection. Furthermore, we show that small clusters of PCs endowed with the proposed computational features in a recurrent network further improve the speed and reliability of the community detection. The proposed learning rule suggests that PCs learn to predict their responses based on the recent input patterns and output activity. We demonstrate the relationship between our learning rule and spike-timing-dependent plasticity (STDP). The implications of the learning rule for the hierarchically Bayesian computation hypothesized in the predictive coding theory will also be discussed.

Disclosures: G. Sivori: None. **T. Fukai:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.04

Topic: B.05. Synaptic Plasticity

Support: PRIN Project 2017 HPTFFC from Italian Ministry of University and Research

Title: Identification of learning-specific changes in the synaptic proteome via proximity labeling with the genetically encoded probe TurboID

Authors: *M. DI CAPRIO[1], A. JACOB[1], F. LATINI[1], M. MAINARDI[2], A. CATTANEO[1]; [1]Scuola Normale Superiore, Pisa, Italy; [2]Scuola Normale Superiore, Natl. Res. Council, Pisa, Italy

Abstract: Memory formation is supported by functional, biochemical and structural changes within neural circuits. Excitatory synapses are a hotspot for these plasticity phenomena. Despite huge progress in the identification of the global synaptic proteome, determining its in vivo state-dependent modifications in response to specific conditions, such as behavioral learning tasks triggering the formation of new memories, remains a daunting task, due to the difficulty of accessing the synapses undergoing long term changes amid the heterogeneous brain tissue. We are contributing to address this experimental problem by taking advantage of the SynActive (SA) approach, which we developed to obtain the expression of genetically encoded reporters or actuators specifically at postsynaptic elements undergoing potentiation. This feature is conferred by regulatory sequences extracted from the 5' and 3' UTRs of the mRNA for the immediate-early gene *Arc*, combined with synaptic protein targeting sequences. Here, we report the generation, characterization and use of a SA-based proteomic tool for the in vivo analysis of the proteome of synapses subjected to learning-dependent potentiation. In a previous study, we used SA to control the expression of a FLAG-tagged version of the postsynaptic hub protein PSD-95. After immunoprecipitation via α-FLAG beads and mass spectrometry, we were able to spot rearrangements of protein networks representing learning-related changes in the composition of synapses. We are now expanding this approach through the creation of a SA-TurboID biotin

ligase, fused to Neuroligin-1, to achieve proximity labeling of synaptic proteins specifically at synapses undergoing potentiation. First, we demonstrated that in cultured hippocampal neurons SA-TurboID-Neuroligin-1 is expressed in an LTP-dependent fashion and the cellular content of biotinylated proteins is increased following LTP induction. Then, we used AAVs to deliver SA-TurboID-Neuroligin-1 to the hippocampus of mice which subsequently underwent contextual fear conditioning. After biotin supplementation and exposure to hippocampus-dependent learning task, hippocampi were dissected and processed for immunoprecipitation of endogenously biotinylated proteins, to be followed by their identification via mass spectrometry. Our strategy allows a state-dependent analysis of the synaptic proteome in different behavioral conditions, and in different phases of a learning task, to enrich currently available synaptomes. This approach can be readily applied to pathological animal models, with the ultimate goal of identifying new potential therapeutic targets.

Disclosures: M. Di Caprio: None. **A. Jacob:** None. **F. Latini:** None. **M. Mainardi:** None. **A. Cattaneo:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.05

Topic: B.05. Synaptic Plasticity

Support: R01HD101642
NIH T32GM008620
NSF GRFP DGE-1839285
ONR N00014-18-1-2114
ONR N00014-21-1-2940

Title: An Analysis of Throughput Across the Primary Hippocampal Circuit

Authors: *C. YANG[1], J. QUINTANILLA[2], B. PRUESS[3], C. M. GALL[4], G. LYNCH[5], B. G. GUNN[2];
[1]UCI, Univ. of California, Irvine Med. Ctr., Irvine, CA; [3]Anat. and Neurobio., [2]Univ. of California, Irvine, Irvine, CA; [4]Dept. of Anat. and Neurobio., Univ. of California at Irvine, Irvine, CA; [5]Univ. California, Irvine, Irvine, CA

Abstract: Episodic memory, the encoding of previously experienced everyday events, has recently become a topic of great interest for neuroscientists. The hippocampus plays a crucial role in the formation and storage of such memory which includes semantic, spatial, and temporal coding. Despite extensive studies of the hippocampal unidirectional tri-synaptic pathway, surprisingly little is known about how patterned input from the entorhinal cortex is transformed across the multiple links (synaptic connections) and nodes [Dentate Gyrus (DG), CA3, CA1] within this circuit. Using slice recordings and single pulse stimulation of the lateral perforant

path (LPP) from entorhinal cortex, we observed both rapid and delayed responses in recordings from the CA1 cell body layer. Cutting the direct LPP connection to CA3 caused the rapid response to disappear, whereas cutting the indirect path to CA3 (LPP-DG-CA3) eliminated the delayed response. Ten pulse trains of theta frequency (5Hz) stimulation amplified the delayed (indirect) response while gamma (50Hz) input resulted in a severe attenuation. The potent gamma filter was localized to the head stage of the circuit: the LPP synapses with the dendrites of the DG granule cells. Beta frequencies (25Hz) were also strongly attenuated but in this case the pertinent and unusual filter was localized within CA3 and hypothesized to involve a candidate subclass of interneurons. The substrates for amplification of the delayed CA1 response during theta stimulation could involve the observed persistent firing of CA3 pyramidal neurons between stimulation pulses. This effect involves the massive CA3 recurrent collateral system. We propose that brief periods of beta and gamma frequency information are routed through a disynaptic network directly to field CA1 (LPP-CA3-CA1) whereas circuit output to theta frequency input will be dominated by a much more complicated set of connections that elicit activation of the CA3 feedback projections. Ongoing efforts to use complex stimulation patterns to drive gamma signals through the indirect (delayed response) circuit will be described. Further investigations will provide results needed for the construction of realistic network models and enable a circuit level understanding of the effects of drugs use in treatments for various neurological diseases.

Disclosures: **C. Yang:** None. **J. Quintanilla:** None. **B. Pruess:** None. **C.M. Gall:** None. **G. Lynch:** None. **B.G. Gunn:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.06

Title: WITHDRAWN

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.07

Topic: B.05. Synaptic Plasticity

Support: ANPCyT PICT2020 #0046

Title: Gamma audiovisual stimulation induces plasticity in granule cells born in the aging hippocampus

Authors: *M. F. TRINCHERO, M. HERRERO, M. MUGNAINI, A. MIRANDA, E. KROPFF, A. F. SCHINDER;
Fundación Inst. Leloir, CABA, Argentina

Abstract: Non-invasive gamma audiovisual stimulation at 40 Hz can reduce levels of amyloid beta peptide and improve memory performance in several mouse models of Alzheimer's disease. While light and sound stimulation ("flickering") was shown to increase the gamma frequency component of hippocampal oscillations, the mechanisms that transduce these stimuli into cellular and circuit changes remain elusive. Because neurogenesis in the aging hippocampus is particularly sensitive to behavioral stimuli, the effects of gamma flickering might be revealed by analyzing its impact on developing new neurons. Using light and sound pulses, we studied the impact of 40 Hz stimuli on the development of neurons born in the dentate gyrus of 8-month-old mice. Gamma flickering enhanced the 40 Hz component in dentate gyrus oscillations and boosted circuit remodeling by neurogenesis, as shown by the accelerated growth of newly generated neurons. These results reveal that audiovisual stimuli awaken mechanisms that promote neuronal plasticity not only under pathological conditions, but also in the healthy aging brain.

Disclosures: M.F. Trinchero: None. **M. Herrero:** None. **M. Mugnaini:** None. **A. Miranda:** None. **E. Kropff:** None. **A.F. Schinder:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.08

Topic: B.05. Synaptic Plasticity

Support: JST ERATO JPMJER1801
JSPS Grants-in-Aid for Scientific Research 18H05525

Title: Synchronous firing promotes formation of synaptic connections in neocortex

Authors: *T. KASHIMA[1], Y. IKEGAYA[1,2,3];
[1]Grad Sch. Pharma Sci., [2]Inst. AI Beyond, The Univ. of Tokyo, Tokyo, Japan; [3]CiNet, Osaka, Japan

Abstract: Synaptic connections are first excessively generated and then reduced to the appropriate amount by selective synaptic pruning during development of the central nervous system. One of the candidate mechanisms underlying the selective pruning is Hebb's rule, which predicts that synaptic connections between neurons that fire synchronously survive the synaptic pruning. To experimentally verify this well-known hypothesis, we applied non-invasive transcranial photostimulation to induce synchronous firing in layer 2/3 neurons of the mouse somatosensory or visual cortex that sparsely expressed channelrhodopsin 2 (ChR2) through in utero electroporation. We stimulated ChR2 on postnatal day 9-to-13 and examined synaptic

connectivity using in vitro whole-cell patch-clamp recordings. The neocortex that received 5-day photostimulation exhibited higher probabilities of synaptic connections between ChR2-positive neurons, compared to ChR2-negative neurons or ChR2-positive neurons in the non-stimulated neocortex. The photostimulation did not change in either the basic electrophysiological properties or the dendritic complexities of the stimulated neurons. However, spines of their basal dendrites were specifically enlarged. These results are consistent with the Hebb's prediction, suggesting that synchronous firing is actively involved in developmental neural circuit formation in the neocortex. The relationship between these artificially created connections and their phenotypes such as orientation selectivity are under consideration.

Disclosures: T. Kashima: None. **Y. Ikegaya:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.09

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

Support: NIH Grant NS062771

Title: Intrinsic and synaptic potentiation contribute to receptive field plasticity in Purkinje cells of the mouse cerebellum

Authors: *T.-F. LIN, S. E. BUSCH, C. HANSEL;
Univ. of Chicago, Univ. of Chicago, Chicago, IL

Abstract: Synaptic plasticity at parallel fiber-Purkinje cell (PF-PC) synapses has been associated with several types of cerebellar learning. In comparison to synaptic plasticity at these synapses, the physiological function of non-synaptic intrinsic plasticity in PCs has been less intensely investigated. PC intrinsic plasticity is expressed by a downregulation of small conductance Ca^{2+} activated K^{+} (SK2) channels. In the current study, we aim to identify the distinctive functions of synaptic long-term potentiation (LTP) and non-synaptic intrinsic potentiation in the intact animal. Although both potentiation mechanisms have been extensively studied in vitro, their relative contributions to plasticity in vivo have not been assessed yet.To determine whether those cellular mechanisms do contribute to PF plasticity in vivo, we stimulated a bundle of PFs via a microelectrode and monitored Ca^{2+} transients in PC dendrites of awake mice (PC-specific expression of GCaMP6f) using two-photon microscopy.In contrast to climbing fiber induced Ca^{2+} transients, PF responses were restricted to a local area on the PF beam. Furthermore, the probability and amplitude of Ca^{2+} events were dependent on stimulus intensity. Tetanizing PFs at 1 Hz for 5 min, we observed a potentiation of PF-evoked Ca^{2+} events (probability and amplitude), which verifies that the potentiation takes place in vivo. To confirm that the potentiation can also happen to physiologically evoked responses, we studied receptive field plasticity by monitoring tactile responses over repeated skin stimulations in awake mice. To

trigger the tactile responses in the test trials, individual airpuffs were delivered to a distinct front paw area about every 1 min while animals were putting their forelimbs on a horizontal bar. To potentiate the tactile response, an airpuff tetanus at 4 Hz was applied to the corresponding paw area for 5 min. After the repetitive stimulation, we observed increased probability of Ca^{2+} events compared to baseline. To identify distinctive roles of synaptic and intrinsic potentiation in modulating receptive fields, we examined the enhancement of tactile responses in "intrinsic plasticity no, LTP yes" mice (L7-SK2 knockout mice) and "intrinsic plasticity yes, LTP no" mice (CaMKII TT305/6VA mice), respectively. Interestingly, neither L7-SK2 knockout mice nor CaMKII TT305/6VA mice show the Ca^{2+} potentiation. This observation suggests the contribution of both mechanisms to receptive field plasticity in intact, awake mice.

Disclosures: **T. Lin:** None. **S.E. Busch:** None. **C. Hansel:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.10

Topic: B.05. Synaptic Plasticity

Support: NIH Grant 1R01NS123424

Title: The effect of inter-pulse variability in electrical deep-brain stimulation on the time course of evoked dopamine release

Authors: N. C. WEINTRAUB[1], A. R. HAMILTON[1], A. VISHWANATH[2], G. HOLGUIN[2], S. L. COWEN[3], ***M. HEIEN**[4];
[1]Chem. & Biochem., [2]Psychology, [3]Dept. of Psychology, [4]Univ. of Arizona, Tucson, AZ

Abstract: Dopamine release in the striatum and cortex is integral to motor control, reward-guided learning, and decision making. Electrical deep brain stimulation (DBS) is an important tool for the causal investigation of neural circuits and the function of dopamine release. DBS is also a valuable tool for treating neurological disorders such as Parkinson's disease, epilepsy, and severe depression. Traditionally, DBS has been applied using fixed inter-pulse interval stimulation at a given frequency. This is surprising as neural circuits are often more responsive to variable and unpredictable input. In this study, we seek to explore the effects of inter-pulse variability used for DBS on the dopamine release in the nucleus accumbens (NAc). We hypothesize that NAc dopamine release will be greatest when inter-pulse intervals are more variable or 'bursty' for a given frequency. Methods: Experiments were performed using anesthetized (isoflurane) male Sprague-Dawley rats (345-400 g, n = 5). Each rat was implanted with a carbon-fiber microelectrode placed in the NAc and a stimulating electrode placed in either the MFB or the mPFC. MFB stimulation allowed investigation of direct activation of dopamine-neuron axons, and mPFC stimulation permitted investigation of the activation of multi-synaptic circuits involved in regulating dopamine release. Ten-second stimulation trains with different

levels of inter-pulse variability were applied once every five minutes. Sub-second changes in dopamine concentration were measured using fast-scan cyclic voltammetry (FSCV). Contrary to our hypothesis, preliminary data indicates that variable stimulation does not affect peak dopamine release measured at the end of a stimulation train; however, inter-pulse variability did shape the time-course of release during a stimulation sequence. Specifically, we observed that dopamine concentration increased during short-lasting high-frequency bursts embedded in the longer stimulation train. We also observed that binning the data in 600 ms increments for stimulation pulses and dopamine concentration best capture the correlation of the short-term stimulation frequency and dopamine release. This indicates that individual stimulation pulses influence stimulated release over a longer temporal regime and longer epochs might be better to use when determining the effect of individual stimulation pulses on evoked dopamine release. Results from these experiments may enhance the understanding of how the timing and variability of DBS pulse sequences modulates the time-course of release.

Disclosures: N.C. Weintraub: None. **A.R. Hamilton:** None. **A. Vishwanath:** None. **G. Holguin:** None. **S.L. Cowen:** None. **M. Heien:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.11

Topic: B.05. Synaptic Plasticity

Support: European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska Curie grant agreement No 814244.

Title: Development of a high content cortical neuroplasticity assay for the assessment of structural plasticity of psychedelics

Authors: S. ENGEL[1], L. MOLL[2,4], S. M. LARDELL[3], J. PIHL[5], P. KARILA[5], M. CHYTIL[1], R. AGRAWAL[1], **N. A. POWELL**[1];
[1]Delix Therapeut., Concord, MA; [2]Cellectricon, Stockholm, Sweden; [3]Cellectricon, Mölndal, Sweden; [4]Dept. of Physiol. and Pharmacol., Karolinska Institutet,, Stockholm, Sweden; [5]Cellectricon AB, Mölndal, Sweden

Abstract: The approved fast- and long-acting antidepressant ketamine has been shown to be a powerful neuroplasticity promoter in vivo, increasing dendritic complexity, promoting dendritic spine growth, and stimulating synapse formation. Similar to ketamine, the psychedelic compounds psilocybin, DMT and LSD have also been shown to promote powerful neuroplasticity, highlighting their potential to treat depression and related brain disorders. However, the side effect profile of psychedelics and ketamine limits their utility as medicines. As current in vitro neurite outgrowth (NOG) assays are typically run in a low throughput manner, high-capacity models capable of reproducibly quantifying compound effects on structural

plasticity will be needed for rational identification and prioritization of new candidate molecules. For this assay development, rat (E18) cortex cells were seeded in low density and cultured in 384-well format. Compounds were added 6 days before fixation of the cultures and processed for immunocytochemistry and stained with antibodies for visualization of nuclei, neuronal soma and neurites. High content imaging and analysis (HCA) was performed to quantify morphological effects induced by tool compounds both on the population- and single cell level. Optimal conditions were identified where cultures were viable yet grew processes sparsely enough to enable HCA. Using these conditions, the effect of tool- and Delix proprietary compounds on neurite parameters were investigated and the 5-HT2A/5-HT2C receptor agonist DOI was identified as a suitable reference compound. To validate the assay in a scenario mimicking a regular lead optimization activity, 155 compounds were tested in concentration response-format in five independent test occasions over ten weeks. The newly developed assay showed excellent reproducibility and was applicable for assessing the neuroplasticity effects of compounds, as demonstrated by the use of both publicly available compounds, such as DOI and donepezil, and Delix proprietary compounds. In conclusion, we have developed a high content neuroplasticity assay with the ability to differentiate compounds both based on their efficacy and potency (i.e. by comparing EC_{50} values). It is thus possible to rank-order compounds, enabling prioritization for inclusion in down-stream models. Further studies are needed to understand how the assay translates to in vivo structural plasticity of compounds, as well as to demonstrate that in vitro neuroplasticity results in the modulation of function of synaptically connected neurons.

Disclosures: **S. Engel:** A. Employment/Salary (full or part-time):; Delix Therapeutics. **L. Moll:** A. Employment/Salary (full or part-time):; Cellectricon. **S.M. Lardell:** A. Employment/Salary (full or part-time):; Cellectricon. **J. Pihl:** A. Employment/Salary (full or part-time):; Cellectricon. **P. Karila:** A. Employment/Salary (full or part-time):; Cellectricon. **M. Chytil:** A. Employment/Salary (full or part-time):; Delix Therapeutics. **R. Agrawal:** A. Employment/Salary (full or part-time):; Delix Therapeutics. **N.A. Powell:** A. Employment/Salary (full or part-time):; Delix Therapeutics.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.12

Title: WITHDRAWN

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.13

Topic: B.05. Synaptic Plasticity

Title: Effect of DMT (N,N-Dimethyltryptamine) on in vitro rat cortical neuron neurite outgrowth and acute in vivo effects on the functional connectivity in pharmacological MRI (phMRI)

Authors: T.-K. STENIUS, R. IMMONEN, J. ROKKA, K. PALDANIUS, M. DUDEK, ***A. SHATILLO**, D. MISZCZUK;
Charles River Discovery Services, Kuopio, Finland

Abstract: DMT and other psychedelics have been reported capable to induce cognitive, antidepressant and anxiolytic effects driven primary through the serotonergic system. Effect of DMT on neuroplasticity in vitro and neuronal activity in vivo has been reported after long stimulation period or chronic follow up, respectively. The objective of this study was to characterize the acute effect of DMT: *in vitro* in cortical neurons neurite outgrowth assay with short 1-hr stimulation, and *in* vivo on brain functional connectivity (FC) and BOLD response in pharmacological MRI (phMRI), as well as 5HT2A occupancy using radioligand binding assay. For *in vitro* study rat cortical cultures were prepared from E18 embryos and were stimulated for 60 minutes with various DMT and ketamine concentrations on DIV3 (days in vitro), followed by 71 h growth period. At DIV6, cultures were fixed and stained using microtubules associated protein (MAP-2) IHC. Evaluation of neurite outgrowth and Sholl analysis were conducted. For *in vivo* study, phMRI imaging was performed at 7T, in ventilated medetomidine anesthetized rats treated with veh+veh, veh+DMT (5 or 10 mg/kg i.p.), or haloperidol 2 mg/kg i.v. + DMT 10 mg/kg i.p. Data were acquired with GE-EPI: 20 min baseline, and 40 min follow-up after compounds injections. BOLD time-series and FC were analyzed. The 5HT2A radioligand binding assay was performed with [^{3}H]MDL100907 incubated prefrontal cortex homogenates from veh and DMT 10 mg/kg treated rats at collection timepoints of 5, 15, 30 and 45 mins. Treatment with ketamine increased the number (10 nM) and total length of processes and branches (0.1 nM) and increased the AUC (0.1 nM) or maximum number of crossings (10 and 1000 nM) in the Sholl plots. DMT stimulation with doses 0.1, 10 and 30 nM increased the number of processes. PhMRI data showed dose dependent BOLD response for DMT (5 and 10mg/kg i.p.) and modulation by antipsychotic haloperidol. DMT (5 and 10 mg/kg i.p.) suppressed striato-cortical, thalamo-cortical and -hypothalamic FC while increased prefrontal cortex connectivity. The FC patterns were partially restored by haloperidol. In radioligand binding assay DMT occupancy in 5HT2A receptors was observed already after 5 min of DMT 10 mg/kg i.p. administration with sustained increasing trend up to 45 mins post-dosing confirming quick entry and binding in the brain. In conclusion, we showed DMT-induced acute effect on neurite outgrow, neuronal activity and FC, accompanied by rapid 5HT2A receptor binding. Next step is to repeat the design with Psilocybin and compare the FC pattern with that of DMT.

Disclosures: T. Stenius: None. **R. Immonen:** None. **J. Rokka:** None. **K. Paldanius:** None. **M. Dudek:** None. **A. Shatillo:** None. **D. Miszczuk:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.14

Topic: B.05. Synaptic Plasticity

Support: DP180101473/Australian Research Council
APP200660/National Health and Medical Research Council

Title: The physiological function of tropomyosin 4.2 in neurons

Authors: *S. GENOUD[1], T. TOMANIC[1], C. CHAICHIM[2], H. STEFEN[1], E. PARIC[1], J. M. POWER[2], T. FATH[1];
[1]Macquarie Univ., Macquarie Univ., Sydney, Australia; [2]Univ. of New South Wales, Sydney, Australia

Abstract: The neuronal actin cytoskeleton is essential for the development and function of neuronal cells, including synapse formation and signal transduction. The regulation of actin dynamics requires interactions of actin with many actin-associated proteins. This process is crucial for synaptic plasticity and subsequently, learning and memory. Tropomyosins (Tpm) are actin-associated proteins, regarded as master regulators of actin dynamics in mammalian neurons. As the Tpm4.2 isoform is highly expressed in the post-synapse, we sought to determine the physiological function of Tpm4.2 in neuronal morphogenesis and signalling. Fluorescence recovery after photobleaching (FRAP) demonstrate that different Tpm isoforms have differential effects on filamentous actin dynamics in dendritic spines, with reduced recovery and diffusion coefficients in mouse primary hippocampal neurons isolated from Tpm4.2 KO mice compared with WT neurons. Primary hippocampal Tpm4.2 KO neurons also demonstrate significant functional differences in their regulation of axonal and dendritic growth, with dendritic complexity being increased early in development. This is evidenced in an increased connectivity during live calcium imaging in mature neurons at 20 days *in vitro* when compared with WT neurons. A significant reduction in frequency and amplitude of spontaneous neuronal activity at 20DIV in Tpm4.2 KO neurons was also observed with live calcium imaging - in line with electrophysiology data reporting reductions in miniature excitatory post-synaptic current (mEPSC) frequency and amplitude. Electrophysiology data also indicated that mEPSC rise time and decay time was increased - a process not dependent on the observed increase in the dendritic field. The knockout of Tpm4.2 does not however, appear to affect spine morphology or the relative proportion of dendritic spine types. In summary, our data suggest that Tpm4.2 plays a role in regulating actin dynamics at the synaptic compartment. Our findings thereby contribute to the knowledge on the physiological function of Tpm4.2 in neurons and the regulation of the actin cytoskeleton in neuronal synapses.

Disclosures: S. Genoud: None. **T. Tomanic:** None. **C. Chaichim:** None. **H. Stefen:** None. **E. Paric:** None. **J.M. Power:** None. **T. Fath:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.15

Topic: B.05. Synaptic Plasticity

Support: KAKENHI 21K08943

Title: Functional and structural changes in spinal dorsal horn neurons after peripheral nerve injury are long term regulated by astrocytes

Authors: *M. KURABE, M. SASAKI, K. FURUTANI, H. BABA;
Niigata Univ, Sch. Med., Niigata Univ., Niigata, Japan

Abstract: Background: Chronic pain remains difficult to treat despite numerous reports on its pathogenesis, including neuronal plasticity in the spinal dorsal horn (SDH). We hypothesized that understanding the plasticity of the SDH at specific time points after peripheral nerve injury (PNI) would not be sufficient to elucidate the mechanisms of chronic pain, and analyzed the contribution of astrocyte proliferation to changes in plasticity of synaptic transmission and neuronal loss after PNI over time in the SDH.**Methods:** Chronic constriction injury (CCI) rat models were used. Synaptic responses and neuronal loss were compared between control, early post-CCI (CCI-E), and late post-CCI (CCI-E) groups following administration of carbenoxolone (CBX), an astrocyte gap junction blocker, for 1-week post-CCI. Changes in synaptic transmission were recorded from SDH neurons by in vivo whole-cell patch-clamp technique. To analyze the neuronal plasticity (loss), the coexpression of NeuN, a marker of neurons, and Pax2, a marker of inhibitory neurons was examined immunohistochemically. In addition, to analyze whether the loss of neurons is accompanied by necroptosis, we analyzed the coexpression of NeuN and RIP3, a marker of necroptosis. **Results:** The frequency of spontaneous excitatory synaptic currents (sEPSCs) increased in CCI-E rats but returned to control levels in CCI-L rats. Amplitude was increased in both rats. In addition, receptive fields (RF) were identified by marking the areas of response to tactile stimuli under voltage-clamp mode; RF size was significantly enlarged in both CCI-E and CCI-L compared to Sham rats. Immunohistological staining revealed that the number of NeuN-positive neurons was significantly reduced in both CCI-E and CCI-L, while inhibitory neurons (Pax2+/NeuN+ cells) were reduced only in CCI-L. The number of RIP3+ and NeuN-positive neurons was markedly increased by CCI. CBX administration for 7 days after CCI suppressed the increase in sEPSCs amplitude and RF expansion. The increase in the number of RIP3+/NeuN+ neurons was also significantly suppressed over the late post-CCI period. **Conclusions:** These results indicate that the activation of astrocyte-neuron interactions in the SDH early after PNI functions as a mechanism for functional and structural plasticity, structurally resulting in loss of neurons with necroptosis and functionally resulting in alterations in synaptic transmission.

Disclosures: M. Kurabe: None. **M. Sasaki:** None. **K. Furutani:** None. **H. Baba:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.16

Topic: B.09. Glial Mechanisms

Title: The NHE1 is suppressed in spinal cord of neuropathic pain models

Authors: *J. WU[1], H. SHIN[1,2], N. SHIN[1,2], W. LEE[4], D. KIM[1,3,2];
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Abstract: One of the underlying pathophysiology of neuropathic pain is central disinhibition. Central inhibition is mainly accomplished via spinal interneurons and brainstem descending pathways as well as classical inhibitory transmitters such as: aminobutyric acid (GABA), glycine, adrenergic, 5-HT and enkephalin. On the other hand, the reduction of intracellular pH during neuroinflammation may either lead to neuronal death, a part of the pathological process. However, how intracellular pH changes affects central disinhibition in neuropathic pain remains unknown. Sodium hydrogen exchanger 1 (slc9a1, NHE1), widely involved in cell volume and pH regulation, is one of the most important acid extruders, inducing extracellular acidification in response to neuronal hyperactivity. Here, we first established a rat spinal nerve ligation SNL model. We found that NHE1 expression was reduced in the spinal dorsal horn of rats on days 3 and 10 after SNL, and furthermore, the vast majority of NHE1 was co expressed with the neuronal cells. In addition, there was a concomitant decrease in GAD67, which is responsible for the synthesis of GABA. When we found after intrathecal injection of NHE1 siRNA nanoparticles on day 3 after SNL surgery, this exacerbated pain in SNL model rats. From this, we speculate that NHE1 reduction in the spinal dorsal horn of SNL model rats may be one of the mechanisms that cause neuropathic pain, which specifically may involve the excitability of NHE1 through intraneuronal pH regulated inhibitory networks, such as the GABA system.

Disclosures: **J. Wu:** None. **H. Shin:** None. **N. Shin:** None. **W. Lee:** None. **D. Kim:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.17

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

Support: VRTC T32 Grant
Unrestricted grant from the research to prevent blindness to the UW Madison

Dept. of Ophthalmology
McPherson Eye research institute Rebecca Meyer Brown Professorship

Title: Luminance dependent compensation of output retinal pathways to perturbed input

Authors: *J. KHOUSSINE[1,2], A. A. SAWANT[3], R. SINHA[4], M. HOON[5];
[1]Ophthalmology and Visual Sci., Univ. of Wisconsin, Madison, WI; [2]Med. Scientist Training Program, Madison, WI; [3]Ophthalmology and Visual Sci., Univ. of Wisconsin Madison, Madison, WI; [4]Dept. of Neurosci., [5]Ophthalmology and Visual Sci., Univ. of Wisconsin, Madison, Madison, WI

Abstract: Retinal output neurons - ganglion cells (RGCs) - generate light-evoked action potentials (spikes) that are heavily shaped by dendritic integration of excitatory and inhibitory synaptic inputs. Alpha RGCs, like many other RGCs, consist of parallel *on* and *off* circuits, which increase their spike output to increments or decrements of light, respectively. It is known that these parallel circuits are interconnected and that the *on* circuit provides inhibitory input to the *off* circuit, which occurs through the mechanism of 'crossover' inhibition. We have generated a CRISPR-mediated knockout of *Grm6*, the principal glutamate receptor responsible for signal transduction in the *on* circuit, to study how both the *on* and *off* alpha RGCs adapt to deficits in *on* pathway input. Specifically, we measured light-evoked responses from *on* and *off* sustained alpha RGCs, respectively, in the *Grm6*$^{-/-}$ mice using single cell electrophysiology. We correlated spike output and excitatory/inhibitory synaptic inputs across light levels with immunohistochemical labeling of synaptic markers across the RGC dendritic arbors. We found that *Grm6*$^{-/-}$ *on* alpha RGCs are unable to generate spikes across light levels, whereas the *Grm6*$^{-/-}$ *off* alpha RGCs generate spikes as expected at high photopic light levels, despite complete elimination of *on* pathway mediated crossover inhibition. Interestingly, we observed that the spike output of *off* sustained alpha RGCs is perturbed by the loss of crossover inhibition at lower mesopic light levels in *Grm6*-deficient retinas. Immunohistochemical labeling of excitatory and inhibitory postsynapses across RGC arbors revealed preservation of excitatory postsynapses across the *on* alpha *Grm6*$^{-/-}$ RGCs. In addition, the ratio of inhibitory and excitatory postsynaptic markers was altered across *off* alpha *Grm6*$^{-/-}$ RGCs. Together, our findings underscore a luminance-dependent functional compensation of the *off* pathway output in the *Grm6*$^{-/-}$ mutants and provide insights into the inter-dependence of parallel neural circuitry in the mammalian retina.

Disclosures: J. Khoussine: None. **A.A. Sawant:** None. **R. Sinha:** None. **M. Hoon:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.18

Topic: B.05. Synaptic Plasticity

Support: NIGMS 1R16GM145548-01
Orville Edward Egbert, M.D. Endowment fund

Title: Kekkon5'S role in dysfunctional inhibitory control, an endophenotype of neurodevelopmental disorders

Authors: *B. HERNANDEZ[1], E. SALDES[1], M. CLAGUE[2], P. SABANDAL[1], K.-A. HAN[1];
[1]Biol. Sci., The Univ. of Texas at El Paso, El Paso, TX; [2]Columbia Univ., New York City, NY

Abstract: The role of Kekkon5 in inhibitory control, an endophenotype of neurodevelopmental disorders
Bryan Hernandez, Erick B Saldes, Maria Clague, Paul R Sabandal, Kyung-An Han
Inhibitory control is a core executive function important for goal-directed behaviors. Dysfunctional inhibitory control is associated with numerous neurodevelopmental disorders (NDDs) such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD). ADHD and ASD involve altered dopamine signaling; however, the mechanism by which alter dopamine signaling leads to dysfunctional inhibitory control remains largely unknown. To address this gap in knowledge, we utilized *Drosophila melanogaster* to perform a functional screen to identify novel genes interacting with the dopamine system for inhibitory control. We identified *kekkon5* (*kek5*), a homolog of human LRFN1 gene, as one of the genes interacting with the dopamine transporter mutation for inhibitory control. Kek5 is a cell adhesion molecule and functions as a negative regulator of BMP signaling. The heterozygous *kek5* (*kek5/+*) or *fumin* (*fmn/+*) mutant showed good inhibitory control, however the double heterozygous *kek5/+;fmn/+* mutant displayed dysfunctional inhibitory control. The progress including the neural site for the *kek5* and *fmn* interaction and the mechanism underlying their interaction for inhibitory control will be presented. This study will provide insight into the mechanism by which cell adhesion molecule interact with dopamine system for inhibitory control.
Keywords: Inhibitory control,kekkon5, cell adhesion molecule, dopamine, *Drosophila*
Funding: RISE, SuRE, Endowment fund

Disclosures: B. Hernandez: None. **E. Saldes:** None. **M. Clague:** None. **P. Sabandal:** None. **K. Han:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.19

Topic: B.05. Synaptic Plasticity

Title: The effects of sedentary aging and exercise on end plate area and morphology in female rats

Authors: *J. M. VANGYSEGHEM, J. M. SPITSBERGEN;
Western Michigan Univ., Western Michigan Univ., Kalamazoo, MI

Abstract: Glial cell line-derived neurotrophic factor (GDNF) is an important neurotrophic support factor for the motor nervous system. Previous studies from our laboratory showed that with aging, there was a decline in GDNF content in skeletal muscle and alterations in size and complexity in motor end plates in male rats. We believe that decline in levels of GDNF concentration may play a role in the decreased complexity in motor end plates. However, little is known about GDNF expression in skeletal muscle and end plate morphology in female rats. Previous work in our lab shows that there is an increase of GDNF content skeletal muscle from female rats during development, followed by a decline with age, but with exercise GDNF content is restored. Because we have seen this relationship between exercise and GDNF concentration in skeletal muscle, we wanted to investigate how aging and exercise is impacting the nervous system in female rats, by looking at the size and complexity of end plates. We hypothesize that end plate size and complexity in female rats will remain stable prior to reproductive senescence and decline thereafter, and that exercise will slow or prevent that decline. To determine if exercise has neuroprotective effects, we took hindlimb skeletal muscle from sedentary and exercised rats between the ages of 1 and 18 months. α-Bungarotoxin was used to stain for acetylcholine receptors at the neuromuscular junction. Slides were viewed using a Nikon Eclipse E750 confocal microscope and end plate size and complexity were analyzed using ImageJ software. The results show that the average area of end plates increased from 4 weeks (84.132±5.054 μm2) to 12 months (362.464±21.955 μm2) with a decrease at 18 months (269.673±24.270 μm2). There was a decrease in end plate complexity from 4 weeks (35.75%±1.06%) to 18 months (5.82%±0.71%). Exercise had no effect on the average area of end plates from 18-month female, however, exercise restored complexity to levels observed in sedentary female rats at 12 weeks of age. Our results show that exercise helped maintain morphology and complexity of end plates in older female (18 months). The morphology and complexity of the end plates from exercised 18 month females were similar to that of 12-week sedentary females, suggesting that exercise is in fact reversing the negative effect of aging on end plates. Our data showed that exercised 18-month end plate complexity was significantly higher than that of similarly age-matched sedentary controls, which has led us to believe that there is a correlation between a decrease in end plate complexity with increased aging in sedentary female rats, and that exercise can help mitigate those effects.

Disclosures: **J.M. Vangyseghem:** None. **J.M. Spitsbergen:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.20

Topic: B.05. Synaptic Plasticity

Support: NIH Grant 1K01HL145339-01A1

Title: Biological sex differences in motor activity and hippocampal postsynaptic density protein 95 expression in the gray short-tailed opossum (Monodelphis domestica) in the context of an environmental enrichment paradigm

Authors: *E. ALANIZ[1], S. HEINGRAJ[3], K. RENTERIA[4], F. DOMINGUEZ[6], M. S. MINOR[5], J. L. VANDEBERG[4], M. GIL[2];
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Abstract: Environmental enrichment (EE) may influence brain development and function throughout the lifespan. The purpose of the present study is to investigate whether environmental enrichment and biological sex influence behavior and neuroplasticity in the gray short-tailed opossum (*Monodelphis domestica*). Experiment 1 tested whether *Monodelphis* interact with enrichment items (cylinders, bones), confirming that this non-traditional animal model is comparable to rodents. Each subject was placed in an empty cage with an enrichment item for 10 minutes, and this was repeated for different items over 6 trials (3 females, 2 males). In some trials, females (M = 416.13, SD = 61.76) had significantly higher mobility durations than males (M = 207.0, SD = 287.6), t(3) = -1.32, p< 0.05). Object interaction frequencies ranged from 24 - 72 interactions per trial. Experiment 2 tested the effects of EE on postsynaptic density protein 95 (PSD-95) in the hippocampus and behavior in young *Monodelphis* (PND 60 - 87). Age-matched animals of both sexes were exposed to four housing conditions for 27 days: no enrichment (control), social enrichment alone, object enrichment alone, and full environmental enrichment (both social and objects). Behavioral data were collected using the open field test; animals were perfused following the last test, and brains were collected and tissue processed using a standard immunohistochemistry (ABC-DAB) protocol to detect PSD-95. Although the ANOVA test was not statistically significant, the results suggest that animals in the social and object enrichment group had higher locomotor activity (*n*= 8, M = 169.34, SD = 49.06) compared to the control group (*n*= 4, M = 129.53, SD = 42.50) environmental enrichment group (*n*= 4, M = 145.85, SD = 59.60), and social enrichment group (*n*= 8, M = 161.05, SD = 31.38). Subjects exposed to the full environmental enrichment condition (both object and social) appeared to have greater PSD-95 cell expression (*n* = 8, M = 66.25, SD = 48.93), compared to those housed in the object enrichment (*n*= 4, M = 57.50, SD = 41.15), social enrichment (*n* = 7, M = 56.14, SD = 14.22), and control (*n*= 4, M = 56.00, SD = 23.41) conditions. Females had higher PDS-95 expression (*n* = 11, M = 66.00, SD = 46.63) compared to their male counterparts (*n*= 12, M = 54.25, SD = 15.53). These findings are preliminary. We are currently analyzing data from other tests (go-no-go task, rota-rod, and object place recognition task) to determine the impact of EE on learning and other motor function variables. *Monodelphis* has long been recognized an ideal model for neurodevelopmental research, and our results suggest that it is also useful for investigating EE effects and biological sex differences.

Disclosures: E. Alaniz: None. **S. Heingraj:** None. **K. Renteria:** None. **F. Dominguez:** None. **M.S. Minor:** None. **J.L. Vandeberg:** None. **M. Gil:** None.

Poster

694. Structural Plasticity: Neurons and Networks

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 694.21

Topic: B.05. Synaptic Plasticity

Support: Brain Injured Childrens After-care Recovery Endeavours
University of Queensland Research Scholarship
Australian NHMRC Boosting Dementia Research Leadership Fellowship (APP1135769)
National Health and Medical Research Principal Research Fellowship (GNT1120615)
Discovery Project from the Australian Research Council (210101712)

Title: Microstructural analysis of the human anterior commissure does not support altered interhemispheric wiring of the anterior commissure in corpus callosum dysgenesis

Authors: T. J. EDWARDS[1,2], ***R. J. DEAN**[5,1], G. A. ROBINSON[3], J. KNIGHT[3], S. MANDELSTAM[6], L. J. RICHARDS[7,4];
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Abstract: Individuals with corpus callosum dysgenesis (CCD) lack the clear disconnection syndrome that is characteristic of individuals in whom the corpus callosum has undergone a callosotomy. One potential explanation for this paradox is that the anterior commissure is remodeled in individuals with these conditions to improve interhemispheric communication. To investigate this possibility, a cohort of sixteen individuals with CCD (and sixteen sex and age-matched neurotypical controls) underwent multi-shell diffusion magnetic resonance imaging (dMRI) at 7T to assess their anterior commissure anatomy for evidence of neuroplasticity, such as an enlargement of the commissure or the presence of novel neocortical connections. No significant differences in the midsagittal anterior commissure areas of the CCD and control group were detected, nor was a tractographic analysis able to identify any novel or re-routed connections projecting through the commissure. Similarly, the anterior commissures of the CCD cohort did not exhibit any significant alterations in axonal intracellular volume or radial diffusivity that would indicate an increase in axon density. Individual variances in the neuroanatomy of the anterior commissure did not correlate with the performance of the CCD group on neuropsychological tasks that are dependent upon interhemispheric communication. We conclude that the anterior commissure is unlikely to be the primary substrate for the compensation of interhemispheric communication in CCD; other mechanisms, such as subcortical drivers, may be involved in mediating bilateral information integration in this unique population.

Disclosures: **T.J. Edwards:** None. **R.J. Dean:** None. **G.A. Robinson:** None. **J. Knight:** None. **S. Mandelstam:** None. **L.J. Richards:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.01

Topic: B.08. Epilepsy

Support: CFNRE Pilot Award

Title: Targeted ultrasound circuit mapping through the development of a focal, cortical epilepsy model in rats

Authors: *S. L. MAI[1], G. K. ADAMS[2], B. G. SCHREURS[3], P. KONRAD[4];
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Abstract: Blood-brain barrier disruption (BBBD) using low-intensity focused ultrasound (LiFU) is already being studied in humans in several clinical trials to deliver a variety of drugs with MRI guidance non-invasively. Potential use is the ability of LiFU-BBBD applied with millimeter precision to treat focal neural circuit disorders, similar to the current use of neuromodulation implants to treat diseases such as epilepsy or Parkinson's disease but without the need for invasive surgery. This project aims to demonstrate the concept of using LiFU-BBBD to temporarily block conduction in a brain circuit where excess, focal electrical activity is present, such as in cortical epilepsy. Here, we employ an established animal model of a focal circuit disorder (tetanus-induced focal cortical epilepsy)[3] to validate the use of LiFU-BBBD for functional localization. In this model, local injections of tetanus toxin to the motor cortex of a rat produce a focal seizure disorder, resulting in frequent seizures measurable by videography and electrophysiology with a low probability of seizure spread[1]. An initial goal of this project is to modify this animal model to allow LiFU MRI targeting of epileptic focus to test local anesthetic delivery using BBBD techniques. By pairing LiFU- BBBD with an intravenous injection of nanoparticles containing lidocaine (which usually are unable to cross the BBB), we are able to determine whether the LiFU stimulation coordinates have successfully targeted the epileptic focus based on whether the seizure activity is reduced[4]. This method allows the functional effect of nanoparticle drug delivery, measured behaviorally and electrophysiologically, to non-invasively identify the locus of a neurological defect. In addition, it provides an innovative approach to study a non-invasive reversible method for treating focal seizures in an animal model through LiFU-BBB drug delivery. This model is designed to allow repeated MRI imaging and delivery of intravascular anesthetic agents to test the concept of MRI-guided localized disruption of cortical circuits. Controlled, reversible anesthetic delivery with LiFU-BBBD can be developed using anesthetic-coupled nanoparticles, which can potentially create a "temporary

lesion" in the brain, that can be controlled for hours or days[2]. With this work, we develop the use of LiFU as a non-invasive method to test new therapeutic targets for lesions or other treatments that can be monitored over several days.

Disclosures: S.L. Mai: None. **G.K. Adams:** None. **B.G. Schreurs:** None. **P. Konrad:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.02

Topic: B.08. Epilepsy

Support: NIH/NINDS Grant NS115049

Title: Temporal ontogeny of epileptogenesis as measured by video/EEG parameters in a transgenic mouse model of progressive, adult-onset epilepsy

Authors: *A. TYULMENKOVA, J. LABRADOR PINO, V. STUBBS, C. ISGOR; Biomed. Sciences, Col. of Med., Florida Atlantic Univ., Boca Raton, FL

Abstract: EEG spikes are correlated with presence and ictogenic location of epilepsy in post-injury human patients. Data from animal models support that the presence, frequency and patterns of EEG spikes are accurate predictors of subsequent experimental epilepsy in acquired models. In this study, we examined the evolution of video/EEG parameters on route to development of epilepsy in a transgenic mouse model of adult-onset epilepsy. Our laboratory uses a transgenic mouse strain that over-expresses the brain-derived neurotrophic factor (BDNF) in the forebrain under the calcium/calmodulin-dependent kinase II alpha promoter (termed TgBDNF mice). TgBDNF mice demonstrate motor seizures in response to cage agitation and tail lifting stimulation. TgBDNF model is suitable to study gradual departure from coordinated, organized network activity towards aberrant, pathologic type over a sizeable time window. We collected video/EEG data from yoked pairs of litter-matched TgBDNF and wild-type controls across ~6 months after skull implantation of EEG arrays at young adulthood (8 wks of age). Mice were seizure induced by cage agitation once a week to track epileptiform activity. Our findings show that TgBDNF mice progress to spontaneous seizures at different rates much in the same way humans and animals with injury-evoked epilepsy do. However, abnormal electrographic phenomena emerge and organize in predictable stages. At initial investigation,TgBDNF mice display isolated uniphasic and biphasic spikes in response to cage shaking, with no indication of behavioral/motor problems. Mice then predictably progress to multiple pre-ictal spike discharges that increase in amplitude and number as a function of episodes of seizure inducing stimulation. Next stage in the ontogeny of epilepsy is marked by transition to poly spikes and wave discharges (SWDs) in response to cage shaking with bouts of behavioral arrest (9-15 sec), indicative of absence seizures. SWDs progress to full motor (tonic/clonic) seizures (Racine stage 5) with dynamically longer periods of postictal generalized

EEG suppression (PGES). With each successive seizure, PGES duration increases drastically with heightened risk of cardio-respiratory arrest. At more severe stages of epilepsy, ictal discharge and PGES are followed by SWDs intertwined with segments of baseline activity during recovery, suggestive of an absent seizure precipitated by a grand mal event. These preliminary data show electrophysiological aberrations present prior to and culminating in convulsive seizures in the TgBDNF mice with a conserved, temporal pattern indicative of gradually altered circuit function.

Disclosures: A. Tyulmenkova: None. **J. Labrador Pino:** None. **V. Stubbs:** None. **C. Isgor:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.03

Topic: B.08. Epilepsy

Support: NIH P50HD105354
NIH R21NS106434
NIH NINDS 5-T32-NS-091006-07

Title: Optogenetic platform for on demand seizures in chronically epileptic mice

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Abstract: Animal models of chronic epilepsy recapitulate key morphological and circuit level aberrations seen in diseased human brains; however, the unpredictable nature of spontaneous seizures limits the usefulness of such models in experiments where the precise moment of seizure onset matters. To overcome that obstacle, we present a method to acutely evoke seizures in the chronically epileptic hippocampus using optogenetic excitation. Our methodology is as follows: In adult Thy1-ChR2-YFP mice (Jax #007612, n = 3), chronic epilepsy is first induced via unilateral intrahippocampal kainic acid injection into the posterior CA3. A month later, seizures are optogenetically evoked in these animals by exciting Thy1+ neurons in the dorsal CA1 ipsilateral to the site of kainic acid injection. The light train for seizure evocation consists of 10 Hz, 25 ms long pulses of a 473 nm laser. The total stimulation duration was varied between 1 and 15 seconds. When the stimulation duration is 3 seconds or longer, we found that seizures are successfully evoked about 90% of the time in chronically epileptic, but not control, Thy1-ChR2-YFP animals. Evoked seizures tend to last between 3 and 15 seconds and the average bandpower of high frequency activity (80+ Hz) is elevated during the seizures. The latency of onset is variable, but is usually under 7 seconds. The ability to create seizures on demand in a chronically epileptic circuit allows researchers to investigate whether timing of therapeutic

intervention matters in regard to the moment of seizure onset in chronically epileptic animals. Further, as seizure take a few seconds to evoke, this model allows researchers to investigate whether activation or inhibition of other neural population can interfere with the seizure generation process. In all, this platform allows for investigation of mechanisms of seizure generation in a chronically epileptic circuit without the drawback of waiting excessive amounts of time for a spontaneous seizure to occur. Further, it enables the investigation of therapeutic intervention in a defined period of time: either pre, during, or post seizure onset.

Disclosures: Y. Chen: None. **B. Litt:** None. **F. Vitale:** None. **H. Takano:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.04

Topic: B.08. Epilepsy

Support: H2020-FETPROACT-01-2018 (RIA) HERMES Grant 824164

Title: In vitro hippocampal spheroids exhibit the spontaneous emergence of epileptiform patterns

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Abstract: Background: Mesial temporal lobe epilepsy (MTLE) is the most common form of epilepsy in adults and the most often drug-refractory. The rodent hippocampus-cortex (hCTX) slice treated with 4-aminopyridine (4AP) is an established and highly valuable model of limbic ictogenesis to address new approaches for seizure prediction and control. Yet, it enables acute studies only and it requires a considerable number of animals. In the effort to reduce/replace animals, we recently proposed *in vitro* neural stem cell-derived organoids mimicking hippocampal cytoarchitecture (Ciarpella et al., iScience 2021, doi: 10.1016/j.isci.2021.103438). However, functional brain region specific organoids are still an open challenge requiring complex and costly protocols and suffering for little reproducibility across laboratories.
Aim: Building upon the pivotal involvement of the hippocampus in MTLE, we explored the potential of primary hippocampal neuron-derived spheroids to recapitulate the pathophysiological hallmarks of MTLE epileptogenesis and ictogenesis.
Methods: We generated spheroids from primary hippocampal neurons of E18 rat embryos and we addressed their developmental functional features *via* 3D microelectrode array at 10, 14, 21, 28 and 35 days *in vitro* (DIV) - 15 spheroids / time point from 6 litters. We compared the spheroid activity with that of 4AP treated rodent hCTX slices. Data are reported as median ± SD.
Results: At 10 and 14 DIV, 40% and 50% of spheroids were active, respectively, and both displayed only slow isolated events with inter-event interval (IEI) of 85.3 ± 23 s. At 21 DIV,

77.8% of spheroids were active and displayed population bursts with shorter IEI (13.4 ± 10 s), recurring either alone (58.3% spheroids) or mixed with ictal-like events (41.6% spheroids). At 28 and 35 DIV, 100% and 88.2% spheroids were active, respectively, and generated 3 distinct activity profiles: (i) fast spiking activity with IEI = 2.8 ± 0.7 s alone; (ii) mixed activity; (iii) purely ictal-like activity which became predominant at 35 DIV (60% spheroids, duration: 150 ± 8.4, interval: 247.6 ± 46.2). These patterns resembled the electrographic features typical of 4AP treated rodent hCTX slices.
Conclusions and outlook: Our work brings a highly reproducible method to generate and maintain long-lasting *in vitro* hippocampal spheroids which display a functional developmental profile and spontaneously acquire features typical of epilepsy. Thus, hippocampal spheroids represent a cost-effective alternative to animal models for developmental studies as well as for investigating epileptogenesis, ictogenesis and therapeutic strategies aimed at preventing them.

Disclosures: **J.W. Ephraim:** None. **G. Panuccio:** None. **G. Palazzolo:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.05

Topic: B.08. Epilepsy

Title: Validation of the tuberous sclerosis complex-associated epilepsy model in tsc2 mutant zebrafish.

Authors: *J. SHIN[1,2], K. LEE[1,3], D. KANG[1], J. KIM[1], S. PARK[1], S. KIM[1,4], S. KIM[2];
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Abstract: Tuberous sclerosis complex (TSC) is a rare genetic disease caused by loss-of-function in either the *TSC1* or *TSC2* genes and is neurologically characterized by benign tumor growth, epilepsy, cognitive deficits, and autism. In TSC, epilepsy is the most common neurologic symptoms, and mostly presenting as infantile spasms (IS). In this study, we performed a behavior, electrophysiological analysis of tsc2-deficient zebrafish larvae with the aim of elucidating the association with IS. To identify epileptic phenotypes, larvae was stimulated by light pulse to trigger photosensitive seizure. Mutants demonstrate elevated locomotor activity beginning with the onset of the light stimulus compared to WT siblings. we recorded electroencephalogram (EEG) from the larval optic tectum and established EEG-based epileptiform events scoring system. Here, we show that Type 1 Interictal- and Type2 ictal-like events were more frequent in $tsc2^{+/-}$ and $tsc2^{-/-}$ larvae compared with WT. In addition, we pharmacologically validated the TSC model by manifesting rescue effect of treatment with rapamycin, a well-known mTOR inhibitor, on locomotor behavior and epileptiform events. To

explore the potentially effective drugs, we generated drug library including FDA-approved drug based on the DEGs identified from the published RNA-seq data in *tsc2*$^{-/-}$ zebrafish. The 2 new drug candidates significantly inhibit spontaneous seizure in *tsc2*$^{-/-}$. These results represent that tsc2-deficient zebrafish larvae are useful preclinical model to evaluate novel TSC-related epilepsy therapeutics screening.

Disclosures: **J. Shin:** None. **K. Lee:** None. **D. Kang:** None. **J. Kim:** None. **S. Park:** None. **S. Kim:** None. **S. Kim:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.06

Topic: B.08. Epilepsy

Support: ODC/Loulou Foundation #CDKL5-21-105-01
NIH NINDS K08NS118107-01

Title: Advancing a mosaic CDKL5 zebrafish model for high-throughput screening approaches

Authors: *C. BAKER[1,2], A. PODURI[1,2], C. M. MCGRAW[1,2,3];
[1]Neurobio., Boston Children's Hosp., Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Neurol., Massachusetts Gen. Hosp., Boston, MA

Abstract: CDKL5 Deficiency Disorder (CDD) is a neurodevelopmental epileptic encephalopathy in which loss-of-function of the X-linked gene CDKL5 leads to seizures and cortical visual impairment (CVI). CDD seizures can begin within the first month of life and are often refractory to medication. The role of X-linked mosaicism in the pathogenesis of CDD remains unclear. Here we produce multiple zebrafish models of *cdkl5* loss-of-function (LOF), characterize effects on seizure-like activity and visual function, and assess their suitability for therapeutic drug screening. We developed (1) acute knockout (KO) fish using CRISPR/Cas9, (2) stable knockouts (from CRISPR/Cas9 and *cdkl5*^{sa21938} acquired from ZIRC), (3) knock-in fish, and (4) fish harboring a mosaic "conditional by inversion" COIN allele knocked into the *cdkl5* locus. The COIN allele is a synthetic intron harboring an inverted exon flanked by oppositely facing degenerate *loxP* sites, which following Cre activity, results either in inversion (leading to truncated mRNA and protein) or deletion at the targeted locus (causing no effect on *cdkl5* mRNA or protein), simulating X-linked mosaicism. Following the establishment of fishlines, we seek to characterize the neurophysiological effects of *cdkl5* deficiency on seizure susceptibility and visual function. Seizure susceptibility is evaluated using (1) calcium imaging via FDSS, (2) tectal EEG, and (3) lightsheet, confocal, and widefield calcium imaging response to proconvulsants (PTZ, kainate, NMDA). Visual function is assayed using the visual motor response (VMR) and the optokinetic response (OKR). There are no observable sexual dimorphisms in zebrafish at the developmental time points tested. Therefore, it is not possible to

discriminate between male and female zebrafish for these experiments. Embryos used for acute knockout experiments were selected at random; all animals from all experimental conditions were handled in a uniform fashion and batch-tested simultaneously. For stable line experiments, we were blind to the genotypes of animals. Our preliminary analyses show that acute *cdkl5* CRISPant KO fish do not exhibit spontaneous seizures or altered seizure susceptibility on FDSS, but they may show altered VMR on two different backgrounds. Meanwhile, some heterozygous *cdkl5*$^{sa21938-/+}$ fish demonstrate increased epileptiform activity on tectal EEG recordings. Together these preliminary findings suggest that certain zebrafish models of CDD may be promising models of the human condition, but further work is needed.

Disclosures: C. Baker: None. **A. Poduri:** None. **C.M. McGraw:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.07

Topic: B.08. Epilepsy

Title: Effect of thrombin in the serum-adapted ionic environment on the induction of epileptiform activity in rat hippocampus in vitro compared to neural activity in temporal lobe model of seizures.

Authors: *A. V. SAVOTCHENKO, M. KLYMENKO;
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Abstract: The mechanisms of epileptiform neuronal activity development under blood-brain barrier (BBB) dysfunction remains relevant in modern psychoneurology. In the present work we mimic some effects of BBB disruption in the hippocampal neurons to examined the effect of serum-adapted ionic environment on the excitability of hippocampal neurons and the role of serum protein thrombin in induction of epileptiform neuronal activity. Comparative analysis of model conditions simulating BBB dysfunction was performed using the lithium-pilocarpine model of temporal lobe epilepsy, which most clearly reflects the disruption of the blood-brain barrier in the acute stage.Using extracellular field potential recordings from CA1pyramidal cell layer of the rat hippocampus we analyzed seizure susceptibility in control and pilocarpine-treated rats immediately after induction of status epilepticus (SE).The changing of ionic extracellular neuronal environment to such serum-adapted contributed to the development of epileptiform activity in hippocampal slices of control rats (n=15). Thrombin (5 U/ml) in the serum-adapted ionic solution significantly enhanced epileptiform activity in CA1 area of the hippocampus of control rats ($p<0.0001$, n=15). Analysis of seizure susceptibility of rat hippocampus after SE, induced by pilocarpine in control ACSF shows no difference in frequency of epileptiform activity ($p=0.1$, n=15) which we observed during recordings from control slices, incubated in the serum-adapted ionic solution with thrombin. The developed method of using a modified ACSF with the addition of thrombin is able to mimic the BBB disruption, observed as a result of status

epilepticus, in vitro. These model conditions can significantly facilitate the study of pathological processes associated with the violation of the integrity of the BBB and minimize the number of animals used in the experiment, as well as alleviate their suffering during the induction of status epilepticus.

Disclosures: A.V. Savotchenko: None. **M. Klymenko:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.08

Topic: B.08. Epilepsy

Support: KAKENHI 16H06532
KAKENHI 19H01142
KAKENHI 19K12190
KAKENHI 19K22990
KAKENHI 21H03606
KAKENHI 21H03532
KAKENHI 20H04341

Title: Comprehensive in vitro analysis of the seizurogenic drugs using voltage-sensitive dye imaging (VSDI) in broad areas around the hippocampal system

Authors: *Y. UTSUMI[1,2], M. TAKETOSHI[2], M. MIWA[3], Y. TOMINAGA[2], T. TOMINAGA[1,2,3];
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Abstract: Central nervous system (CNS) toxicity is a critical factor when considering possible adverse effects during non-clinical and clinical trials in drug development. Seizure and convulsions frequently appear in CNS toxicity and are the leading cause of drug development attrition. We aim to establish a novel in vitro assay system using voltage-sensitive dye (VSD) imaging. VSD allows us to record the membrane to monitor potential changes in the neuron's entire membrane components under a field of view. We have already reported some results using electrically evoked responses in hippocampal slices (350 μm thick) from the two age groups (four to seven and eight to ten weeks). Electrical stimulation was applied to the Schaffer collateral pathway from a stimulation electrode near the CA1-CA3 border. The responses were recorded every 30 seconds using an imaging system (MiCAM02, Brainvision Ltd.), along with simultaneous field potential recordings from the stratum radiatum. Four convulsive compounds of picrotoxin (PiTX; 1, 10, and 100 μM), SR95331 (Gz; 0.1, 1, and 10 μM), 4-aminopyridine (4AP; 1, 40, and 100 μM), and pilocarpine (Pilo; 10, 30, and 100 μM) were tested. We applied

the drugs with cumulative ascending concentrations for 20 minutes per concentration. We also designed the tests to include the stimulus-response relationships during perfusion. PiTX and Gz (GABA receptor antagonist) enhanced the duration of the response in the stratum radiatum (SR). An application of 4AP induced significantly slowed components in the SR. Pilo suppressed EPSP (excitatory postsynaptic potential) and, thus, action potential. To access the firing property of the pyramidale cells, we introduced a ratio (PR ratio) between the response in the strata pyramidale and radiatum. The PR ratio increase if the cells show enhanced EPSP spike firing coupling (E-S coupling). PiTX and Gz enhanced the PR ratio, 4AP slightly enhanced it, and Pilo decreased it. The result highlights that a VSD recording can show the difference in the mode of the action of those seizurogenic drugs. To seek a better assay for seizure liability, we tested the same drugs on the perirhinal cortex (PC) and the entorhinal cortex (EC). We found that 4AP induced seizure-like oscillatory responses at 10 to 20 Hz spread along almost the entire area of the PC and EC. PiTx increased responses against stimulation in the PC. Pilo increased responses against stimulation in the PC. The result shows the usefulness of the VSD method in seeking the difference in neuronal mechanisms in seizurogenic drugs. In addition, the comprehensive widefield recording system is helpful for the cortical broad seizure liability assessment.

Disclosures: **Y. Utsumi:** None. **M. Taketoshi:** None. **M. Miwa:** None. **Y. Tominaga:** None. **T. Tominaga:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.09

Topic: B.08. Epilepsy

Support: Medical Research and Development (AMED) grant number JP21dm0207069
JSPS/MEXT KAKENHI grant numbers 17K19466
JSPS/MEXT KAKENHI grant numbers 19H03343, 17H05752, 16H01344 and 20H05916
Takeda Science Foundation to M.Mid., and Shiseikai Scholarship Fund for basic researcher of medical science

Title: Reversible absence seizure model transgenic mouse

Authors: *M. S. ABDELAAL, K. F. TANAKA;
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Abstract: Absence seizure is a nonconvulsive childhood seizure characterized by spike-and-wavedischarges (SWDs). In patients, SWDs naturally regress by mid-adolescence, but in existinggenetic animal models of absence seizure, SWDs persist throughout life. The reason why absenceseizures naturally regress is not totally known. Here, we generated P*valb*-tTA::tetO-ArchT(PV-ArchT) double transgenic mice by using the tetracycline-controlled gene induction

system. UsingtTA-tetO system, a tTA was expressed under the control of parvalbumin (PV) promoter, andArchT-GFP was induced in doxycycline (DOX)-dependent manner. We found that the ArchT washighly expressed in the thalamic reticular nucleus (TRN) in the absence of DOX. We surprisinglyobserved cortical SWDs without light activation of the ArchT opsin. The cortical SWDs in PV-ArchT were characterized by bilateral 7-11 Hz and associated with behavioral arrest. DuringSWDs, EMG amplitudes were very low, however, mice kept their postures and did not fall.Furthermore, ethosuximide, the first-line treatment for the absence seizure in humans,significantly abolished SWDs events. These data provide that PV-ArchT line is a new mousemodel of absence seizures through physiological, and pharmacological analyses and behavioralfeatures. Then, we addressed whether the childhood-onset absence seizure phenotype regressedby the removal of ArchT or not. To this end, we switched the diet of PV-ArchT mice from normalfood to DOX at P60. We found that SWDs disappeared gradually 2 months after DOX initiation.These results have emphasized that the absence seizure phenotype of PV-ArchT mice isreversible. Our findings about the SWDs reversibility can be helpful to understand the cause ofregression.

Disclosures: M.S. Abdelaal: None. **K.F. Tanaka:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.10

Topic: B.08. Epilepsy

Support: NIH Grant EY027380-04

Title: Chronic developmental inhibition of $Na_v1.6$ channels causes a spontaneous seizure phenotype in Xenopus laevis tapdoles

Authors: *A. C. THOMPSON, C. A. TORO, C. D. AIZENMAN;
Dept Neurosci., Brown Univ., Providence, RI

Abstract: It is estimated that epilepsies relating to voltage-gated sodium channel subtype $Na_v1.6$ account for 1% of the 3.4 million cases of epilepsy in the US. Roughly half of patients are severely impaired and unable to talk or walk, and up to 10% of children with this disorder suffer sudden and unexplained death. To be able to develop effective treatment strategies, first we must understand the cellular mechanisms by which neurons and circuits transition and become abnormally highly excitable as a result of $Na_v1.6$ channel dysfunction. Because seizures manifest in a newborn's first months, this suggests that the neuronal and circuit changes that trigger seizures occur during later stages of embryonic development. Therefore, there is a need for an experimentally tractable model system with the necessary levels of analysis, ranging from single synapses to circuits to behavior, which can be used to study the molecular determinants of these events during embryogenesis. Here, we address this need by characterizing a *Xenopus* tadpole

model of developmental $Na_v1.6$ channel dysfunction induced by rearing *Xenopus* tadpoles in the specific $Na_v1.6$ channel inhibitor MV1312. The result was a spontaneous seizure phenotype that included neuronal and circuit hyperexcitability. We previously showed that acute MV1312-exposure decreases neuronal excitability of *Xenopus* tectal cells by attenuating the amplitude of Na^+ currents. Here, we use whole-cell patch clamp electrophysiology to extend these findings and show that chronic developmental exposure to MV1312 caused a maladaptive compensatory increase in Na^+ currents and, hence, the excitability of *Xenopus* tectal neurons. By monitoring the behavior of freely-swimming tadpoles, we show that tadpoles reared in MV1312 exhibit a spontaneous seizure phenotype. To measure how $Na_v1.6$ channel dysfunction affects neuronal connectivity within the optic tectum, we show the effect of developmental exposure to MV1312 on the dendritic morphology of tectal neurons. Taken together, these results describe a new model to study how $Na_v1.6$ channel dysfunction affects the cellular mechanisms of neuronal and circuit development and function with a range of levels of analysis during the disease-relevant window of embryonic development.

Disclosures: **A.C. Thompson:** None. **C.A. Toro:** None. **C.D. Aizenman:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.11

Topic: B.08. Epilepsy

Support: NCH startup funding

Title: Novel Knockout Mouse Model of SLC35A2 Epilepsy and Brain Malformation.

Authors: *H. YOON[1], R. R. CORRIGAN[2], T. A. BEDROSIAN[2];
[1]Nationwide Children's Hosp., [2]IGM, Nationwide Children's Hosp., Columbus, OH

Abstract: SLC35A2-congenital disorder of glycosylation (SLC35A2-CDG, also known as congenital disorder of glycosylation type llm), is an X-linked disorder associated with infantile seizures, hypsarrhythmia, hypotonia, and brain malformation (Quelhas *et al*, 2021). Also, somatic variants in *SLC35A2* have been linked to malformations of cortical development (MCD) and drug-resistant epilepsy (Sim *et al*, 2018 and Bonduelle *et al*, 2021). SLC35A2 is a UDP-galactose translocator that aids in glycan synthesis by providing galactose to the Golgi and ER (Barbara *et el*, 2014). SLC35A2 loss of function has been clearly associated with disease, but pathogenesis remains understudied. An animal model would be useful to study the mechanism of disease. We generated a floxed mouse carrying loxP sites around exon 3 of *Slc35a2*. First, to model the SLC35A2-CDG patient genotype, we crossed floxed mice with E2a-Cre mice to generate germline knockout of *Slc35a2*. Secondly, we modeled focal loss of *Slc35a2*, as observed in MCD patients, by crossing floxed mice with an Emx1-Cre line to generate forebrain-specific knockout of *Slc35a2*. We were able to successfully generate heterozygous female

Slc35a2 knockout mice with E2a-Cre and Emx1-Cre expression, respectively. Interestingly, hemizygous germline knockout male mice are not observed, and all hemizygous forebrain knockout male mice did not survive past 6 weeks (80% of them died within 4 weeks after birth, n=10). Hence, we focused on heterozygous females for additional study. In germline knockout mice, we confirmed the reduced amount of SLC35A2 in the heterozygous brain (about 50% compared to wild-type brain). In addition, body and brain weight at P21 were significantly reduced compared to wild type (40% and 25% reduction). Brain lateral ventricles were significantly enlarged, and the thickness of the cortex was reduced compared to wild type. In the forebrain-specific knockout model, intensity of SLC35A2 immunofluorescence signal was significantly reduced in heterozygous females. Reduced body weight in this line was not observed, but righting reflex was diminished. Currently, experiments are ongoing to fully examine the behavioral, neuroanatomical, and seizure phenotypes of these mice in order to understand their relevance as disease models. In our study, we generated a novel conditional knockout mouse model of *Slc35a2*. We were able to confirm the reduction of *Slc35a2* in our model and preliminary results suggest that these mice show some phenotypes relevant to human disease. Our new murine model is expected to contribute to understanding disease pathogenesis, which will open up new avenues for disease treatment plans.

Disclosures: H. Yoon: None. **R.R. Corrigan:** None. **T.A. Bedrosian:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.12

Topic: B.08. Epilepsy

Support: NIH Grant R21NS116546

Title: Alterations in sleep homeostasis following sleep deprivation in resistant and susceptible mouse models of temporal lobe epilepsy

Authors: *D. J. LASKY[1], J. R. ISAACSON[2], S. S. VATTEM[2], S. J. REWEY[2], M. V. JONES[1], R. L. MAGANTI[2];
[1]Neurosci., [2]Neurol., Univ. of Wisconsin–Madison, Madison, WI

Abstract: Sleep and epilepsy have a bidirectional relationship in which seizures disrupt sleep and sleep deprivation exacerbates seizures. Sleep is regulated partly by sleep homeostasis, which raises “sleep pressure” during wake and dissipates it during sleep, and is monitored by changes in delta power (0.5-4 Hz) in the EEG during NREM sleep. We hypothesize that sleep homeostasis is impaired in epilepsy and are testing this in the kainic acid (KA) model of temporal lobe epilepsy. Epilepsy-resistant (C57BL/6J) and epilepsy-susceptible (DBA/2N) mice were subjected to EEG and EMG electrode implantation. After a 2-3 day recovery, C57s received KA doses (i.p.) of 10 mg/kg followed by 5 mg/kg alternating with 2.5 mg/kg until status

epilepticus had been reached, with DBAs receiving roughly two-thirds those doses. Status epilepticus was defined as 2 Racine class 5 seizures in 20 minutes and saline-injected mice served as a control. Four weeks later, the mice were recorded across a baseline day, three days of sleep deprivation and a recovery day. Sleep deprivation was achieved by gentle cage movement or brush contact in response to drowsiness or low-frequency EEG activity. The vivarium followed a 12:12 hour light-dark cycle, with sleep deprivation beginning 1 hour after lights-on and lasting for 4 hours. Sleep was scored using EEG/EMG data by researchers blinded to treatment and was divided into Wake, NREM sleep and REM sleep. MATLAB scripts were used to quantify and normalize delta power to allow for interanimal comparisons. C57 and DBA animals were divided into treatments of saline, KA epileptic, and KA non-epileptic, and had their hourly mean NREM delta power (mNREMδ) computed for all days. C57 mice, regardless of treatment, did not display a clear surge in mNREMδ following sleep deprivation. In fact, across all days of recording, there were no obvious differences in C57s between treatments. In contrast, all DBA mice experienced a distinct surge in mNREMδ following sleep deprivation. There were also clear differences in DBAs between treatments, with the KA mice expressing less mNREMδ during lights-on. Of the two mouse strains considered, the historically epilepsy-resistant C57s displayed mNREMδ that was independent of KA, suggesting that their sleep properties have little dependence on injection status or epileptic state. Unlike C57s, the epilepsy-susceptible DBAs experienced a surge in mNREMδ following sleep deprivation. These results suggest that sleep homeostasis may be impaired in a strain-dependent manner in the KA model and that predispositions toward epilepsy and sleep disorders may be correlated.

Disclosures: D.J. Lasky: None. **J.R. Isaacson:** None. **S.S. Vattem:** None. **S.J. Rewey:** None. **M.V. Jones:** None. **R.L. Maganti:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.13

Topic: B.08. Epilepsy

Support: NIH Grant 1R21NS122011-01

Title: Deep Learning Classifier for the Combined Scoring of Sleep-Wake and Seizures in Mice

Authors: *B. HARVEY[1], V. OLÁH[2], L. AIANI[1], L. ROSENBERG[1], M. ROWAN[2], N. PEDERSEN[1];
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Abstract: The relationship between sleep and seizure is complex and bidirectional, including seizure-frequency-associated sleep fragmentation as well as sleep-deprivation-induced increases in seizures. In order to provide better throughput for sleep studies in Intra-Amygdalar Kainic Acid (IAKA) Temporal Lobe Epilepsy (TLE) model mice, we have designed a data processing

pipeline and Keras-based deep learning classifier for sleep staging and seizure scoring. While sleep-wake classifiers and seizure detection algorithms abound, the combination is difficult given the abnormal EEG background in mice with epilepsy. We obtained electrocorticogram (ECoG), electromyogram (EMG), video and bilateral hippocampal depth electrode data from mice implanted using a customized 3D-printed headplate designed in our lab. Our dataset included 1300 12-hour recordings from a group of 47 mice (including 23 mice that developed spontaneous seizures and 10 control mice), that included 642 seizures. We used 70% of the data for training and 30% for testing. The classifier was trained on manually scored 20-second epochs from existing downsampled recordings (from 2kHz to 200Hz), using Fourier bins of alpha, beta, delta, gamma, and theta frequency bands in recordings from this montage. With a sequential model, the classifier has achieved >90% scoring accuracy in most categories for our epileptic mice. This reliable classification will allow for rapid combined sleep-wake and seizure scoring in our IAKA sleep-wake paradigm. Using this classifier to improve our throughput, we hope to improve the mechanistic and symptomatic understanding of sleep disruption in epilepsy, leading to improved patient treatment and outcomes.

Disclosures: **B. Harvey:** None. **V. Oláh:** None. **L. Aiani:** None. **L. Rosenberg:** None. **M. Rowan:** None. **N. Pedersen:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.14

Topic: B.08. Epilepsy

Title: Audiogenic seizure modeling SUDEP (Sudden and Unexpected Death in Epileptic Patients) - a new double mouse model based on a bidirectional genetic selection

Authors: *B. MARTIN, C. GEFFROY, G. DIEUSET;
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Abstract: Sudden and Unexpected Death in Epileptic Patients (SUDEP) rate is about three times that of the general population. Mouse models of SUDEP use audiogenic seizures (AGS), which are seizures induced with a sound stimulation. Immediately after the sound presentation, the mouse manifests a stereotyped behavior for which one can identify successively a wild running, clonic seizures, a tonico-clonic seizure when the mouse falls on its flanks and a tonic seizure with an extension of the limbs toward the tail, followed or not by death. Only a few inbred strains of mice are AGS prone and the vast majority of studies involve DBA/2 or DBA/1 strains. Recently, we have reported that the 129/SvTer mouse strains brings beneficial advantages especially when surgery is needed. Anyway, the full penetrance of the trait is not observed with these strains. To compensate this limitation, but also to improve the potentiality of the model, we are creating two selected lines, LAGS+ and LAGS- (lethal audiogenic seizure±) derived from a 4-way cross procedure involving the strains 129/SvTer, BALB/cJ, DBA/1J and DBA/2J. The

improvement is 1/ offering two lines with high tonic audiogenic seizure rate (up to 99%), 2/ with a susceptibility still present at 3 month old (up to 99%), 3/ with a body corpulence compatible with surgery. Moreover the diverging improvement remains in the fact that one line (LAGS+) presents lethal tonic audiogenic seizures and the other line (LAGS-) presents non-lethal tonic audiogenic seizures. The common traits of selection are: 1/ presence of a tonic audiogenic seizure characterized by a muscular hypertonicity observed two times at 30 day old and 90 day old; 2/ body corpulence compatible with surgery. The diverging trait of selection is: For LAGS+ line, tonic seizure followed by a muscular relaxation and death; for LAGS- line, tonic seizure followed by a muscular relaxation, gasping and recovery. Nota bene: For the faisability of the selection, mice presenting a tonic seizure followed by a muscular relaxation and respiratory arrest during 5 sec are resuscitated with a respirator and considered as LAGS+. After more than 9 generations of selection, LAGS+ line presents 99% of lethal tonic seizures after an audiogenic stimulation with a white noise (110 dB SPL) at 30 day old. On the contrary, at the same age, LAGS- line presents 99% of tonic seizures, lethal for only 16% of the subjects. At 90 day old, when mice that have been successfully tested at 30 day old are retested, for LAGS+, 92% of the mice present a tonic seizure, lethal in 98% of the cases whereas, for LAGS-, 93% of the mice present a tonic seizure, lethal in 0% of the cases. Selection is still in progress.

Disclosures: **B. Martin:** None. **C. Geffroy:** None. **G. Dieuset:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.15

Topic: B.08. Epilepsy

Support: NINDS grant NS107148
University of Kentucky CCTS and NRPA grants

Title: Characterizing sleep and epileptic activity in a mouse model of juvenile batten disease

Authors: *D. IRADUKUNDA[1], J. WANG[1], L. Z. GUO[2], K. M. KANE[3], A. SUBRAMONIAM[2], C. J. MCLOUTH[4], B. F. O'HARA[2], Q. WANG[3], S. SUNDERAM[1];
[1]F. Joseph Halcomb III, MD, Dept. of Biomed. Engin., [2]Dept. of Biol., [3]Dept. of Ophthalmology and Visual Sci., [4]Dept. of Behavioral Sci., Univ. of Kentucky, Lexington, KY

Abstract: CLN3 disease, also known as juvenile Batten disease, is a rare pediatric inherited neurodegenerative disease caused by mutations in the *CLN3* gene. Children with CLN3 disease develop progressive blindness, cognitive and motor deficits, speech difficulties, sleep disturbances, and seizures that worsen over time after 4 to 6 years of seemingly normal development. Seizures are known to be correlated with poor sleep in many epilepsies and other neurodegenerative conditions. In animal studies using an electroencephalogram (EEG), increased spiking activity has been correlated with reduced delta power; this suggests a possible interaction

with non-rapid eye movement (NREM) sleep, which is characterized by slow delta oscillations. However, no study of the mechanism by which poor sleep may correlate with - and perhaps promote - epileptic activity in CLN3 disease has been conducted. Here, we employ a mouse model to investigate sleep and epileptic aspects of CLN3 disease, which are highly disruptive to patients' everyday life. All animal procedures were performed with IACUC approval at the University of Kentucky. A non-invasive piezoelectric motion sensor was utilized to generate a "PiezoSleep" signal to distinguish between sleep and wakefulness for *Cln3* knockout (*Cln3KO*; Jax#029471; n=6F, 2M) and WT (C57BL/6J, Jax#000664; n=7F, 5M) mice (4-7 months). A subset of these mice, including nine adult female mice (*Cln3KO*, n=4; WT, n=5; 5-16 months) were instrumented for EEG and monitored for an average of 7 days each on a 12h:12h light/dark cycle. Epileptiform spikes were detected from the recorded EEG signals as voltage deflections greater than 5 standard deviations above the mean of the signal and full width at half maximum amplitude of 5-200 ms. Our PiezoSleep data show a difference in both sleep percentage and sleep bout length between *Cln3KO* and WT mice. Our EEG data further demonstrate that spikes are more prevalent in *Cln3KO* mice compared to WT mice ($p<0.05$) regardless of age, confirming that *Cln3KO* mice exhibit epileptiform activity. In further analysis of the collected EEG data (ongoing), we expect to determine whether spiking activity is modulated by changes in sleep composition and architecture in *Cln3KO* mice. Characterization of sleep and epileptic activity in the animal model of CLN3 disease will lead to a better understanding of the correlation between sleep disturbances and seizures in CLN3 disease, with possible implications for disease management strategies.

Disclosures: D. Iradukunda: None. **J. Wang:** None. **L. Z. Guo:** None. **K. M. Kane:** None. **A. Subramoniam:** None. **C. J. McLouth:** None. **B. F. O'Hara:** None. **Q. Wang:** None. **S. Sunderam:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.16

Topic: B.08. Epilepsy

Support: NIH R01NS119483

Title: Spike ripple electrographic biomarker in a cortical photothrombotic epilepsy mouse model

Authors: *D. C. SHAW[1], K. KONDABOLU[2], M. A. KRAMER[3,4], C. J. CHU[5,6], X. HAN[2,4]; [1]Grad. Program in Neurosci., [2]Dept. of Biomed. Engin., [3]Dept. of Mathematics and Statistics, [4]Ctr. for Systems Neurosci., Boston Univ., Boston, MA; [5]Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [6]Harvard Med. Sch., Boston, MA

Abstract: Epilepsy is a neurological disease affecting 50 million people worldwide, a third of which are unresponsive to pharmacological interventions. For these patients, the next best

treatment options are either resective surgery or neuromodulation, both of which require accurate localization of the brain region responsible for producing seizures, known as the epileptogenic zone (EZ). While interictal large-amplitude deflections (spikes) and high-frequency oscillations (ripples) found in EEG recordings are well known electrographic biomarkers for the EZ, spikes suffer from low spatial specificity and ripples exhibit limited pathological specificity. Combined spike ripple (SR) events have recently been established as a promising biomarker for the identification of the EZ that overcomes the limitations of spikes or ripples alone. However, the mechanisms underlying SR production are largely unknown, which makes it difficult to further refine the detection and disruption of SR events for neuromodulatory interventions, such as neurostimulation that has been recently approved by the FDA for treatment of epilepsy. To allow for systematic investigation of the cellular and network mechanisms of SRs and to aid EZ identification, we performed local field potential (LFP) measurement across multiple brain regions in a cortical photothrombotic epilepsy mouse mode. Specifically, we induced a unilateral photothrombotic stroke in the primary motor cortex and recorded LFPs bilaterally in both the motor cortex and other brain regions involved in the motor pathway, such as the striatum and the thalamus. We detected robust pathological LFP activity that was initiated in the injured motor cortex, and SR events with features consistent with those observed in the EEGs of patients with epilepsy. Additionally, we detected intermittent large amplitude delta oscillations that are consistent with intermittent focal slowing seen in patients with damaged neural tissue, further confirming that the photothrombotic mouse model robustly induced strokes and long-lasting pathological brain rhythms. Together, these results demonstrate that the SR biomarker is present in the photothrombotic epilepsy mouse model, establishing a new experimental model for studying the cellular and network mechanisms of SRs and their role in epilepsy.

Disclosures: D.C. Shaw: None. **K. Kondabolu:** None. **M.A. Kramer:** None. **C.J. Chu:** None. **X. Han:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.17

Topic: B.08. Epilepsy

Title: The amygdala-kindling model: Toward the development of a high performance screening platform to accelerate the identification of novel anti-seizure medications

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SynapCell, Saint Ismier, France

Abstract: Epilepsy is a chronic neurological disorder, with a prevalence close to 1%, which is characterized by the recurrent appearance of spontaneous seizures due to pathological hyperexcitability and sudden abnormal discharge of neurons in the neuronal network. The most

common epileptic syndrome in adults is temporal lobe epilepsy (TLE). Although more than 20 new Anti-Seizure Medications (ASMs) have been introduced in the past 30 years, there is continuing clinical demand for more efficacious and better tolerated ASMs, especially with regard to the substantial portion of about 30% drug-resistant epilepsy patients.
"Gold standard" approaches such as intrahippocampal kainate injection, 6-Hz psychomotor seizures, kindled seizures, and kindling acquisition, still remain important resources. The amygdala-kindling model is highly predictive for detecting clinically effective drugs for the treatment of focal onset seizures and is thus considered a model for difficult-to-treat types of seizures. This study was designed to assess the detailed pharmacological profile of the amygdala-kindling model when challenged with different types of ASMs at effective doses (Diazepam, Ethosuximide, Carbamazepine, Retigabine and Levetiracetam).
Rats were electrically kindled via a chronically implanted electrode in the amygdala. After establishing reproducible stimulation thresholds for eliciting afterdischarges (afterdischarge threshold [ADT]) in the EEG, the rats were alternately treated with ASMs or their respective vehicle (cross-over design). Aside from the ADT, we evaluated the seizure severity (SS), seizure duration (SD), and after discharge duration (ADD) in 3 different structures implanted with electrodes (Amygdala, Parietal and Prefrontal cortex).
Differential pharmacological responses were observed and emphasized the role of amygdala-kindled rats as a highly predictive model of drug efficacy against seizures as in TLE. For instance, diazepam at 3 mg/kg produced seizure control as measured by a reduction in motor components of the seizure and a reduction in ADD. Conversely, ethosuximide at 100 mg/kg did not show any effect on motor components of the seizure nor on ADD.
This study was intended to shed light on translational aspects of the amygdala-kindling model as a potential asset for characterizing new entities with improved tolerability and efficacy. The combination of this model and a cross-over design will provide a decision-enabling screening platform for the identification of novel compounds for the prevention, treatment, and modification of epilepsy, wherein pharmacoresistant seizures constitute the greatest challenge for treatment.

Disclosures: **J. Volle:** A. Employment/Salary (full or part-time):; SynapCell. **C. Habermacher:** A. Employment/Salary (full or part-time):; SynapCell. **B. Caraballo:** A. Employment/Salary (full or part-time):; SynapCell. **C. Dumont:** A. Employment/Salary (full or part-time):; SynapCell. **E. Gronlier:** A. Employment/Salary (full or part-time):; SynapCell. **H. Gharbi:** A. Employment/Salary (full or part-time):; SynapCell. **Y. Roche:** A. Employment/Salary (full or part-time):; SynapCell.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.18

Topic: B.08. Epilepsy

Support: NIH Grant

Title: Stxbp1 variants increase seizure susceptibility in c. elegans electroshock model

Authors: *N. SUTHAKARAN[1], P. GONZALEZ[1], S. STILLEY[1], K. MCCORMICK[2], T. BROCK[2], C. HOPKINS[2], K. DAWSON-SCULLY[3];
[1]Biol. Sci., Florida Atlantic Univ., Boca Raton, FL; [2]InVivo Biosystems, Eugene, OR; [3]Psychology and Neurosci., Nova Southeastern Univ., Davie, FL

Abstract: Approximately one-third of epileptic patients do not respond to current available treatments. This is likely due to the lack of knowledge of the underlying mechanistic abnormalities that cause epilepsy and factor into determining individual responsiveness to medication. Genome-wide association studies of epilepsy patients have emerged in recent years to reveal genetic variants that contribute to various forms of epilepsy. A 2008 landmark study identified de novo mutations in STXBP1 to be the cause of early infantile epileptic encephalopathy in five patients. STXBP1 encodes the syntaxin-binding protein 1, which is crucial for nerve cell communication. Recently, an exome sequencing study reported the STXBP1 to be the second most commonly mutated gene, especially in patients with early-onset epileptic encephalopathies and catastrophic infantile epilepsy cases. A new era of therapies could be tailored to the molecular genetic defects that prompt the development of individual epilepsies, i.e., personalized medicine. In order to create a model to discover new gene-focused therapeutics, we utilize a "humanized" *C. elegans* model, where the human wild-type STXBP1 functionally replaced the worm orthologue, UNC-18. We ran humanized *C. elegans* and clinical variants reported in ClinVar in our electroshock behavioral assay, to quantitatively measure the variant epilepsy phenotypes, through time to recovery upon electroshock. Our preliminary studies show pathogenic STXBP1 variants in worms cause functional impairments and increased susceptibility to seizure-like activity upon electroshock administration. Our approach is a cost-effective in vivo method to establish pathogenicity of genetic variants and create a new avenue to identify novel therapeutic gene targets.

Disclosures: N. Suthakaran: None. **P. Gonzalez:** None. **S. Stilley:** None. **K. McCormick:** None. **T. Brock:** None. **C. Hopkins:** None. **K. Dawson-Scully:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.19

Topic: B.08. Epilepsy

Support: Wellcome Trust #102037
NU-007346

Title: Modelling monogenic epilepsy in human brain slice cultures

Authors: *F. MCLEOD[1], A. DIMTSI[1], D. LEWIS-SMITH[2,3], R. THOMAS[2,3], G. CLOWRY[1], A. TREVELYAN[1];

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Abstract: Background
Early infantile developmental and epileptic encephalopathies of genetic origin are devastating conditions, but the pathological mechanisms often remain obscure. A major obstacle is the difficulty of studying human cortical brain development, *in utero*. To date, no *in vitro* preparations have been developed that accurately reproduce the complex cellular networks found beyond the first trimester.
Methods
To address this, we established human brain slice cultures prepared from ethically sourced, 14-17 post conception week (pcw) brain tissue (www.hdbr.org). The gross anatomical structures of the marginal zone, cortical plate and subplate are maintained in these cultures for several months, while new synaptic networks form.
Results
We used this model system to examine variants in STXBP1, which encodes a critical presynaptic protein. Specifically, we induced STXBP1 haploinsufficiency, thereby mimicking a common genetic cause of developmental and epileptic encephalopathy. STXBP1 was enriched near spine-like structures and along putative axons of subplate neurons at 16-17 pcw. We achieved a ~50% reduction in STXBP1 expression, using a short hairpin RNA interference introduced by adeno-associated viral vectors, and quantified the effects using confocal microscopy and electrophysiological techniques. The induced STXBP1 haploinsufficiency had divergent effects upon glutamatergic and GABAergic synaptic number and function, without altering subplate neurite length and number. Furthermore, live imaging of synaptic vesicles with reduced STXBP1 levels revealed impaired spontaneous neurotransmitter release with slower release kinetics.
Conclusion
We provide a critical proof-of-principle for how to investigate the aetiology of monogenic epilepsy in prenatal neurodevelopment.

Disclosures: F. McLeod: None. **A. Dimtsi:** None. **D. Lewis-Smith:** None. **R. Thomas:** None. **G. Clowry:** None. **A. Trevelyan:** None.

Poster

695. Epilepsy: Model Development

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 695.20

Topic: B.08. Epilepsy

Title: An ex vivo model to study fast ripple high-frequency oscillations detected by SEEG using dedicated surgical specimens from pediatric focal epilepsy patients

Authors: *A. CATTANI[1], S. WANG[2], M. LEVESQUE[2], J. ATKINSON[1], J.-P. FARMER[1], M. AVOLI[2], R. W. R. DUDLEY[1];
[1]Mcgill Univ. - Montreal Children's Hosp. - Neurosurg. Dept., McGill Univ., Montreal, QC, Canada; [2]Montreal Neurolog. Inst., Montreal Neurolog. Inst., Montreal, QC, Canada

Abstract: Objective
High-frequency oscillations (HFOs, 80-500 Hz), specifically fast ripples (FRs, >250Hz), are recorded from ictogenic brain areas and are commonly observed in pediatric patients with drug-resistant epilepsy during stereoelectroencephalography (SEEG) evaluation. Detection of FRs helps to delineate the seizure onset zone for surgical resection increasing seizure freedom rates. Here, we investigate single neuron activity from dedicated pediatric epilepsy surgery specimens containing FRs during pre-surgical evaluation in order to establish an ex vivo model to study these important electrophyiological biomarkers toward a better understand of their epileptogenesis and potential pharmacological treatment.
Methods
Electrophysiological recordings were performed in acute slices from pediatric epilepsy surgery specimens containing high FRs rates (> 6 per minute), as detected by pre-surgical SEEG evaluation. Cell attached and whole-cell patch clamp recordings in voltage and/or- current-clamp modes were obtained from neurons located in cortical layers II to V. Spontaneous excitatory post-synaptic currents (sEPSCs) and ictal seizures-like events (SLEs) were analyzed.
Results
Twenty-five cells were recorded from 62 slices obtained from 6 patients. Thirteen spontaneous SLEs were recorded and high frequency of sEPSCs were identified in 8 neurons within the FRs resection areas**.** Pharmacology showed strong AMPA and Kainate component in cells recorded within FRs areas since most of EPSCs were blocked by NBQX. Field potential recordings were not able to improve localization of FRs in the slice.
Conclusion
Surgical specimens taken from areas of SEEG-detected FRs can be used as an *ex vivo* model to study FRs and to assess the impact of pharmacological interventions on these epileptogenic pertubations. This may allow for new insights aiming glutamate in the treatment of pharmaco-resistant epilepsy in pediatric patients.

Disclosures: A. Cattani: None. **S. Wang:** None. **M. Levesque:** None. **J. Atkinson:** None. **J. Farmer:** None. **M. Avoli:** None. **R.W.R. Dudley:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.01

Topic: B.08. Epilepsy

Title: Spatiotemporal profile of neuronal excitability during acute focal seizures in cortex

Authors: *P. SHAH[1], T. A. VALIANTE[2], A. M. PACKER[3];
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Abstract: Seizures are widespread disruptions in the brain that plague neurological patients. Seizures arise due to a dramatic imbalance of neuronal excitability, but we lack a precise understanding of the dynamics of how this imbalance occurs. In the cortex, it is proposed that the structure and timescales of excitatory/inhibitory neuronal connectivity leads to the observed propagation of the seizure wavefront. In this study, we experimentally test the excitability of cortical neurons in real-time during seizure propagation *in vivo* using all-optical imaging. We evoked acute seizures with focal injection of 4-aminopyridine (4-AP) and performed widefield optogenetics and two-photon all-optical imaging in cortical Layer 2/3. We analysed the photostimulation evoked responses of the overall field-of-view (during widefield stimulation) or individual neurons (during all-optical stimulation) during pre-4AP (baseline) and post-4AP (inter-ictal and ictal) periods. Under widefield stimulation, targeting a large number of neurons, we find an overall increase in the photostimulation response magnitude during inter-ictal periods compared to baseline. Using all-optical imaging, we show that individual neurons can be effectively stimulated during inter-ictal periods comparable to baseline. However, during seizure propagation, neurons distal to the seizure wavefront are more excitable than neurons proximal to the seizure wavefront, and more excitable than neurons recruited into the seizure wavefront. Further work will assess whether recurrent excitability of surrounding non-stimulated cells is also affected during the evolution of seizures. In conclusion, all-optical imaging allowed for interrogating excitability during focal seizures, demonstrating a spatially complex profile of excitability relative to the evolving seizure in the cortex.

Disclosures: P. Shah: None. **T.A. Valiante:** None. **A.M. Packer:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.02

Topic: B.08. Epilepsy

Support: NIH R01-NS096976-07

Title: Rigorous evaluation of putative antiseizure drugs in scn1lab mutant zebrafish

Authors: *P. WHYTE-FAGUNDES[1], C. MANUKYAN[2], F. FIGUEROA[1], S. C. BARABAN[1];
[1]UCSF, San Francisco, CA; [2]UC Berkeley, Berkeley, CA

Abstract: Dravet syndrome (DS) is a severe pediatric epilepsy primarily caused by *de novo* mutation in a voltage-activated sodium channel gene (SCN1A). Patients face life-threatening seizures that are largely resistant to available antiseizure medications (ASM). Existing preclinical animal models of DS are used to identify novel ASMs for these patients. Among these, *scn1lab*

mutant zebrafish that exhibit spontaneous seizure-like activity were developed in our laboratory and successfully identified “standard-of-care” ASMs used in this patient population (e.g., valproate, benzodiazepines, stiripentol), as well as novel serotonin-modulating drugs (e.g., fenfluoramine, clemizole, and lorcaserin). Our phenotypic screening platform consists of two stages: (i) a locomotion-based assay measuring high-velocity convulsive behavior and (ii) an electrophysiology-based assay using *in vivo* local field potential recordings to quantify seizure-like events. Unfortunately, more widespread use of our zebrafish *scn1lab* model has led to modifications in these well-established assays and in turn, confused drug discovery claims. Here, we curated a list of 9 antiseizure drug candidates identified in the preclinical DS model literature: donepezil, soticlestat, lisuride, vorinostat, mifepristone, pargyline, 1-EBIO, chlorzoxazone and AA43279. To rigorously evaluate drug efficacy, we tested these drug candidates in *scn1lab* mutants and age-matched wild-type (WT) controls. We first tested each drug at 3 different concentrations on 3 independent trials in the locomotion assay. Only lisuride, pargyline and 1-EBIO were positive hits from this screen and proceeded to electrophysiological testing to validate network-level seizure-like event suppression. Electrophysiology also included soticlestat, a cholesterol 24-hydroxylase inhibitor in Phase 3 clinical trials, as no preclinical data was available. Interestingly, we found exposing WT larvae to soticlestat induced seizure-like discharges. As our results failed to replicate clear antiseizure efficacy for any of the drugs tested, and yielded a potential adverse side-effect for at least one, it highlights the necessity for strict scientific standards in preclinical identification of effective patient treatment options.

Disclosures: P. Whyte-Fagundes: None. **C. Manukyan:** None. **F. Figueroa:** None. **S.C. Baraban:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.03

Topic: B.08. Epilepsy

Support: NIH Grant 1R21NS121644-01A1
Cure Grant
T32 Grant NS007453

Title: Altered PI3K/mTOR signaling within the forebrain leads to respiratory deficits and SUDEP

Authors: *P. WOLLER[1], D. TIWARI[2], E. ZELEN[2], C. GROSS[2], S. A. CRONE[3];
[1]Neurosci. Grad. Program, Univ. of Cincinnati, Cincinnati, OH; [2]Div. of Neurol., [3]Div. of Pediatric Neurosurg., Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH

Abstract: Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in epileptic individuals and may be caused by cardiorespiratory deficits. Abnormalities in the

PI3K/mTOR signaling pathway contributes to seizure development and increased SUDEP risk. Forebrain structures can influence breathing, presumably through connections to brainstem respiratory centers, but whether altered forebrain activity can lead to SUDEP is unknown. We developed a genetic mouse model of SUDEP in which excitatory forebrain neurons lack PTEN, an inhibitor of the mTOR pathway. We show that these mice have irregular breathing (even in the absence of overt seizures) that we hypothesize contributes to SUDEP. Through continuous (24hr /day) cortical electroencephalography (EEG), diaphragm electromyography (EMG), and video recordings we have assessed the onset and frequency of breathing abnormalities as well as seizures in the weeks leading up to and including the death of these mice. Our findings lay the groundwork for investigating the relationship between breathing abnormalities and SUDEP in epilepsy disorders caused by altered PI3K/mTOR signaling.

Disclosures: P. Woller: None. **D. Tiwari:** None. **E. Zelen:** None. **C. Gross:** None. **S.A. Crone:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.04

Topic: B.08. Epilepsy

Support: NIH Grant R01NS116357
CURE Taking Flight Award
AES Junior Investigator Award
AES Predoctoral Award

Title: Progressive Hippocampal Entorhinal Desynchronization in Chronically Epileptic Mice

Authors: *Y. FENG[1], L. PAGE-HARLEY[1], K. DIEGO[2], Z. DONG[1], S. I. LAMSIFER[3], A. JURKOWSKI[1], J. SCHNIPPER[1], D. J. CAI[1], T. SHUMAN[1];
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Abstract: Temporal lobe epilepsy is one of the most common types of epilepsy in adults and causes pervasive memory impairments which impact patients' quality of life. In pilocarpine treated epileptic mice, we have recently found desynchronized interneuron firing between the CA1 and dentate gyrus regions of the hippocampus (HPC). The medial entorhinal cortex (MEC) is the upstream region sending and receiving inputs into and from HPC. However, it remains unclear whether synchronization deficits in HPC reflect impaired inputs from MEC and when these deficits emerge. Cognitive processes require precise communication between circuits, suggesting that altered timing between HPC and MEC may contribute to epilepsy-associated cognitive deficits. We have found progressive spatial memory deficits in epileptic mice that emerge between 3 and 8 wks after pilocarpine. In this project, we tested whether MEC-HPC

synchronization is disrupted in epileptic mice. We performed simultaneous in vivo electrophysiology with 512 channel silicon probes in HPC and MEC of head-fixed epileptic and control mice running in virtual reality. We recorded at two timepoints (3 and 8 wks after pilocarpine) to capture synchronization changes during the progression of memory impairments. Within HPC, we found epileptic mice show theta power and coherence deficits early at 3wk post pilocarpine. We also found inhibitory cells in CA1 and DG are less phased locked to CA1 theta oscillations from 3wk timepoint. Within MEC, epileptic mice show not only decreased theta coherence between MEC layer2 (MECII) and 3 (MECIII) only at the later timepoint. But also disrupted excitatory and inhibitory neuron phase locking of MECII cells to local MECII theta. Between MEC and HPC, we found misaligned communication in epileptic mice emerge at the later timepoint. Theta coherence between MEC-HPC was significantly decreased at 8wk but not 3wk post pilocarpine. Interestingly, MECII inhibitory cells show disrupted phase locking to CA1 theta oscillations from early time point. Together, these data reveal three main points. First, both HPC and MEC are desynchronized in the chronic phase of pilocarpine-induced epilepsy with altered theta power, coherence, and phase locking of single units. Second, HPC desynchronization emerges earlier than MEC, matching the earlier timeline of seizure onset. Third, we identified progressive impairments in the synchrony within MEC and between the MEC and HPC circuit throughout the development of epilepsy, which matches the timeline of progressive memory deficits. These findings suggest that MEC desynchronization likely contributes to poor spatial memory and coding found in epileptic mice.

Disclosures: **Y. Feng:** None. **L. Page-Harley:** None. **K. Diego:** None. **Z. Dong:** None. **S.I. Lamsifer:** None. **A. Jurkowski:** None. **J. Schnipper:** None. **D.J. Cai:** None. **T. Shuman:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.05

Topic: B.08. Epilepsy

Support: NIMDS Grant R01NS090645

Title: Reduced GABA signaling in larval zebrafish affects brain development and visual processing

Authors: *C. R. DUFFY[1], Y. LIU[2], Y. CHEN[3], B. LIU[2], D. S. SHELTON[5], P. MA[4], P. A. KNER[2], J. D. LAUDERDALE[1];
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Abstract: Maintaining the proper excitatory/inhibitory balance is vital for proper development of neural circuitry. Gama aminobutyric acid (GABA) is a key inhibitory neurotransmitter, and

decreased GABA levels during development are linked to health issues such as epilepsy, autism, and anxiety. GABA is made by the conversion of glutamate into GABA by glutamic acid decarboxylase (GAD). Zebrafish have three gad genes: the paralogs *gad1a* and *gad1b*, and *gad2*. At 5 days post fertilization (dpf) the *gad1b* paralog is expressed in the optic tectum and superficial interneurons, which receive retinal signal. Also, *gad1b* is expressed in the amacrine cells of the retina, meaning gad1b is relevant in visual processing. We created *gad1b*-null zebrafish which have reduced GABA levels and neural hyperactivity. This provides a unique model to study the effects that reduced GABA signaling has on neural circuitry and visual processing. We measured the optomotor response, a reflexive vision stabilizing response where animals swim to minimize the image motion across the retina, of the *gad1b* mutants and wildtype (WT) fish at 7dpf. We found gad1b mutants showed significantly less optomotor responses than WT fish. This is consistent with the idea that a lack of lateral inhibition in the retina is causing an influx of signal that fails to be translated into an appropriate response. Using light sheet imaging and a transgenic fluorescent calcium indicator, we recorded neural activity of WT , *gad1b* mutants, and WT treated with pentylenetetrazol (PTZ), a convulsant. In comparison to the WT and WT treated with PTZ , the *gad1b* mutants show increased synchronicity between the left and right sides of the tectum, suggesting that the connections between the two sides of the brain increases. This is indicative of lessened developmental apoptosis, leading to increases in neuron numbers. Preliminary cell counts of *dlx5a/6a* expressing interneurons within the optic tectum at 4, 6, and 8dpf show decreases in neuron numbers with development. In our *gad1b* mutants, we see increases in interneuron numbers compared to WT at 8dpf. With this evidence, we are gaining insight into how decreased GABA levels can alter the development of neural circuitry and cause abnormal responses to perceived sensory stimuli.

Disclosures: C.R. Duffy: None. **Y. Liu:** None. **Y. Chen:** None. **B. Liu:** None. **D.S. Shelton:** None. **P. Ma:** None. **P.A. Kner:** None. **J.D. Lauderdale:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.06

Topic: B.08. Epilepsy

Support: NINDS/NIH T32 NS-45540

Title: Impaired CA3 dynamics in a rodent model of temporal lobe epilepsy

Authors: *B. L. BOUBLIL, G. TARCSAY, C. B. DANG, U. J. REDIC, L. A. EWELL; Anat. and Neurobio., Univ. of California, Irvine, Irvine, CA

Abstract: In epilepsy, hippocampal CA3 is thought to be critically involved in seizure generation because of the strong recurrence there. Despite this, little is understood about how CA3 function may be altered in epilepsy. First, to determine whether CA3 exhibits structural

changes we performed a histological analysis on tissue from epileptic and control mice. Mice received stereotaxic suprahippocampal injections of kainic acid (KA) (n = 14, 8 females, 6 males) and were perfused 6 weeks later for histological analysis. The area of CA3 tended to be smaller on the KA injected side compared to the contralateral side (mean ± SEM; KA, 0.53, ± 0.3 mm^2; contra, 0.60, ± 0.3 mm^2; paired t-test, $p \leq 0.14$). The amount of mossy fiber input normalized to CA3 area tended to be smaller on the KA injected side (mean ratio ± SEM; KA, 0.35, ± 0.04; contra, 0.42, ± 0.01; paired t-test, $p \leq 0.15$). Additionally, we observed extreme variation in the amount of mossy fiber input on the KA injected side with some animals having none. Such variation was only present on the KA injected side (F-test, $p \leq 0.001$). Together these results indicate that CA3 undergoes subtle structural changes and in some cases loses input from the dentate gyrus. To test how CA3 function may be altered by these changes, we performed high density single unit recordings in epileptic and saline control mice. Mice were trained to forage in two familiar environments, one black and one white, while tetrodes were slowly advanced towards the CA3 subregion. Once tetrodes reached their target, we recorded hippocampal neural activity while mice explored both familiar and novel environments. Initial experiments show hyperexcitable CA3; nearly 100 % of cells that were recorded had place fields in the black-white familiar environments compared to the 30-40% of CA3 cells that are active in control animals. Further analyses are underway to determine whether CA3 place field size and stability are altered in familiar environments and to determine dynamics of remapping in novel environments. By better understanding CA3 dynamics and how they change with epilepsy we can gain insight into impaired memory processing in epilepsy.

Disclosures: B.L. Boublil: None. **G. Tarcsay:** None. **C.B. Dang:** None. **U.J. Redic:** None. **L.A. Ewell:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.07

Topic: B.08. Epilepsy

Support: NAIST Shien Zaidan

Title: Three-dimensional neuronal imaging using dually implanted needle-type image sensor and head-mountable microscope for untangling temporal lobe epilepsy

Authors: *J. P. OLOROCISIMO[1], M. C. GUINTO[1], R. SIWADAMRONGPONG[1], L. AKBAR[1], G. LI[2], K. XINGYUAN[2], R. R. PINEDA[3,4], P. R. REGONIA[3,4], Y. OHTA[1], M. HARUTA[1], K. TAKAHASHI[2], K. ICHIKAWA[2], H. IIDA[2], J. YOSHIMOTO[3], K. IKEDA[3], J. OHTA[1];
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Abstract: Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy; however, the mechanism and treatment for this condition remain elusive. Thus, we aim to develop new methods for elucidating the neural circuit dynamics of TLE. Our goal is to implement new neuronal imaging strategies in freely-behaving mice to observe epilepsy in multiple regions and layers of the hippocampus. By doing so, we hope to untangle the role of different neuronal populations involved in this widespread disease.
Our strategy employs two technological modalities: a novel needle-type implantable CMOS image sensor developed in the lab (CIS NAIST) and an open-source head-mountable microscope (UCLA Miniscope). First, we designed and fabricated the CIS NAIST device, which is a lensless microimaging sensor that is less than 2 mm^2 in size and 0.05 g in weight. The device can be directly implanted into the brain and visualize multiple layers due to its vertical orientation. Additionally, we assembled the UCLA Miniscope to enable single-cell imaging in the horizontal plane in freely-moving conditions. Thus, the combination of both modalities would allow for three-dimensional imaging of the hippocampus during epilepsy.
After seizure induction, we observed three distinct patterns of increased activity across the hippocampal layers. These patterns were also associated with different neuronal network properties and behavioral states. We found that the dentate gyrus had a significantly higher activity compared to the CA1 in one pattern associated with high amplitude and peak frequencies. In conclusion, by implementing our device and strategy, we could better examine the neuronal dynamics of TLE and provide new insights into its etiology and pathology.

Disclosures: J.P. Olorocisimo: None. **M.C. Guinto:** None. **R. Siwadamrongpong:** None. **L. Akbar:** None. **G. Li:** None. **K. Xingyuan:** None. **R.R. Pineda:** None. **P.R. Regonia:** None. **Y. Ohta:** None. **M. Haruta:** None. **K. Takahashi:** None. **K. Ichikawa:** None. **H. Iida:** None. **J. Yoshimoto:** None. **K. Ikeda:** None. **J. Ohta:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.08

Topic: B.08. Epilepsy

Support: CONACYT-226454
CONACYT-256448

Title: Tabernaemontana arborea and ibogaine induce paroxysmal activity in mice

Authors: *D. MARTINEZ-VARGAS[1], F. KRENGEL[3], R. REYES-CHILPA[3], B. VILLASANA-SALAZAR[1], J. D. GONZÁLEZ-GÓMEZ[1], E. URBINA-TREJO[1], F. SANTOS-VALENCIA[1], M. E. GONZÁLEZ-TRUJANO[2];

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Abstract: Several Apocynaceae species, most notably *Tabernanthe iboga*, *Voacanga africana*, and many *Tabernaemontana* species, produce ibogan-type alkaloids. Although a large amount of information exists about the *Tabernaemontana* genus, knowledge concerning biological activity remains lacking for several species, especially related to their effects on the central nervous system. The aim of this study was to evaluate the effect of *Tabernaemontana arborea* Rose ex J.D.Sm. (*T. arborea)* hydroalcoholic extract and two of its main alkaloids (ibogaine and voacangine) on electroencephalographic (EEG) activity alone and in the presence of the chemical convulsant agent pentylenetetrazole (PTZ) in mice. Seventy-two mice were implanted for EEG recording and were divided into twelve groups (n = 6) to receive an acute dosage of 1) saline solution, 2) vehicle, 3-5) hydroalcoholic extract of *T. arborea* (30, 56.2, and 100 mg/kg, i.p.), 6,7) ibogaine or voacangine (30 mg/kg, i.p.) wich were administered 30 min before the PTZ injection (85 mg/kg, i.p.). The EEG activity was recorded during all experiments. Data showed that the PTZ-induced seizures were not modified in the presence of *T. arborea*, ibogaine, or voacangine (latency, number, or duration of generalized tonic-clonic seizures). However, sudden death was observed in mice treated with *T. arborea* extract at 100 mg combined with PTZ. Because *T. arborea* extract (100 mg) and ibogaine (30 mg) *per se* provoked paroxysmal activity in the EEG, both were explored in the presence of a serotonin 5-HT_{1A} receptor antagonist WAY100635 (WAY). For this, WAY was administered 15 min before treatments in the following groups: 8–9) WAY1 (0.32 and 1 mg/ kg, i.p.) combined with *T. arborea* extract (100 mg/kg, i.p.), or 10) with ibogaine (30 mg/kg, i.p.). Additionally, Groups 11–12) received the serotonin 5-HT_{1A} receptor agonist 8-OH-DPAT (1 mg/kg, s.c.) or WAY (1 mg/kg, i.p). Data showed that animals treated with WAY (1 mg) significantly increased the latency at the first paroxysm ($p < 0.005$) with a significant reduction in the number of paroxysms ($p < 0.001$) compared to *T. arborea* (100 mg) group. Ibogaine was the main constituent responsible for the paroxysmal effect of the *T. arborea* extract with a significant increase in the number of paroxysms ($p = 0.005$). The antagonist WAY (1 mg) abolished the paroxysmal activity provoked by *T. arborea* (100 mg) but not that observed with ibogaine, corroborating the participation of a serotoninergic mechanism in the *T. arborea* effects. In conclusion, high doses of the *T. arborea* extract induced abnormal EEG activity due in part to the presence of ibogaine and involving the serotonin 5-HT_{1A} receptor participation.

Disclosures: D. Martinez-Vargas: None. **F. Krengel:** None. **R. Reyes-Chilpa:** None. **B. Villasana-Salazar:** None. **J.D. González-Gómez:** None. **E. Urbina-Trejo:** None. **F. Santos-Valencia:** None. **M.E. González-Trujano:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.09

Topic: B.08. Epilepsy

Support: NIH Grant MH107182
NIH Grant NS114977

Title: Prenatal deletion of forebrain Ank2 causes seizure-related phenotypes by reshaping the synaptic proteome

Authors: *S. YOON[1], M. D. SANTOS[1], M. FORREST[1], C. PRATT[1], N. KHALATYAN[2], P. MOHLER[3], J. SAVAS[2], P. PENZES[1];
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Abstract: Rare genetic variants in *ANK*2, which encodes ankyrin-B, are associated with neurodevelopmental disorders, however, their pathogenesis is not well understood. To investigate the role of *Ank2* in the brain and behavioral development, we used *Ank2* brain-specific conditional knockout mouse models. The mice with prenatal deletion in cortical excitatory neurons and oligodendrocytes ($Emx1^{\Delta ankyrin\text{-}B}$), but not with postnatal deletion in forebrain excitatory neurons ($CaMKII\alpha^{\Delta ankyrin\text{-}B}$), displayed severe spontaneous seizures, increased mortality, hyperactivity, and social deficits, but no cognitive deficits. Calcium imaging of cortical slices from $Emx1^{\Delta ankyrin\text{-}B}$ mice showed increased neuronal calcium event amplitude and frequency, along with network hyperexcitability and hypersynchrony. Quantitative proteomic analysis of cortical synaptic membranes using tandem mass tags and liquid chromatography-triple stage mass spectrometry revealed upregulation of AMPA receptor and dendritic spine plasticity-regulatory proteins, and downregulation of intermediate filaments. Characterization of the ankyrin-B interactome identified interactors associated with autism and epilepsy risk factors and synaptic proteins, including GluA2. The AMPAR antagonist, perampanel, restored cortical network activity and partially rescued survival in $Emx1^{\Delta ankyrin\text{-}B}$ mice. Our findings suggest that abnormal network activity and synchrony, leading to seizures, could be a primary pathogenic mechanism in some forms of ASD, which can be reversed by the pharmacological targeting of proteomic alterations.

Disclosures: S. Yoon: None. **M.D. Santos:** None. **M. Forrest:** None. **C. Pratt:** None. **N. Khalatyan:** None. **P. Mohler:** None. **J. Savas:** None. **P. Penzes:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.10

Topic: B.08. Epilepsy

Support: NIH R01NS105628
NIH R01NS102937

Title: Dysregulation of the HPA axis worsens epilepsy outcomes

Authors: *T. BASU[1], P. ANTONOUDIOU[2], G. L. WEISS[1], J. LAZE[4], D. FRIEDMAN[5], O. DEVINSKY[6], J. L. MAGUIRE[3];
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Abstract: Psychiatric comorbidities in people with epilepsy (PWE) occur at very high incidence rates and females are twice as likely than males to suffer from depression. Hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis is a common feature underlying both depression and epilepsy. People who suffer from major depressive disorder exhibit elevated corticotropin releasing hormone (CRH) and cortisol levels, and they have a 4-7 fold higher risk of having an unprovoked seizure and/or developing epilepsy. In epilepsy, HPA axis activation accelerates epileptogenesis and cortisol levels are chronically elevated in PWE and correlate with seizure severity. We have shown that seizures activate the HPA axis through downregulation of the potassium-chloride cotransporter, KCC2, in CRH neurons that lie at the apex of the pathway. To further investigate the bidirectional relationship between mood disorders and epilepsy, we generated mice that lack KCC2 in CRH neurons (*KCC2/Crh* mice), which impacts seizure burden, affective behavioral states, and hippocampal neuropathology associated with TLE. We find that chronically epileptic *KCC2/Crh* mice exhibit sex specific differences in seizure burden and vulnerability to affective states. Additionally, about 40% of male *KCC2/Crh* mice die immediately following a seizure event, suggesting that HPA axis dysregulation may contribute to Sudden Unexpected Death in Epilepsy (SUDEP) and the *KCC2/Crh* mice may be a novel, non-genetic model of SUDEP. Attenuating HPA axis hyperactivation reduces seizure burden in epileptic *KCC2/Crh* male mice. Finally, ELISA analysis of cortisol (corticosterone in mice), CRH, and ACTH suggests that persistent and excessive HPA axis activity in chronic epilepsy may lead to a collapse in its regulation, leading to increased risk for mood disorders and SUDEP. These data indicate that therapeutically targeting the HPA axis in a sex specific manner may be beneficial in slowing disease progression, alleviating comorbid affective disorders in PWE, and reducing risk of SUDEP.

Disclosures: T. Basu: None. **P. Antonoudiou:** None. **G.L. Weiss:** None. **J. Laze:** None. **D. Friedman:** None. **O. Devinsky:** None. **J.L. Maguire:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.11

Topic: B.08. Epilepsy

Support: DFG Grant HA1443/11-1
BrainLinks-BrainTools Center Freiburg
Center for Basics in Neuromodulation Freiburg

Title: Hippocampal low-frequency stimulation and its effects on learning and memory in a mouse model of epilepsy

Authors: *E. PASCHEN[1,2], P. KLEIS[1,2], J. LINK[1], U. HÄUSSLER[1,3], C. A. HAAS[1,3];
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Abstract: Mesial temporal lobe epilepsy (MTLE) is the most common form of focal, pharmacoresistant epilepsy in adults and is often associated with hippocampal sclerosis (HS). For MTLE patients, one alternative to surgical resection of the epileptic focus is electrical deep brain stimulation in the hippocampus. Commonly, high-frequency stimulation is applied for seizure interruption but the efficacy is low in the presence of HS. For these patients, low-frequency stimulation (LFS) represents an alternative treatment option to prevent seizure occurrence. We showed previously in an *in vivo* mouse model of MTLE that continuous 1 Hz-LFS in the sclerotic hippocampus interferes with the generation of focal, spontaneous epileptiform activity and evoked generalized seizures (Paschen et al., *eLife*, 2020). Here, we aimed to infer the potential impacts of 1 Hz-LFS on hippocampal functions such as learning and memory. To this end, we injected kainate or saline unilaterally into the hippocampus of C57BL/6 mice and implanted one electrode for local field potential (LFP) recordings in each hippocampus and a stimulation electrode in the sclerotic hippocampus. In the chronic epileptic stage, we sequentially investigated mobility and anxiety, as well as learning and memory. We performed behavioral tests including open field, light-dark box, and the Barnes maze in epileptic and healthy control mice that were either stimulated (30 min, 1 Hz-LFS) or not stimulated before each training or test trial. Six hours of LFP recordings before and after the behavioral tests served as verification for epileptiform activity. We found that (i) chronically epileptic mice were more anxious than healthy controls but they were not impaired in their mobility. (ii) 1 Hz-LFS did not alter mobility or anxiety either in epileptic or in healthy control mice. (iii) 1 Hz-LFS did not impair spatial learning and memory performance, since despite stimulation mice were able to navigate successfully in the Barnes Maze. Our results indicate that hippocampal 1 Hz-LFS reliably suppresses the generation of epileptiform activity without affecting mobility and anxiety, or impairing hippocampus-related cognitive functions. Thus, 1 Hz-LFS may constitute a promising approach for seizure control in MTLE with HS.

Disclosures: E. Paschen: None. **P. Kleis:** None. **J. Link:** None. **U. Häussler:** None. **C.A. Haas:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.12

Topic: B.08. Epilepsy

Title: Neuronal and Behavioral Consequences of Early-life Seizures

Authors: *S. TOWNSEND[1,3], S. SRAN[3], J. J. WESTFALL[3], T. A. BEDROSIAN[2,3];
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Abstract: Studies have reported the comorbidity between epilepsy and autism is as high as 40%. This high rate of comorbidity may be related to the fact that both diseases are associated with developmental neuronal abnormalities, including structural, transcriptional, and epigenetic changes. Early life seizures have been correlated with neuronal loss, memory impairment, and negative cognitive outcomes. Likewise, autism is associated with neuronal and synaptic abnormalities leading to deficits in communication and social behavior, as well as repetitive behavior. While both etiologies are multi-factorial, there is clearly a link between the two diseases. Therefore, it is a critical need to understand how early-life seizures are affecting the trajectory of brain development. Here we aim to correlate early-life seizures with a comprehensive set of behavioral, transcriptional, and epigenetic outcomes in mice. To study how early-life seizures affect brain development, we propose to develop an early-life seizure model in wild type CD-1 mice that will induce changes to hippocampal- dependent behavior and neuronal activity. Recent studies have shown that Pentylenetetrazol (PTZ), a GABA-A receptor antagonist, promotes archetypal histological, transcriptional, and epigenetic changes in the brain that induce autism-like social and cognitive impairments in mice. Mice were exposed to either Saline or PTZ to induce repeated seizures (daily, postnatal days 1-30) during a critical window of hippocampal development. Characterization of consequences of early-life seizures were tested beginning at 1 month of age using a suite of assays that test for sociability, memory, learning, and repetitive behaviors to elucidate autistic-like behavior. Lastly, by way of single-cell multiomics (RNA-seq and ATAC-seq; 10x Genomics) we will identify transcriptional and epigenetic signatures of early-life seizures by assaying both gene expression and chromatin accessibility at multiple timepoints (1 -hr, 24-hr, 1-week, 1- month). Mice were exposed to either PTZ or Saline at postnatal day 7. Following seizure induction brains were then harvested at the 1hr and 24hr timepoints. From single cell RNAseq data we were able to see an increase in neuronal activity as there was increased expression of Immediate Early Genes (IEGs) at the 1-hr timepoint. Further analyses are ongoing. Together, these findings will elucidate the association between early-life seizures and neuronal/behavioral consequences, which may help inform the connection between autism and epilepsy.

Disclosures: S. Townsend: None. **S. Sran:** None. **J.J. Westfall:** None. **T.A. Bedrosian:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.13

Topic: B.08. Epilepsy

Support: CURE Taking Flight Award
NIH F32NS116416

Title: Closed-loop control of inhibitory theta phase locking and its influence on seizure activity and cognition

Authors: *Z. CHRISTENSON WICK[1], P. A. PHILIPSBERG[1], S. I. LAMSIFER[1], E. KATANOV[3], C. KOHLER[4], D. J. CAI[2], T. SHUMAN[1];
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Abstract: The precise timing of single-unit spiking relative to network-wide oscillations (i.e., phase locking) has long been thought to maintain excitatory-inhibitory homeostasis and coordinate cognitive processes. We recently found that epileptic mice with spontaneous seizures and cognitive deficits show altered inhibitory theta phase locking in the dentate gyrus, but the causal influence of this phenomenon has never been determined. Thus, we aimed to causally test the hypothesis that inhibitory theta phase locking can bidirectionally control seizures and cognitive performance in control and epileptic mice. To test these hypotheses, we developed a low-latency closed-loop optogenetic system to bidirectionally control inhibitory phase locking to theta in head-fixed control and pilocarpine-treated epileptic mice navigating a virtual track. Using opto-tagging strategies, we first identified the preferred firing phase of parvalbumin+ and somatostatin+ dentate interneurons in control and epileptic mice. We then applied our closed-loop system to lock the spiking of these dentate interneurons to their preferred or non-preferred phase of theta while measuring seizure activity and accuracy of navigation. Using our closed-loop optogenetic system in awake behaving mice, we have succeeded in precisely altering the phase locking of hippocampal interneurons and we have preliminary evidence that there is a cell-type specific deficit in phase locking of parvalbumin+ dentate interneurons in chronic temporal lobe epilepsy. We have also found evidence suggesting that, in epileptic mice, re-aligning inhibitory spiking to the preferred phase of theta diminishes seizure activity compared to stimulating at a non-preferred phase of theta. Further preliminary data show that precise theta phase locking of dentate gyrus inhibitory neurons may influence performance on a demanding dentate-dependent navigation task. Theta phase locking of inhibitory spiking likely plays an important and causal role in two of the most concerning elements of epilepsy: seizures and cognitive deficits. Gaining deeper insights into the impacts of inhibitory theta phase locking may reveal its potential as an epilepsy therapeutic uniquely capable of treating both seizures and cognitive deficits.

Disclosures: Z. Christenson Wick: None. **P.A. Philipsberg:** None. **S.I. Lamsifer:** None. **E. Katanov:** None. **C. Kohler:** None. **D.J. Cai:** None. **T. Shuman:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.14

Topic: B.08. Epilepsy

Support: 3R03NS111493-01S1 Research Supplement to Promote Diversity in Health-Related Research

Title: Characterization of Spatial Memory Deficits and Cell Loss in Pilocarpine Induced Chronically Epileptic Mice

Authors: *K. DIEGO, Y. FENG, Z. T. PENNINGTON, T. SHUMAN;
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Abstract: Temporal lobe epilepsy is one of the most common forms of epilepsy in adults and causes pervasive memory impairments that significantly impact the quality of life. Systemic injections of pilocarpine elicit continuous, persistent limbic seizures in the rodent model of temporal lobe epilepsy (TLE). Previous studies have shown that memory deficits and cell loss occur in both humans and rodents in epilepsy. However, detailed characterization throughout epileptogenesis remains underexplored. Therefore, we investigated spatial memory using novel object location and tested anxiety levels using a light-dark box test in epileptic and control mice. We also performed immunohistochemistry post-mortem in order to shed light on the timeframe of neuron death in a cell-type-specific manner in both hippocampus (HPC) and medial entorhinal cortex (MEC). As a result, we found progressive spatial memory deficits in epileptic mice that emerge between 3 and 8 weeks after pilocarpine. The HPC and MEC are two major regions with extensive pathology in TLE, but the timeline of cell loss in these regions has not been explicitly characterized. To characterize cell-type specific cell loss, we collected and sectioned HPC and MEC brain slices for immunohistochemical staining at three different time points (2 days, 3 weeks, and 8 weeks post-pilocarpine). We then stained for NeuN, parvalbumin (PV), and Fluoro-Jade C (FJC). Preliminary analysis from FJC staining shows severe ongoing cell apoptosis occurred at 2 days after pilocarpine injection in MEC layer 3 (MECIII) and the CA1 region, a critical region located in the hippocampus important for the formation of spatial memories. Together, this data reveals a progressive impairment in spatial memory through the development of epilepsy. Immunohistochemistry staining confirms that most cell apoptosis occurs during the early stage of TLE development in both HPC and MEC early in the progression of memory deficits.

Disclosures: K. Diego: None. **Y. Feng:** None. **Z.T. Pennington:** None. **T. Shuman:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.15

Topic: B.08. Epilepsy

Support: National Research Foundation of Korea (NRF) grant funded by the Korea government No. 2021R1I1A1A01047392
NRF by the Korea government No. 2020R1A2C2013216
NRF by the Korea government No. 2019M3C1B8090803
NRF by the Korea government No. 2019M3C1B8090802

Title: Optogenetic neuromodulation of hippocampal network in a rat epilepsy model.

Authors: *Y. KIM[1], S. KIM[2], Y. CHOI[1], Y. LEE[3], S. HWANG[3], Y. LEE[3], S. JUN[3], H. LEE[1]; [1]Neurol., [2]Med. Sci., [3]Electronic and Electrical Engin., Ewha Women's Univ., Seoul, Korea, Republic of

Abstract: Temporal lobe epilepsy (TLE) is the most common form of epilepsy. High-frequency oscillations (HFOs, ripples 80-250 Hz, fast ripples 250-500 Hz) are widely known as promising biomarkers for TLE patients and epilepsy animal models. HFOs are commonly observed in seizure-onset zones and increased during the ictal state compared to the interictal period.
In this study, we tested optogenetic neuromodulations to generate seizure-like events (SLEs) and verified the effect on neural activities in a pilocarpine-induced chronic TLE rat model. For optogenetic induction of SLEs, CAMKII neurons were targeted for ChR2 expression in hippocampus. 1.5µl AAV5-CaMKIIa-hChR2-EYFP injected into the right hippocampus (ML: +3.2 mm, AP: -4.56 mm, DV: -3.8 mm from bregma). After 6 weeks, optical fiber and local field potential (LFP) microelectrodes were implanted and a 473 nm blue-light was delivered with 500 ms pulse duration, 50% duty cycle, starting at 22 mW/mm^2 intensity. Light intensity was increased twice of the previous intensity after 10-min break until SLEs were induced or up to the light power of 88 mW/mm^2. We assessed dynamic alterations of neural activities between light stimulation and baseline in different frequency bands including delta (2-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), gamma (30-80 Hz), ripple (80-250 Hz), fast ripple (250-500 Hz), and ultra-fast ripple (500-1000 Hz) by calculating the power spectral density (PSD) value that reflects the power of the EEG signals. Optogenetic stimulations of ChR2 expressing excitatory neurons in hippocampus induced neural activity changes and alterations at the intensity of 88 mW/mm^2, particularly high-frequency neural activities. We observed increased PSD value of 250-500 Hz fast ripple and 500-1000 Hz ultra-fast ripple during ChR2 activation period compared to the baseline recording (PSD values: fast $ripple_{stimulation}$ = 0.0067 dB vs. fast $ripple_{baseline}$ = 0.00292 dB ($p<0.001$); ultra-fast $ripple_{stimulation}$ = 0.0064 dB vs. ultra-fast $ripple_{baseline}$ = 0.003 dB ($p<0.001$)).
The overall results demonstrate that optogenetic neuromodulation of ChR2 expressing excitatory neurons in hippocampus induces the occurrence of high-frequency associated with SLEs in a chronic TLE rat model. Optogenetics is a useful tool to provide better understanding of the mechanisms of seizure generation and termination in neuronal circuit levels, and optogenetic neuromodulation may help to control these activities in epilepsy animal models. We now plan to expand these optogenetic neuromodulations targeting hSyn neurons for eNpHR3.0 expression to determine the effectiveness of SLEs inhibition.

Disclosures: **Y. Kim:** None. **S. Kim:** None. **Y. Choi:** None. **Y. Lee:** None. **S. Hwang:** None. **Y. Lee:** None. **S. Jun:** None. **H. Lee:** None.

Poster

696. Epilepsy: *In Vivo* and Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 696.16

Topic: B.08. Epilepsy

Support: National Research Foundation of Korea (NRF) grant 2021R1A6A3A13043922
National Research Foundation of Korea (NRF) grant 2021R1I1A1A01047392
National Research Foundation of Korea (NRF) grant 2020R1A2C2013216
National Research Foundation of Korea (NRF) grant 2019M3C1B8090803
National Research Foundation of Korea (NRF) grant 2019M3C1B8090802

Title: Behavioral abnormalities and neuron-glial interactions in animal model of temporal lobe epilepsy

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Abstract: Temporal lobe epilepsy (TLE) is often accompanied by comorbid behavioral abnormalities such as memory impairment and/or depression-anxiety. The role of neuron-glial interaction in regulating neural activity has been suggested as one of the pathophysiologic mechanisms of epilepsy. However, its association with comorbid behavioral abnormalities in epilepsy has not yet been established. This study investigated whether dynamic interactions between neurons and glial cells lead to coexisting behavioral outcomes in TLE rat model. Status epilepticus (SE) was induced by pilocarpine focal injection to right hippocampus in male SD rat, and continuous video and local field potential (LFP) monitoring was performed. Seizure severity was estimated as spontaneous recurrent seizure (SRS) according to the modified Racine classification. Behavioral testing of animals with Open Field Test (OFT), Elevated Plus Maze (EPM), Forced Swimming Test (FST), and Morris Water Maze (MWM) was performed at 8 weeks after the initial SE. After behavioral testing, brains were sectioned for immunohistochemical staining using neuronal marker (NeuN), allograft inflammatory factor 1 (IBA-1) and glial fibrin acid protein(GFAP) antibodies.
Pilocarpine focal injection to hippocampus induced acute SE and the consequent SRSs in 4-8 weeks since the initial SE. Compared to control group (SE vs control), epileptic rats showed increased total cross number (121.6 ± 22.1 vs 91.0 ± 14.2) and decreased center square duration times (5.8 ± 2.2 sec vs 13.5 ± 4.2 sec) in OFT, decreased duration time in EPM open arms (16.15 ± 1.67 sec vs 24.10 ± 3.66 sec), increased immobility times in the FST (19.7 ± 3.0 sec vs 13.2 ± 0.7 sec), and longer time to find platform in MWM (53.35 ± 15.28 sec vs 28.74 ± 23.39 sec) at 8 weeks. In addition, epileptic rats revealed decreased NeuN cells in CA1 and CA3 (22.4 ± 3.04 vs 28.0 ± 7.03 and 16.9 ± 2.74 vs 23.3 ± 3.12 per unit square 200X200 μm2, respectively, increased IBA-1(+) glia cells in CA3 (5.9 ± 2.6 vs 4.7 ± 1.8 per 200X200 μm2), and increased GFAP cells in CA1 and DG (27.6 ± 6.6 vs 19.2 ± 3.9 and 29.8 ± 4.8 vs 21.6 ± 4.2 per 200X200 μm2. Seizure severity and behavioral test scores were tested for possible relationship between NeuN, IBA-1 or

GFAP positive cell counts.
In addition to the occurrence of SRS, depression and anxiety-like behaviors were significantly increased at 8 weeks after the initial SE. Our results suggest that behavioral comorbidities could be closely associated with epileptogenesis and/or neuron-glial interactions.

Disclosures: S. Kim: None. **Y. Kim:** None. **Y. Choi:** None. **H. Lee:** None.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.01

Topic: B.08. Epilepsy

Support: German Research Foundation Grant HA 1443/11-1
BrainLinks-BrainTools Center Freiburg
Center for Basics in Neuromodulation Freiburg

Title: Optogenetic low frequency stimulation of hippocampal and entorhinal principal cells for seizure suppression in a mouse model of mesial temporal lobe epilepsy

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Abstract: Mesial temporal lobe epilepsy (MTLE) is the most common form of drug-resistant epilepsy in adults, characterized by focal seizures typically originating from the hippocampus or entorhinal cortex. Deep brain stimulation represents a promising alternative approach to resective surgery for alleviating intractable seizures in MTLE patients. Usually high-frequency stimulation is applied in the hippocampus or thalamic nuclei. However, it tends to have low seizure-suppressive efficacy in MTLE patients with hippocampal sclerosis (HS), presumably due to extensive neuronal loss and glial scarring. Small cohort studies suggest low-frequency stimulation (LFS) might be a better strategy for treating drug-resistant MTLE patients with HS. Here, we build on our previous preclinical findings showing that 1 Hz LFS of entorhinal afferents in the sclerotic hippocampus prevents spontaneous seizure activity during stimulation in chronically epileptic mice (Paschen *et al.*, 2020, eLife). However, it is unclear which cell populations mediate these anti-epileptic effects. We aim to determine if the seizure suppressive effect of 1 Hz LFS is the strongest when applied to dentate granule cells (DGCs) in (1) the sclerotic dorsal hippocampus, (2) the non-sclerotic ventral hippocampus or (3) to principal cells of the medial entorhinal cortex (mEC). We induced chronic epilepsy in mice by unilateral intrahippocampal injection of kainate (KA). Principal cell populations in mEC or dentate gyrus (DG) were targeted either with a stereotactic injection of a Channelrhodopsin2(ChR2)-encoding viral vector or using a transgenic mouse line (Rbp4-Cre-Ai32), which expresses ChR2

selectively in DGCs. Subsequently, mice were implanted with a recording electrode in each hippocampus at the level of KA injection. An optic fiber was placed either (1) into the sclerotic DG or together with an additional recording electrode into the ipsilateral (2) ventral DG or (3) the mEC. During the chronic phase of epilepsy (>20 days after KA), three-hour-long local field potential recordings were acquired from freely moving mice with or without 1 Hz optogenetic stimulation. We found that the most substantial seizure-suppressive effect was achieved by 1 Hz LFS of the DGCs in the sclerotic hippocampus. In contrast, stimulation of the DGCs in the non-sclerotic hippocampus and principal cells in mEC did not alter the duration and number of spontaneous focal seizures. Our results suggest that 1 Hz pacing of DGCs at the seizure focus is critical for the seizure-suppressive effects of LFS.

Disclosures: P. Kleis: None. **E. Paschen:** None. **J. Link:** None. **U. Häussler:** None. **C. Haas:** None.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.02

Topic: B.08. Epilepsy

Support: NIHR01NS094399

Title: Optimization of ictal aborting stimulation using the dynamotype model

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Abstract: Electrical stimulation is an increasingly popular method to terminate epileptic seizures; yet it is not always successful. One of the potential reasons for inconsistent efficacy is that stimuli are applied empirically, without considering the underlying dynamical properties of a given seizure. In this work, we use a computational model of seizure dynamics to show that different seizure types have vastly different responses to controlling stimuli. We use the Taxonomy of Seizure Dynamics to model different onset dynamotypes, then determine the ability of ictal stimulation to abort seizures after they have started. Within the model, the aborting input is realized as an applied stimulus trying to force the system from a bursting state to a quiescent or resting state. This transition requires bistability, which is not present in all onset dynamotypes. We examine how topological and geometric differences in bistable phase spaces affect the probability of termination as the seizure progresses from onset to offset. We find that the most significant determining factors are (1) the presence or absence of a baseline (DC) shift and (2) the dynamotype (onset/offset bifurcations) during the seizure. Generally, we find that seizures that have a DC shift are far more likely to be terminated than those without because they are not as sensitive to the phase at which stimulation occurs. Furthermore, we observe that the

probability of termination varies throughout the seizure's duration and is highly correlated to its dynamotype. Our model provides a method to predict the optimal method of termination for each dynamotype. We conclude that strategies for aborting seizures with ictal stimulation must account for seizure dynamotype to optimize efficacy.

Disclosures: M. Szuromi: None. **V.K. Jirsa:** None. **W. Stacey:** None.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.03

Topic: B.08. Epilepsy

Support: H2020-MSCA-IF-2014 Re.B.Us Grant 660689
H2020-FETPROACT-01-2018 (RIA) HERMES Grant 824164

Title: Biohybrid restoration of the hippocampal loop controls limbic ictogenesis

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Abstract: Background and rationale: Mesial temporal lobe epilepsy (MTLE) is the most common epileptic syndrome in adults and the most often drug-refractory. Deep brain stimulation (DBS) promises to improve the clinical condition of drug-refractory MTLE patients; however, DBS still relies on trial-and-error and cannot guarantee a seizure-free life. Most importantly, while the hippocampus-cortex loop is typically compromised in MTLE, DBS does not restore its circuitry. Previous studies using in vitro models of limbic ictogenesis have demonstrated the anti-ictogenic role of the CA3-driven interictal pattern (Barbarosie and Avoli, J Neurosci 1997, doi: 10.1523/jneurosci.17-23-09308.1997) and the feasibility of deploying its temporal profile for open-loop stimulation to control limbic ictogenesis (Caron et al., Biology 2022, doi: 10.3390/biology11030371). This evidence paves the way to an interictal-based grammar for closed-loop DBS to treat MTLE.
Aim: Here, we explore the feasibility and efficacy of a hippocampus-cortex bridging approach to achieve the functional restoration of the hippocampal loop and control limbic seizures. Specifically, we use the CA3-driven interictal discharges as feedback signal to trigger electrical stimulation in the subiculum and re-establish the hippocampus output to the cortex. As the biological pathway closing the loop in the other direction (i.e., from the cortex back to the hippocampus) is preserved, this strategy establishes a biohybrid loop.
Methods: We performed microelectrode array (MEA) closed-loop electrophysiology in mouse horizontal hippocampus-cortex slices (n = 9) treated with 4-aminopyridine (250 μM). Quantification of ictal activity is reported as P_ictal, defined as the percentage of the overall

duration of ictal discharges relative to the duration of the observation window. Statistical analysis is based on one-way ANOVA followed by the Games-Howell post-hoc test. Data are expressed as mean ± SEM.
Results: Biohybrid bridging of hippocampus and cortex achieved a P_ictal reduction of 95.45±2.26% (range: 80-100%); further, its efficacy depended on continuous operation, since stimulus withdrawal lead to the re-emergence of ictal activity similar to pre-stimulus baseline (P_ictal - baseline: 19.97±1.83; bridge: 0.77±0.34; recovery: 20.07±2.19. $F(df) = 50.58(2)$; $p < 0.0001$).
Conclusions and outlook: Our work opens the possibility for a bridging neuroprosthesis for epilepsy treatment that does not depend on seizure detection/prediction algorithms, but relies on endogenous interictal patterns, thus outclassing the conceptual design and, possibly, the performance of current DBS.

Disclosures: D. Caron: None. **G. Panuccio*:** None.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.04

Topic: B.08. Epilepsy

Title: Developing a real time adaptive closed-loop neural activity suppression controller for seizure prevention

Authors: *Z. T. SANGER[1], A. LAMPERSKI[2], T. I. NETOFF[1];
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Abstract: Electrical stimulation has been an effective neuromodulation tool for seizure suppression in only a portion of the refractory epilepsy patient population. Stimulation parameter optimization has been a long-standing challenge in the field of neuromodulation. Many current seizure neuromodulation approaches are either open-loop or response feedback controlled. Developing a seizure prevention approach that is adaptive, not only to potential seizure events, but variations in nervous system activity between different seizure events would allow for better closed loop control. Here we are testing a closed loop controller algorithm to suppress neural activity based on neural states. This controller consists of a state estimator and then determines optimal stimulus to return the neural activity to a quiescent state. First, the unscented Kalman filter estimates the state space matrices (A,B,C,D) of the given LFP signal of interest. Then, these state space matrices are used to build a predictive model of the LFP. Using this model, a linear quadratic regulator (LQR) determines the optimal stimulus to apply to suppress activity. The controller was tested in a biophysical computational model of epileptiform activity and the VanAlbada model which simulates the relationship between brain regions as the controller stimulates in the sub-thalamic nucleus (STN) while recording in the globus pallidus externus (GPE). Simulations show reduction in the mean power over the low frequency bands. This

controller is particularly exciting because with millisecond level real time state space adjustment, optimal stimulation for non-stationary highly dynamical systems is possible. Because of this capability, stimulation waveforms for a wide variety of neuromodulation applications could be determined using this controller.

Disclosures: Z.T. Sanger: None. **A. Lamperski:** None. **T.I. Netoff:** None.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.05

Topic: B.08. Epilepsy

Title: Initial evidence, safety and feasibility of Intersectional Short Pulse stimulation, a novel spatio-temporally focused closed-loop neuromodulation for drug resistant focal epilepsy

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Abstract: Epilepsy affects an estimated 50-70 million people worldwide and presents a significant disease burden. The seizures of approximately the third of patients with epilepsy are not adequately controlled by pharmacotherapy. While surgical approaches can be curative, not all patients are candidates if potential risks outweigh possible benefits. For patients with drug-resistant epilepsy (DRE), who are not eligible for resective or ablative surgery, neuromodulation has been increasingly a therapeutic choice. Currently, available neuromodulation modalities are either spatially non-specific (ANT DBS and VNS) and/or temporally suboptimal by not delivering stimulation directly to the seizure focus at the time of seizures, while RNS is requiring invasive brain surgery. Non-invasive brain stimulation methods, like Transcranial Magnetic and Direct Current Stimulations for epilepsy, carry no surgical risk, however, they either cannot be converted to a wearable device or fail to deliver effective current densities to interfere with seizure activity. We developed a closed-loop neurostimulation method, 'Intersectional Short Pulse Stimulation (ISP) to inject sufficiently high current into the brain by means of subgaleal strip electrodes while keeping sensation tolerable. Subgaleal electrodes do not require skull penetration, thus reducing the surgical burden. ISP achieves high focal charge density by sequences of rotating dipoles on a millisecond resolution. Previously our group verified the spatial and temporal specificity of ISP in a rodent model of absence epilepsy; in humans, we

demonstrated that effective current density can be achieved in deeper brain areas in a cadaver model, while we have proven ISP can modulate the posterior dominant rhythm in healthy volunteers. Here we report the results of the first in-patient experiments of the novel, closed-loop therapeutic system which consists of subgaleal electrode array, signal amplifier, real-time EEG processing and stimulation electronics delivering ISP stimulation via the recording electrodes. The device performs real-time seizure detection and terminates seizures by delivering high-intensity electrical impulses to induce closed-loop interference with the initiating seizure oscillations. We implanted five patients with DRE. All patients tolerated the stimulation without any detrimental side effects. Closed-loop stimulation resulted in rapid termination of seizures arising in deeper cortical foci before generalization. Our results provide proof of concept for personalized, closed-loop therapy to treat epilepsy by terminating seizures before generalization.

Disclosures: Z. Chadaide: None. **D. Fabó:** F. Consulting Fees (e.g., advisory boards); Neunos Zrt. **L. Barcsai:** None. **A. Pejin:** None. **T. Foldi:** None. **K. Furuglyas:** None. **Z. Somogyvari:** None. **T. Gyurkovics:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neunos Zrt. **M. Nadasdi:** None. **P. Rafi:** None. **A. Kamondi:** None. **G. Buzsaki:** F. Consulting Fees (e.g., advisory boards); Neunos Zrt. **O. Devinsky:** F. Consulting Fees (e.g., advisory boards); Neunos Zrt. **L.G. Eross:** F. Consulting Fees (e.g., advisory boards); Neunos Zrt. **A. Berenyi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neunos Zrt.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.06

Topic: B.08. Epilepsy

Support: The Health and Medical Research Fund (HMRF), Food and Health Bureau, Hong Kong Special Administrative Region Government (9211293).

Title: Therapeutic potential of novel anatomical target of deep brain stimulation in mice model of epilepsy

Authors: *G. KUMAR, V. Y. Y. CHU, C. H. E. MA;
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Abstract: Epilepsy is a neurological disorder affecting ~1% of the population and the causes are unknown in about 50% of global cases. Currently available therapeutic interventions provide limited efficacy and serious adverse effect and about 30% patients develop resistance to antiepileptic drugs. Drug resistance epilepsy (DRE) patients have low chance of seizure control with medication and in some cases, surgical treatment also fails. Therefore, deep brain stimulation (DBS) has been used as an adjuvant therapy in medically intractable epilepsy and it

showed significant reduction in seizure frequency (70%). However, side effect associated with DBS such as pain, depression and suicide tendency due to modulation of limbic system are major limitations. Hence, we identified a novel anatomical target in the midbrain and connects cerebral cortex, thalamus, basal ganglia, cerebellum, and spinal cord via afferent and efferent projections. It receives direct afferent cortical fibres input from primary & somatosensory motor area and their cholinergic ascending fibres projects to all thalamic nuclei suggesting its therapeutic potential implication in seizure control. It acts as major communication relay centre for motor control in cerebellum, basal ganglia component and motor cortex. It controls the muscle tone and locomotion through mesopontine tegmentum and pontomedullary reticulospinal system. We hypothesized the novel target can modulate the vital foci of epilepsy based on the anatomical projection via (a) thalamus, (b) cortical & subcortical limbic structures (c) cerebellum (d) basal ganglion and (e) descending motor pathway from brain stem to spinal cord. We explored the DBS efficacy of novel target in pentylenetratrazole (PTZ) induced epilepsy in mice. Mice received DBS stimulation at 20Hz frequency, 100μA pulse amplitude, 80μs pulse width for 1 hour on a daily basis for 7 days. Strikingly, novel target-DBS significantly controlled the seizure by increasing the latency to myoclonus, clonus & generalised tonic colonic (GTC) and decreasing GTC duration, reducing the number of epileptic discharge (electroencephalogram) as compared to saline treated group. Electrophysiological property of novel target neurons was evaluated after 1 hour of PTZ challenge. DBS treated mice showed significantly decreased neuronal spike firing rate, increased the interspike interval, decreased local filed potential and beta band power spectral density as compared with PTZ group. In summary, low frequency novel target-DBS controls the seizures and restores the electrophysiological property of neurons in mice model of epilepsy.

Disclosures: G. Kumar: None. **V.Y.Y. Chu:** None. **C.H.E. Ma:** None.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.07

Topic: B.08. Epilepsy

Support: Institutional Support
NIH R56 NS115978

Title: Spatial optimization of hippocampal stimulation in a mouse model of acute seizure activity

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Abstract: Rationale: Drug-resistant epilepsy affects approximately 1 million people in the United States. Neurostimulation devices provide an alternative treatment option for refractory seizures but are generally less effective than surgical resection. This difference may be due to suboptimal device settings, electrode placement, or other patient factors. The most common refractory focal epilepsy in adults is temporal lobe epilepsy, which is often treated with neurostimulation of the hippocampus. There is some clinical evidence for regional differences in the clinical response to hippocampal neurostimulation, which could be taken advantage of by directional neurostimulation electrodes. However, the optimal spatial parameters for hippocampal electrode placement, directionality, and stimulation settings are unknown. **Methods:** Temporal and spatial dynamics of neurostimulation were investigated in the intrahippocampal kainate mouse model of acute seizures. Mice were anesthetized, and kainic acid was stereotactically injected via a small cranial window into the dentate gyrus. Screw electrode electrocorticography was recorded and processed using a bandpass filter. Ictal spiking activity was quantified from differential recordings in an automated pipeline analysis using z-score filtering. Animals developed persistent seizure activity, during which high-frequency neurostimulation (100-Hz) was applied in the *bilateral CA1, ipsilateral subiculum, ipsilateral CA3, ventral-hippocampal commissure, and medial septum* locations. **Results:** *Temporal:* High-frequency stimulation of the CA3 region resulted in a reduction in seizure activity when comparing spike rates before (2.8 spikes/sec) and after (1.2 spikes/sec) stimulation ($p < 0.01$). Only CA3 stimulation demonstrated a statistically significant reduction in spike frequency. **Conclusions:** These results demonstrate spatial variability between hippocampal regions using direct hippocampal stimulation. High-frequency stimulation of the CA3 hippocampal region was most effective in suppressing KA-induced seizure activity. These findings describe spatial and temporal aspects of intrahippocampal neurostimulation in an acute animal model of temporal lobe epilepsy, which may have important clinical implications in treating refractory epilepsy.

Disclosures: T.J. Foutz: None. **N. Rensing:** None. **D.M. Durand:** None. **M. Wong:** None.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.08

Topic: B.08. Epilepsy

Support: NIH U01 NS108929-01 (subaward 38854/00)

Title: The impact of intracranial stimulation on interictal epileptiform activity in patients with epilepsy

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Abstract: Epilepsy is a leading neurological disorder that impacts over 3.4 million individuals nationwide. For those who suffer from epilepsy, memory deficits are a prevalent concern and a well-documented health issue in which both short- and long-term memory are negatively impacted. This is especially concerning as self-reported memory is a significant predictor of quality of life in these individuals. Thus, elucidating the neural underpinnings of epilepsy-induced memory disruption is vital to improving patient care. Interictal epileptiform activity (IEA) is one factor of the disorder that has consistently been shown to be associated with cognitive impairment in persons with epilepsy (PWE), making it a rational potential target for treatment of memory disruption. However, there is limited research on effective therapies specifically aimed at reducing IEA burden in PWE. This study aimed to close the gap in this research by retrospectively investigating the potential of intracranial stimulation to lower IEA rates in subjects undergoing intracranial electroencephalography (iEEG) monitoring. 135 subjects from multiple institutions with medication-refractory epilepsy undergoing iEEG monitoring performed multiple sessions of a free recall task that included both non-stimulated and stimulated trials. To determine the impact of stimulation on IEA rates, we calculated a baseline IEA rate (number of interictal discharges per trial, averaged over trials) for each subject based on their non-stimulated sessions, then subsequently compared those to the IEA rates during stimulation sessions. IEA for every participant was detected using our previously validated automated detector and processing pipeline. Our preliminary results show a significant effect of stimulation on overall IEA rate. Free recall sessions that delivered stimulation reduced the number of interictal epileptiform discharges over the testing period, on average, compared to non-stimulated sessions. This is the first study of this magnitude to provide evidence of electrical stimulation reducing IEA burden in PWE. These results are a major step towards not only increasing our knowledge of IEA, but also for developing effective therapies aimed specifically at lowering IEA rates to potentially improve memory in PWE. Ongoing work is narrowing the scope of this investigation by exploring the impact of stimulation type and stimulation locations on IEA rates. Additionally, we aim to relate these findings to the cognitive outcomes associated with reduced IEA burden.

Disclosures: **S.A. Steimel:** None. **R.J. Quon:** None. **S. Meisenhelter:** None. **R.E. Gross:** 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 U01 NS108929-01. **B.C. Lega:** 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 U01 NS108929-01. **M. Sperling:** 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 U01 NS108929-01. **M.J. Kahana:** 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 U01 NS108929-01. **B.C. Jobst:** A. Employment/Salary (full or part-time):; Louis and Ruth Frank Professorship of Neurosciences award. B. Contracted Research/Research Grant (principal investigator for a drug study,

collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; PI for NIH U01 NS108929-01 (subaward 38854/00).

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.09

Topic: B.08. Epilepsy

Support: NIH Grant UH2/UH3-NS95495
NIH R01-NS092882

Title: Characterizing human brain long-term impedance dynamics

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Abstract: *Objective* Electrical impedance of cortical tissue plays an important role in a variety of phenomena, ranging from the coordinated neural activity at various scales to clinical applications for electrical brain stimulation (EBS). Although changes in impedance after surgical electrode implantation and around seizures have been reported, there have been few chronic studies in humans. In this study we investigated long-term impedance dynamics in humans with temporal lobe epilepsy (TLE).
Methods Four patients with drug resistant TLE were implanted with bilateral thalamus. amygdala and hippocampus electrodes (FDA-IDE: G180224). EBS was continuously delivered to the thalamus with intermittent gaps. The impedance was sampled nonuniformly, ~4 samples/hr, over multiple months. The impedance change after implantation was modeled with a piecewise parabolic and exponential function to approximate the initial implant effect and recovery behavior of impedance. Seizure-related impedance changes were analyzed using cross-correlation between impedance and seizures ±12 hours around a seizure onset, using both true and surrogate seizures.
Results The half-life (HL), tau*ln(2) characterizing the time scale of impedance increase, was longer in the more epileptogenic thalamus (left HL [95% CI] = 1.73 [1.67, 1.79] days v.s. right 1.05 [1.01, 1.11] days), suggesting epilepsy related difference in tissue electrical properties. Impedance of thalamus in EBS therapy gaps was fit using exponential model, showing left (2.88±0.24 hrs, error: ±1 SEM) and right (2.64±0.24 hrs) HL were similar, but shorter than those immediately after implantation ($p < 0.001$), indicating different mechanisms. In hippocampus, left was significantly shorter than right HL ($p < 0.001$). Seizures and surrogate seizures show a peak in correlation in hippocampus and a valley in thalamus around seizure onsets.
Conclusion The initial implant effects are well modeled by a parabolic behavior, and after ~4

days increase to a stable baseline within 15 days. The mechanisms for this behavior remains unclear. Similarly, an exponential impedance increase occurs with stopping brain stimulation but markedly faster, suggesting different mechanisms. Lastly, we tested hypothesis that seizure onsets may be phase locked to the circadian cycle of impedance. The cross-correlation of seizures was higher than surrogate seizures in thalamus, indicating the difference was pathological in this brain area. These analyses suggest that dynamic changes of impedance after implantation, between consecutive stimuli, and around epileptic seizures might be correlated with pathological brain tissue electrical properties.

Disclosures: **J. Cui:** None. **F. Mivalt:** None. **V. Kremen:** None. **S. Vladimir:** None. **B.H. Brinkmann:** None. **J.J. Van Gompel:** None. **K.J. Miller:** None. **W.A. Gregory:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Summit RC+S TM, Medtronic Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cadence Neuroscience Inc., NeuroOne, Inc..

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.10

Topic: B.08. Epilepsy

Support: Edmond J Safra 2017 Grant Fonds de Dotation Clinatec
Edmond J Safra 2018 Grant Fonds de Dotation Clinatec
Commissariat à l'Energie Atomique et Alternative CEA

Title: An Implant prototype for hippocampal cooling reduces epileptic seizure frequency in a Non Human Primates model

Authors: *T. COSTECALDE[1], N. TORRES[1], E. MASSON[1], J. MOLET[1], C. CHABROL[1], F. SAUTER-STARACE[1], D. RATEL[1], T. AKSENOVA[1], S. CHABARDÈS[2], N. AUBERT[1]; [1]Univ. Grenoble Alpes, CEA, LETI, Clinatec, Grenoble, France; [2]Neurosurg. Department, CHU Grenoble Alpes, grenoble, France

Abstract: Rationale Epilepsy remains one of the most common neurological disease. This pathology have an incidence of 50 to 100 000 people per year and affects around 50 million patients in the world. Currently, antiepileptics drugs are the gold treatment but are effective only in 60-70% of patients. For some drug-resistant patients, neurosurgery, vagus nerve stimulation or deep brain stimulation can offer treatment options able to partially reduce seizures. Since several years, non-pharmacological potential new treatments have been investigated including an interesting new approach using focal cooling. In the literature, some results in preclinical models showed that a cooling at 21°C can decrease the frequency of epileptic seizures. In our laboratory (Clinatec), we started a program focus on focal cooling treatment. Our aim is to provide a

medical device able to offer a focal cooling in deep brain region as hippocampus to treat epilepsy. Therefore, we developed a preclinical implantable device to deliver this cooling to obtain information concerning the parameters needed to reduce seizures (target temperature, duration⋯). This characterization will be very useful to advance on the development of a clinical device (power, alimentation⋯). Methods We developed a complex prototype targeting the hippocampus [1] which is able to i) induce an epileptic zone via a cannula for penicillin injection, ii) generate cooling in this deep brain area, iii) record brain activities by electrodes and iiii) measure temperature at different levels of the implant thanks to implanted sensors. Two sources of cold are required to produce low temperature at the cooling tip: a thermostatic bath with circulation of alcohol at -20°C and a thermoelectric cooler (Peltier). Results The cooling probe of the device was validated using a thermal camera and every sensors were calibrated. Based on these measurements, we quantified a 20°C drop of the temperature at tip of the device (hemisphere of radius 1.5 mm). Then, it has been implanted in non human primates to generate long term epileptic crisis induced by penicillin injection and block them by focal cooling. A reduction in the number of hippocampal seizures was observed at a delta T of 20°C (4.34 seizures per 20 min vs 1.38 seizures per 20 min). Conclusions Here, we present a new solution to perform focal brain cooling, based on a thermoelectric solution for deep brain regions. This device allows also to record brain activities offering the possibility to predict crisis and therefore consider a closed loop system. 1. Patent: Sonde implantable pour dispositif de refroidissement localisé et dispositive incluant ladite sonde. Number 1762393. France.

Disclosures: **T. Costecalde:** None. **N. Torres:** None. **E. Masson:** None. **J. Molet:** None. **C. Chabrol:** None. **F. Sauter-starace:** None. **D. Ratel:** None. **T. Aksenova:** None. **S. Chabardès:** None. **N. Aubert:** None.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.11

Topic: B.08. Epilepsy

Support: Edmond J Safra 2017 Grant Fonds de Dotation Clinatec
Edmond J Safra 2018 Grant Fonds de Dotation Clinatec
Commissariat à l'Energie Atomique et Alternative CEA

Title: Focal brain cooling for seizure control in a primate model of epilepsy

Authors: *N. TORRES[1], E. MASSON DE MONTALIVET[1], J. MOLET[1], T. COSTECALDE[1], N. AUBERT[1], F. SAUTER[1], D. RATEL[1], S. CHABARDÈS[2], B. Y. PIALLAT[3];
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Abstract: Rationale: Epilepsy remains a serious and challenging neurological disorder. Based on literature review, about 30% epileptic patients could meet the criteria of drug-resistant epilepsy (DRE), requiring additional intervention. An important percentage could benefit from ablative surgery, or deep brain stimulation in selected targets, with diverse degrees of success. One emerging strategy is focal cooling. Cooling effect on epilepsy attenuation is known since decades. Brain cooling involves application of hypothermia to the epileptic focus. Authors have shown suppression of epileptic discharges when cooling is applied in brain surface. However, no data is available about the necessary temperature to stop seizures in deep-seated areas (i.e. hippocampus). Here we present the first results of a prototype of implantable device capable to deliver the cooling effect hippocampal seizures in a non-human primate (NHP) model, in order to stablish which parameters are necessary to reduce seizures Methods: A prototype cooling lead was inserted unilaterally in the NHP hippocampus. The device has several temperature sensors and a cannula for penicillin injection in order to create an epileptic zone (EZ) near the cooling tip. Penicillin was injected (5000-7000 UI in 10 minutes) into the hippocampus. Signal was recorded using a sEEG lead implanted 2 mm from the EZ. Recordings were acquired during 5-7 hours periods. After a period of stabilization, focal cooling was applied and temperature and electroclinical events were measured. Results: Hippocampal seizures were obtained after 40-120 min post injection. Seizures duration was constant (58.5± 11 s) and the frequency of seizures stabilized 120 min post injection. Seizures were detected off-line using a customized detection algorithm. A reduction in the number of hippocampal seizures was seen at temperatures of 20°C when compared with control (Control: 4.34 ± 1.704 seizures par 20 min vs Cooling 20°C : 1.38 ± 1.004 seizures par 20 min). There was no change in seizure duration during focal cooling. Hippocampal sclerosis**, comparable** to grade three sclerosis in humans was found in the injection site. Conclusions: Focal cooling of the EZ could be an alternative treatment for DRE, with lower risk of irreversible functional loss compared to surgery. Until now, important technological limitations, like heat dissipation, and all the regulatory constraint has kept this physical phenomenon to be fully in use as a therapeutic tool for DRE. In our study, we present a new approach to perform focal brain cooling, based on an implant capable of reaching deep-seated structures in the brain.

Disclosures: N. Torres: None. **E. Masson de Montalivet:** None. **J. Molet:** None. **T. Costecalde:** None. **N. Aubert:** None. **F. Sauter:** None. **D. Ratel:** None. **S. Chabardès:** None. **B.Y. Piallat:** None.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.12

Topic: B.08. Epilepsy

Support: NIH grant MH119880

Title: Circumscribing femtosecond laser cuts severing supragranular layers attenuate seizure initiation and propagation without structural or functional impact in a mouse model of focal epilepsy

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Abstract: Epilepsy is a debilitating disease that affects about 3% of people and 5% of dogs worldwide. Focal epilepsy is characterized by seizures that initiate in one location of the brain and propagate out to others. Unfortunately, medical management is ineffective in about 45% of focal epilepsy patients and the alternative is invasive neurosurgical approaches that often leave patients with significant neurologic deficits. Recent research has shown that acutely induced seizures mainly propagate through lateral connections in supragranular layers of the cortex. Previously it had been hypothesized that severing these connections would disrupt the initiation and propagation of seizures. However, there was not a way to severe these specific layers without causing significant damage to surrounding structures in the brain. Using tightly-focused femtosecond infrared laser pulses, we were able to make micrometer-scale, sub-surface incisions in the cortex of rodents with minimal collateral damage. In this study we tested the long-term efficacy of cuts produced using this laser scalpel, localized to layers II-IV, and encircling a chronic neocortical seizure focus in blocking seizure propagation, as well as determining the effect these cuts have on neuronal structure and function. Epileptiform activity was induced through a microinjection of iron chloride. In mice without laser cuts over 85% of seizures propagated across the cortex while in mice with laser cuts only 5% of seizures propagated. Chronic speckle imaging indicated that blood flow to the circumscribed region was not significantly decreased, and further histologic inspection showed very modest glial scarring at the cut locations, with no overall disruption of cortical architecture. Functional behavioral analysis with laser cuts localizing the to forelimb motor cortex found only a minor acute deficit on a complex reaching task that quickly improved. Ultimately, this new neurosurgical approach was able to effectively block seizure propagation while minimally effecting both the structure and function of surrounding brain tissue, suggesting that this new approach could provide a more minimally invasive and effective solution for people with focal epilepsy.

Disclosures: S. Lieberman: None. **D.A. Rivera:** None. **R. Morton:** None. **A. Hingorani:** None. **T.L. Southard:** None. **L. Johnson:** None. **J. Reukauf:** None. **R.E. Radwanski:** None. **M. Zhao:** None. **N. Nishimura:** None. **O. Bracko:** None. **T.H. Schwartz:** None. **C.B. Schaffer:** None.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.13

Topic: B.08. Epilepsy

Support: USC Provost New Strategic Directions for Research Award (PNSDRA)

Title: Localizing Epileptogenic Zone Using Presurgical Resting-State Functional MRI Connectivity

Authors: W. JEONG[1], A. JOSHI[2], *J. B. TREWEEK[1], R. LEAHY[2];
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Abstract: Epilepsy surgery has a high chance of improving epilepsy symptoms for patients with intractable epilepsy. Although surgical treatment occupies a major place in epilepsy therapy, risks include postsurgical complications, deficits in cognitive abilities, and psychosis. Therefore, precise identification and localization of the epileptogenic zone during presurgical investigation is necessary to lower postsurgical risks and maximize the therapeutic benefit of surgery. Many epilepsy centers rely on intracranial recordings such as subdural grid electrocorticography (SDG) and stereoelectroencephalography (SEEG) to navigate the surgery. However, despite the efficacy of these methods, invasive recordings not only present additional health risks for the patient but also carry the increased medical and cost burden of additional surgical procedures. Non-invasive recording techniques such as electroencephalography (EEG) and structural magnetic resonance imaging (MRI) could be applied instead, however they provide limited ability to localize the epileptogenic zone, particularly in non-lesional cases. Here we present a preliminary analysis of the ability to reduce the need for invasive monitoring by localizing the epileptogenic zone from presurgical resting-state functional MRI (rfMRI) via the analysis of brain connectomics.
To localize the epileptogenic hemisphere, we co-registered presurgical rfMRI data of intractable epilepsy patients (n = 30, collected from Yale medical center) to a standard atlas using BrainSuite (Shattuck et al., 2002). Then, we performed the BrainSync transformation (Joshi et al., 2018) to temporarly synchronize time-series across subjects. This then allows direct pairwise comparison of rfMRI time-series at homologous locations across patients. In this we identify regions in each patient where the resting time-series, and its correlations throughout the brain, differs from a normative (control) distribution. We compared the maximum deviation from control values and the size of the abnormal region between the left and the right hemisphere and classified the epileptogenic hemisphere based on these two features using the polynomial kernel support vector machine (SVM). Our method showed 71.6% accuracy (weighted-average F1 score) in classifying the epileptogenic hemisphere.
This preliminary result indicates the potential for rfMRI to identify the hemisphere containing the epileptogenic zone. Further improvements in methodology and larger data-sets should lead to further improvements in determining the laterality of the epileptogenic zone, and more precise localization of the epileptogenic zone itself.

Disclosures: W. Jeong: None. **A. Joshi:** None. **J.B. Treweek:** None. **R. Leahy:** None.

Poster

697. Epilepsy: Non-Pharmacological Approaches to Treatment

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 697.14

Topic: B.08. Epilepsy

Support: NIH, NINDS 1R21NS090250

Title: Aerobic Chronic Exercise alters hippocampal DNA methylation in the Kainate experimental rodent model of Temporal Lobe Epilepsy

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Abstract: Epilepsy and its associated comorbidities have a significant disabling impact on quality of life for many who are affected. Thus, there is a need for alternative and complementary treatment options that help beyond seizure control. Clinical and pre-clinical studies indicate positive effects of exercise programs on seizure control, including improvements in cognitive function. Prior studies indicate that epigenetic mechanisms are altered in the epileptic hippocampus. However, whether exercise can modify DNA methylation (DNAme) epigenetic mechanisms and subsequent positive effects in epilepsy, remains unclear. In the epileptic hippocampus we investigated two forms of DNAme contributing to regulation of gene expression in the brain, 5-methylcytosine (5-mC) and 5-hydroxymethycytosine(5-hmC). We found significant decreases in 5-hmC bulk levels in the hippocampus from both Kainate (KA) experimental rodent model of temporal lobe epilepsy (TLE) and in human TLE patients, thus, we hypothesized that exercise alters transcriptional reprogramming through 5-hmC DNAme. Fisher 344 rats (male, 180 grams) were intraperitoneally injected with KA (9mg/kg) to induce Status Epilepticus (SE) or prolonged seizure activity. KA induced SE was terminated using Diazepam (10mg/kg). Six weeks post-SE animals developed chronic spontaneous reoccurring seizures (SRS). Chronic epileptic animals were then enrolled in an incremental aerobic protocol designed to exercise these rats at 70% VO2max. While one bout of *acute* aerobic exercise did not change hippocampal 5-mC or 5-hmC bulk levels, we found that *chronic* aerobic exercise global 5-hmC, not 5-mC, levels significantly altered in the epileptic hippocampus in a subfield specific manner. RNAscope analysis further suggest that these changes are occurring in cells within area CA1 and Dentate gyrus region of the hippocampus. Current studies are ongoing to determine the gene transcription profile of neuronal cell-types within the epileptic hippocampus that is modified by chronic exercise. Together, these results suggest that exercise modifies 5-hmC DNAme mechanisms to alter transcriptional states in the epileptic hippocampus, further increasing our understanding of the molecular genetic effects of exercise in TLE.

Disclosures: S.C. Sint Jago: None. **T. Nguyen:** None. **F. Mejia:** None. **J. Homola:** None. **F.D. Lubin:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.01

Topic: B.08. Epilepsy

Support: NIH/NINDS R01NS115800
Iowa Neuroscience Institute
NIH/NINDS R01NS098590
UNIDM/Tross Family Fund

Title: Lacosamide decreases neonatal seizures without increasing apoptosis in mice

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Abstract: Many seizing neonates fail to respond to first-line anticonvulsant medications. Phenobarbital, a $GABA_A$ receptor allosteric modulator, has low efficacy in treating neonatal seizures and causes neuronal apoptosis. Yet, it is one of the most used anticonvulsants in this age group. In neonatal mice, phenobarbital's poor effectiveness is due to high intraneuronal chloride concentration causing depolarizing actions of GABA. Therefore, another approach to treating neonatal seizures could be using anticonvulsants that do not rely on GABAergic modulation. We evaluated if lacosamide, a non-GABAergic anticonvulsive drug, decreases seizure-like activity in neonatal mice and if it increases apoptosis *in vitro* and *in vivo*. *In vitro*, we measured the effect of different lacosamide concentrations on seizure-like activity induced by the pro-convulsant drug 4-aminopyridine in neonatal (postnatal day P8-11, both sexes) and adult (1-1.6-month-old, male) neocortical brain slices (layer IV/V; C57BL/6J mice). *In vivo*, we recorded the effect of different lacosamide concentrations on neonatal behavioral seizures (P11-12, both sexes) induced by kainic acid (i.p). We measured neocortical apoptosis *in vitro* and *in vivo* using the TUNEL method. Our results revealed that lacosamide reduced epileptiform activity in neonatal and adult neocortical brain slices in a concentration-dependent manner and to a similar degree. The ratio of seizure-like events (events lasting longer than 10 seconds) to total events also decreased with lacosamide in neonates and adults. *In vivo*, 40 mg/kg and 50 mg/kg concentrations of lacosamide reduced the duration and number of behavioral seizures while also increasing the latency to convulsive seizures. Lacosamide did not increase total or neuronal apoptosis in the neocortex *in vitro* or *in vivo*. In conclusion, lacosamide reduces neocortical seizure-like activity in neonatal mice *in vitro* and *in vivo*, with no increase in apoptosis. Our results support the use of lacosamide to treat neonatal seizures, with the advantage of not increasing apoptosis.

Disclosures: R.L. Langton: None. **S. Sharma:** None. **G.C. Tiarks:** None. **A.G. Bassuk:** None. **J. Glykys:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.02

Topic: B.08. Epilepsy

Support: 781259

Title: Anti-apoptotic effect of dapsone in a model of status epilepticus induced with kainic acid-induce in rats

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Abstract: Status epilepticus (SE) is a serious condition with long-term consequences. International League Against Epilepsy defined SE as “a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures. long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures”. Excitotoxicity has been described as an increase in excitatory neurotransmission mediated by glutamate that can cause neuronal damage due to prolonged excitatory neurotransmission. Dapsone (DDS) has been reported to have an anticonvulsant effect in animal models and human patients. The mechanism through which DDS acts is not yet known, however; dapsone may act as an antagonist of the neurodegenerative effects induced by NMDA agonists. The objective of this study was to characterize the antiapoptotic and neuroprotective effects of DDS treatment in a model of SE induced by kainic acid (KA). Methods: SE was induced in Wistar male rats (250 to 280 g), using KA 5 mg/kg, ip following by doses (2.5 mg/Kg) administered at intervals of 1 h, until behavioral SE. After KA administration (25 h) degenerated neurons in the hippocampus were counted, using Fluoro Jade-B staining and caspases 8 and 3 activities were determined. Results: A lower number of degenerated neurons in the hippocampus was observed by effect of DDS by doses 12.5 mg/kg (1159.6$\pm$85.02) and 25 mg/kg (1041.13$\pm$123.67) versus vehicle group (1549.16$\pm$85.03). In the other hand, the activities of caspases 8 (60.2$\pm$3.93) and 3 (63.16$\pm$6.5) were increased by AK in the vehicle group. This effect was decreased activities of caspases 8 and 3 by DDS doses of 12.5 mg/kg (31.34$\pm$6.15 and 26.94$\pm$6.9 respectively) and 25 mg/kg (34.36$\pm$5.6 and 29.63$\pm$5.27 respectively), showing its ability to inhibit apoptosis markers ($p<0.05$). Conclusions: The results demonstrate the neuroprotective effect of DDS to decrease the neurodegeneration and caspases activity. Most of the drugs prescribed in patients with epilepsy are anticonvulsants, but not neuroprotective. DDS is an excellent candidate for the treatment of patients with SE.

Disclosures: **A. Ruiz-Diaz:** None. **A. Diaz-Ruiz:** None. **M. Islas:** None. **C. Rios:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.03

Topic: B.08. Epilepsy

Support: NIH Grant R37 NS119012
NIH Grant RO1 NS120945
NIH Grant RO1 NS040337

Title: Beta-hydroxybutyrate reduces neuronal excitability and seizures

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Abstract: The ketogenic diet is a treatment for epilepsy; it elevates β-hydroxybutyrate levels. We investigated the effect of (β-HB) ketone body on continuous hippocampal stimulation-induced status epilepticus in c57BL/6 mice and *in vitro* coronal sections of GCamp7-AAV injected hippocampus after high potassium perfusion. The 7-8 weeks old C57Bl/6 mice were implanted with insulated stainless-steel electrodes in the left hippocampus and bilateral supra-dural cortical electrodes, a reference electrode at cerebellum. A week after implantation, animals received continuous hippocampal stimulation to induce status epilepticus (SE). The animals in self-sustaining SE were injected intraperitoneally with β-HB (1g/kg) 15 minutes after stimulation, seizure duration and severity were evaluated. Separately, the 4-6 weeks old c57BL/6 mice were injected with Cam-Cre driven GCamp7-AAV into the hippocampus. 10-14 days after injection, the 300µm coronal sections of hippocampus were sliced using a vibratome in well-oxygenated ice-cold slicing buffer (95% O_2/ 5% CO_2; 4°C). Following incubation in well-oxygenated artificial cerebrospinal fluid (aCSF), they were visualized under green fluorescence filters to locate CA1 region. The CA1 neural network was stimulated by applying aCSF with high potassium (5mM) for 15 min. We further exposed the neurons to 2.5mM β-HB in 5mM K^+ aCSF for 15 min followed by a 15 min high K^+ containing aCSF washout to affirm the effect of β-HB on neural stimulation.β-HB treatment significantly reduced SE duration (mean SE duration in saline *vs* β-HB treated mice 205.6 and 104.3 min; n=8 each, P = 0.0454; unpaired t-test). Interestingly, seizures though shorter were more severe in the β-HB -treated group (median of saline and β-HB 3.66 and 2.9; n=12, P<0.0001; Mann Whitney U test) compared to saline-injected mice. In the *in vitro* analysis, high K^+ solutions caused increased fluorescence across CA1 and some neurons showed flickering fluorescence. We observed that β-HB application significantly reduced flourescent intensity and stopped flickering in the CA1 region of the hippocampal slices as compared to the baseline (5mM K^+ aCSF) (%ΔF/F Baseline vs. β-HB 15.91 and -7.874%, n=3, P<0.0001; Brown-Forsythe and Welch ANOVA test). Similarly, the β-HB washout with high K^+ reversed its effect (%ΔF/F β-HB vs washout -7.874 and 8.034%; n=3, P<0.0001; Brown-Forsythe and Welch ANOVA test). A ketone body, β-HB holds a promising effect against seizures as they can reduce hyperexcitability and have an antiseizure effect. Thus, delving into the metabolic substrate receptors can address the in-depth physiological relevance of the antiseizure efficacy of the ketogenic diet.

Disclosures: S. Sharma: None. **D. Skwarzynska:** None. **K. Rekawek:** None. **J. Kapur:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.04

Topic: B.08. Epilepsy

Title: Anticonvulsant effect of cannabidiol and dapsone on pentylenetetrazole-induced seizures in rats

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Abstract: Epilepsy is a chronic neurological disorder, manifested by recurrent and spontaneous seizures, as well as electroencephalographic changes, which affects more than 70 million people worldwide. It is of multifactorial origin. Despite the development of new antiepileptic drugs in recent decades, 30% of patients with epilepsy continue to have seizures, drug-resistant epilepsy, which is associated with premature death, injuries, comorbid psychiatric and psychological disorders, severe economic and social impairment, high risk of suicide and sudden unexpected death. The growing research for the development of new antiepileptic drugs, such as CBD (Cannabidiol) have drawn attention because it is a non-psychoactive compound that has shown anticonvulsant properties, in addition to the fact that antioxidant and anti-inflammatory properties have been observed, among others. Dapsone has an anticonvulsant effect, since it is able to inhibit/reduce seizures of hippocampal and amygdala origin, which implies an efficacy to control the spreading of neuronal discharge from epileptogenic sites to the rest of the brain. In this study, the anticonvulsant effects of those drugs on Pentylenetetrazole-induced seizures were compared. Sub convulsive doses of PTZ were administered, starting at 40 mg/kg intraperitoneally, followed by a dose of 20 mg/kg, 10 minutes later, and a dose of 10 mg/kg, again 10 minutes later. Epileptic seizures were evaluated by the Racine scale. If they did not present tonic-clonic seizures, doses of 10 mg/kg were administered in the same time interval until reaching a maximum of 90 mg/kg of PTZ. Control group received SS, while treated groups received (i.p.) doses of either cannabidiol (CBD) of 6.25, 12.5 and 25 mg/kg, or i.p. dapsone (DDS) doses of 6.25, 9.37, 12.5 and 25 mg/kg, all groups were subjected 30 minutes later to PTZ-induced seizures, as above described. All animals were evaluated using the Racine scale until reaching phase 4 (tonic-clonic seizures). Both anticonvulsant compounds report different levels of anticonvulsant effectiveness, in addition to antioxidant and anti-inflammatory properties, so both can be therapeutic alternatives for drug-resistant epilepsy.

Disclosures: **V. Baron-Flores:** None. **F. Ortega-Martinez:** None. **D. Islas-Diaz:** None. **A. Diaz-Ruiz:** None. **C. Rios:** None. **B. Garcia-Martinez:** None. **A. Mata-Bermudez:** None. **A. Moreno-Rocha:** None. **M. Romero:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.05

Topic: B.08. Epilepsy

Support: Supported in part by a grant (LO 274/15-1) from the Deutsche Froschungsgemeinschaft (Bonn, Germany)
PhD scholarship from the Studienstiftung des deutschen Volkes (Bonn, Germany) for Björn Welzel
PhD scholarship from the Konrad-Adenauer-Stiftung (Berlin, Germany) for Marie Johne

Title: Midazolam prevents the adverse outcome of neonatal asphyxia

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Abstract: Birth asphyxia (BA) is the main cause of neurological complications in newborns and can lead to hypoxic-ischemic encephalopathies and neonatal seizures. Despite their high incidence and severity, no sufficiently effective anti-seizure drugs are available for the treatment of neonatal seizures. Besides these acute seizures, BA can lead to vast long-term consequences including developmental impairments, behavioral and cognitive alterations, and epilepsy. There is an ongoing clinical debate on whether neonatal seizures add to this adverse outcome. As reported in a previous study, a single dose of the potent benzodiazepine midazolam (1 mg/kg i.p.) directly after asphyxia suppresses acute neonatal seizures in 50% of the rat pups in a non-invasive model of BA. This prompted us to study the impact of midazolam, which is used as a second-line drug for the treatment of neonatal seizures and also exerts anti-inflammatory effects, on the long-term consequences of BA in animals with and without neonatal seizures. In the novel non-invasive model of BA used in our studies, intermittent asphyxia is induced for a total duration of 30 minutes by three cycles of 7 minutes 9% O_2 and 3 minutes 5% O_2 each, with a steady level of 20% CO_2 at postnatal day 11. Additionally, behavioral and cognitive tests were performed over a period of 14 months and histological alterations were assessed at different time points. All vehicle-treated animals showed acute seizures after asphyxia, cognitive and behavioral alterations, neurodegeneration in the hippocampus and thalamus, aberrant mossy fiber sprouting, and neuroinflammation in gray and white matter. The post-asphyxia administration of

midazolam prevented the behavioral, cognitive, and neurodegenerative alterations and prevented or decreased neuroinflammation after asphyxia. Only in the thalamus, differences between animals with and without neonatal seizures after midazolam treatment could be observed, as animals with seizures showed increased neurodegeneration. No sex differences were observable. This study indicates that midazolam has a strong disease-modifying effect and could improve the treatment and outcome for children with BA. Seizures do not seem to contribute to the adverse outcome after BA. Next, we plan to test whether other multi-target drugs or multi-drug treatment protocols with anti-seizure effects and other rationally chosen drugs, e.g., anti-inflammatory agents, could be a promising treatment approach for BA.

Disclosures: B. Welzel: None. **R. Schmidt:** None. **M. Johne:** None. **W. Löscher:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.06

Topic: B.08. Epilepsy

Support: NIH Grant NS113955
NIH Grant NS112788

Title: Novel naphthalenyl substituted aminothiazoles derived from riluzole prevent acute neural excitotoxic injury in a rat model of temporal lobe epilepsy

Authors: T. KYLLO[1], V. SINGH[2], H. SHIM[2], L. SINGH[2], H. M. NGUYEN[2], Y.-J. CHEN[2], E. TERRY[1], H. WULFF[2], *J. D. ERICKSON[1];
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Abstract: Epileptic seizures lead to neural excitotoxic injury in vulnerable forebrain neurons in the kainic acid (KA) animal model of temporal lobe epilepsy (TLE). Here, we have further characterized neural activity regulated methylaminoisobutryic acid (MeAIB)/glutamine transport activity in mature rat hippocampal neuronal cultures that is potently inhibited by riluzole (IC50=860nM), a benzothiazole approved for the treatment of amyotrophic lateral sclerosis (ALS). We screened a library of riluzole derivatives that identified the aminothiazole SKA-41 followed by a second screen of SKA-41 derivatives and synthesized several novel chlorinated aminothiazoles (SKA-377, SKA-378, and SKA-379) that were also potent transport inhibitors *in vitro* and brain penetrant following systemic administration. When administered before KA, SKA-378 (30mg/kg) did not prevent status epilepticus (SE) but still prevented neural injury in the hippocampus and in other limbic areas after 3d. When SKA-379, SKA-378, SKA-377, SKA-41 or riluzole were administered 1 h after KA-induced SE, neural injury in vulnerable hippocampal excitatory (CA3/CA1) and inhibitory (hilar) neurons was also attenuated. Kinetic analysis of SKA-378 and riluzoles' blockade of transport *in vitro* indicates that inhibition occurs

via a non-competitive, indirect mechanism. While sodium channel NaV1.6 antagonism blocks activity-regulated MeAIB transport and SKA-378 is the most potent inhibitor of NaV1.6 (IC50=20μM) compared to NaV1.2 (IC50=118μM) *in vitro*, pharmacokinetic analysis suggests sodium channel blockade may not be the predominant mechanism of neuroprotection by these compounds *in vivo*. Our results indicate that aminothiazole derivatives of riluzole may be useful agents to explore novel mechanisms involved in the prevention of neural hippocampal injury by SE that can lead to TLE.

Disclosures: T. Kyllo: None. **V. Singh:** None. **H. Shim:** None. **L. Singh:** None. **H.M. Nguyen:** None. **Y. Chen:** None. **E. Terry:** None. **H. Wulff:** None. **J.D. Erickson:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.07

Topic: B.08. Epilepsy

Support: ALF
Swedish Research Council

Title: Epilepsy development in Syn2KO mice treated with interleukin-6 receptor antibody

Authors: J. WICKHAM, F. BÄCKSTRÖM, M. AHL, C. T. EKDAHL;
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Abstract: Autism spectrum disorder (ASD) and epilepsy are neurodevelopmental disorders that often are observed as comorbidities. Individual diagnosed with ASD show impaired social behavior and multiple genetic risk factors have been identified that affect the susceptibility for both conditions, including mutations in the Synapsin (Syn) genes. Mice lacking Syn 2 (Syn2KO) have ASD-like behavior, epileptic seizures and neuroinflammatory changes including elevated interleukin (IL)-6 levels in brain. Due to the possible systemic and innate inflammatory component of both ASD and epilepsy, systemic immunomodulation is an appealing approach to improve outcome in these disorders. In this study we evaluated the effects of systemic IL-6R antibody (ab) treatment during epilepsy development or after seizure onset in Syn2KO mice. Syn2KO mice were systemically treated with a monoclonal IL-6R ab by weekly intraperitoneal injections, saline was injected as a control. We used two different treatment groups, one receiving IL-6R ab injections starting at 1 month of age, prior to seizure onset. The other group received IL-6R ab treatment starting at around 3 months of age, after seizure onset. Syn2KO mice suffer from stress induced epileptic seizures and were provoked three times a week by moving them by the tail from their home cage to a new cage, starting at 2 months of age, to see if the treatment effected seizure frequency. We investigated if the IL-6R ab treatment influenced cognition by performing several behavioral tests and after euthanization the inflammatory response was evaluated using immunohistochemistry, Western Blot and ELISA. We observed

reduced seizure frequency during provocation in Syn2KO mice treated for 4 months with systemic IL-6R ab, starting prior to seizure onset (n =30, median 1.5 %) compared to saline treated Syn2KO mice (n =25, median 15 %), Mann-Whitney test. p-value=0.0029. No change in seizure frequency was observed if treatment was initiated after the initial seizure onset. We did not detect any changes in social behavior, anxiety, anhedonia, or spatial memory after systemic IL-6R ab treatment. Brain tissue from Syn2KO mice showed discrete changes in neuroinflammation with altered microglia morphology, reduced tumor necrosis factor alpha (TNF-α) levels, and unaltered levels of excitatory/inhibitory synaptic proteins after both early and late IL-6R ab treatment. Collectively, these results indicate the possibility of seizure reduction by early IL-6R ab treatment during epilepsy development in the Syn2KO mice with ASD-like behavior, without significantly reversing the known cellular pathology the brain.

Disclosures: J. Wickham: None. **F. Bäckström:** None. **M. Ahl:** None. **C.T. Ekdahl:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.08

Topic: B.08. Epilepsy

Support: NINDS NS088776

Title: The Impact of Supplemental Vitamin D on Motor Learning and Seizure Progression in Mice with Hyperactive mTOR induced Epilepsy and Ataxia

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Abstract: Genetic mutations that cause hyperactive mechanistic target of rapamycin (mTOR) signaling in the cerebellum lead to disrupted cerebellar signaling, debilitating motor impairments, and may contribute to the development of epilepsy. Recent studies have demonstrated that the mTOR inhibitor rapamycin can reduce mTOR signaling and reduces seizures; however, long-term use of rapamycin can produce non-specific effects. Thus, a critical need for better therapies to treat individuals with hyperactive mTOR induced motor impairments and epilepsy remains. Vitamin D is a safe, over-the-counter supplement that has been shown to suppress mTOR signaling and abate seizure severity. However, it has not been determined if vitamin D can ameliorate the development of motor impairments and epilepsy induced by hyperactive mTOR signaling. Here, we determine the effects of supplemental vitamin D in a mouse model of hyperactive mTOR induced epilepsy and ataxia. Male and female neuronal subset specific *Pten* knockout (KO) and wildtype (WT) mice were provided either a diet supplemented with 20,000 IU/g of vitamin D3 or a standard mouse chow containing 1,500 IU/g of vitamin D3 starting at 4 weeks and were maintained on the diet for the remainder of the

experiment. At 6 weeks, mice underwent testing for motor coordination and motor learning in the sticker removal and rotarod tests. Mice were then recorded 1 hour a day for 5 days on weeks 9 and 10 to determine the time to the first seizure, seizure frequency, and the total duration of time spent seizing. Our preliminary data show KO mice exhibit an increased latency to remove a sticker compared to WT mice, independent of diet, $p < .01$. KO mice on the standard diet, but not the vitamin D diet, required more attempts to remove the sticker compared to WT mice, $p < .05$. On the rotarod test, KO mice spent less time on the rotarod compared to WT mice, $p < .001$; with no effect of vitamin D. The time until a seizure was detected was greater in KO mice on the vitamin D diet compared to KO mice on the standard diet, $p < .05$. There was no effect of vitamin D on the frequency or total duration of seizures exhibited. Utilizing neuronal subset specific *Pten* KO mice, our preliminary data show that a high dose vitamin D diet may be capable of reducing seizure latency and improving some motor coordination skills caused by hyperactive mTOR signaling.

Disclosures: D.A. Narvaiz: None. **J. Pilcher:** None. **G. O'Neill:** None. **K. Blandin:** None. **D. Tran:** None. **J.N. Lugo:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.09

Topic: B.08. Epilepsy

Title: Characterizing a Novel Compound Class and their Potential as Anti-Seizure Drugs in C. elegans

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Abstract: Epilepsy is a widely prevalent disease within the United States. It is estimated that about 1.2% of the total American population has active epilepsy, a condition of the brain that causes seizures. These seizures are marked by chemical alterations in neuronal firing that can cause abnormal behavior, sensations, muscle spasms, and loss of consciousness. Although the prevalence of seizures and epilepsy is high, effective treatments are limited and fail to provide effective treatment for nearly one-third of adult epileptic patients. Due to this shortcoming, our lab developed an electroshock assay to examine seizure duration in *C. elegans.* The electroshock assay can be used as a small molecule screening platform for the identification of antiseizure agents and the subsequent characterization of their structure-activity relationship (SAR). The objective of this project is to evaluate a novel class of synthetic bridged bicyclic compounds that can ameliorate seizure-like behavior using the electroshock assay to examine seizure duration in *C. elegans*. The use of *C.elegans* allows for a rapid and efficient method of compound screening that may take years in other higher-order model organisms. In the present study, we evaluate the

efficacy of various analogs of our designed synthetic compounds, some of which have proved efficacious even in the pico-molar range in reducing seizure duration during the electroshock assay. These SAR studies have allowed us to discern structural features that will prove critical in future studies of this system, including the search for potential mechanisms of action of our novel compounds.

Disclosures: S.E. Stilley: None. **K.P. Yadavalli:** None. **S.D. Lepore:** None. **K. Dawson-Scully:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.10

Topic: B.08. Epilepsy

Support: NINDS grant #1U54NS079202

Title: Effects of the intramuscular midazolam dose archiving the therapeutic plasma concentration in humans on seizure thresholds in mice

Authors: *D. ZOLKOWSKA[1], C.-Y. WU[1,2], C. L. STONE[1], M. A. ROGAWSKI[1,3];
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[3]Dept. of Pharmacology, Sch. of Medicine, Univ. of California, Davis, Sacramento, CA

Abstract: Midazolam (MDZ) is widely used as an initial treatment for seizure emergencies, including acute repetitive seizures and status epilepticus. In the present study we sought to determine the minimum plasma and whole brain level of MDZ associated with seizure threshold elevation. We first determined plasma and brain MDZ levels following an intramuscular (IM) MDZ dose of 0.23 mg/kg, which had been found in a previous study to produce a peak (C_{max}) plasma MDZ level in mice that is similar to the C_{max} achieved following IM MDZ treatment with the recommended human MDZ dose of 10 mg. Trunk blood samples and the whole brain were collected at intervals. MDZ levels were measured in plasma and brains using LC-MS/MS (for plasma LLOQ=50 pg/mL; for brain LLOQ=100 pg/mL). C_{max} values for plasma and brain were 152.14 ± 20.96 ng/ml (T_{max}, 1 min) and 128.12 ± 3.95 ng/g (T_{max}, 5 min), respectively. At 2 h, MDZ was still detected in plasma (0.38 ± 0.10 ng/ml) in all animals and in brain (<0.69 ± 0.18 ng/g) in 5 of 8 animals. At 4 h, MDZ was present in plasma at quantifiable levels in only 3 of 8 mice and was not measurable in brain in any animals. Seizure threshold was assessed from 5-60 min following a MDZ dose of 0.23 mg/kg. Additional groups of mice received doses spanning the range 0.03-0.12 mg/kg; threshold determination in these groups was at 5 min. The doses of IV PTZ causing myoclonic body twitches and clonic and tonic seizures were determined. Pretreatment with MDZ at the 0.03 mg/kg IM dose increased the threshold for clonic and tonic seizures in 50% of animals at 5 min. Larger doses caused a greater fraction of animals to exhibit

threshold increases. MDZ at the 0.23 mg/kg IM dose markedly increased the threshold for all seizure signs at 5 min and the effect was still present 60 min following injection. In conclusion, the extrapolated peak plasma level following the 0.03 mg/kg MDZ dose is about 16 ng/mL and represents the EC_{50} level for seizure threshold elevation. The maximum 0.23 mg/kg dose, which produced a peak plasma level in the range of 150 ng/mL and a similar brain level, caused extreme seizure threshold elevations that were persistent. Peak plasma and brain levels of MDZ following IM administration are similar but the peak in brain levels is delayed to 5 min.

Disclosures: D. Zolkowska: None. **C. Wu:** None. **C.L. Stone:** None. **M.A. Rogawski:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.11

Topic: B.08. Epilepsy

Support: National Health and Medical Research Council Grant 1136241
National Health and Medical Research Council Grant 1132524
National Health and Medical Research Council Grant 1123564
National Health and Medical Research Council Grant 1143848
National Health and Medical Research Council Grant 2001572
National Health and Medical Research Council Grant 2000660
Australian Research Council Grant DP210101957

Title: Treatment of epilepsy using a targeted p38γ kinase gene therapy

Authors: *N. MOREY, M. PRZYBYLA, J. VAN DER HOVEN, Y. KE, F. DELERUE, J. VAN EERSEL, L. ITTNER;
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Abstract: Neuronal hyperexcitation engages post-synaptic toxic signalling (excitotoxicity), in turn driving downstream clinical phenotypes in multiple neurological disorders. Microtubule-associated protein tau (tau) has been implicated in this process; accrual of hyperphosphorylated tau at the post-synapse drives excitotoxicity in epilepsy, dementia, and stroke alike. In contrast, site-specific phosphorylation of tau at residue Threonine 205 (T205), by the kinase p38γ was previously shown to disengage tau from toxic pathways, serving a neuroprotective function in Alzheimer's disease. To probe the mechanistic relevance of this post-synaptic tau/p38γ interaction in epileptogenesis, we generated two mouse models of severe, refractory epilepsy disorders: a genetic model of the infantile-onset epileptic encephalopathy Dravet syndrome, and a chemically-induced seizure mouse model that recapitulates aspects of temporal lobe epilepsy, to study acute and chronic seizure phenotypes. Using a viral-mediated gene delivery approach, neurotropic AAV was administered for neuronal expression of a constitutively active form of p38γ ($p38\gamma^{CA}$) to enhance kinase activity. Across the genetic and chemically-induced epilepsy

mouse models, we show that, compared to administration with a non-therapeutic control, p38γ activity-enhancing treatment prior to seizure onset is neuroprotective: reduced seizure susceptibility, restored neuronal firing patterns, reduced hyperactive behaviours, and ameliorated epilepsy-induced deaths were observed. Furthermore, we show that $p38\gamma^{CA}$ treatment administered only following seizure onset ameliorates temporal lobe epilepsy phenotypes, including reduced incidence of recurrent seizure-induced mortality and normalised neuronal network profiles. Furthermore, we show p38γ-mediated phosphorylation of tau at T205 is essential for neuroprotection in epilepsy, as lack of this critical interaction reinstates pathological features and accelerates epileptogenesis *in vivo*. Hence, our work provides scope to harness p38γ as a future therapy applicable to both acute and chronic neurological conditions.

Disclosures: **N. Morey:** None. **M. Przybyla:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder: p38gamma gene therapy. **J. van der Hoven:** None. **Y. Ke:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder: p38gamma gene therapy. **F. Delerue:** None. **J. van Eersel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder: p38gamma gene therapy. **L. Ittner:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder: p38gamma gene therapy.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.12

Topic: B.08. Epilepsy

Support: National Research Foundation of Korea (NRF), Korea government, Ministry of Science and ICT. 2019R1A3B2066619
National Research Foundation of Korea (NRF), Korea government, Ministry of Science and ICT. 2020R1A6A3A13076897
Suh Kyungbae Foundation
SoVarGen

Title: Antisense-oligonucleotide therapy targeting BRAF alleviates pediatric brain tumors with intractable epilepsy

Authors: *S. KIM[1], H. JUNG[1], H. KOH[2], J. LEE[1];
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Abstract: BRAF mutations leading to aberrant MAPK/ERK signaling are one of the major driver mutations in low-grade pediatric brain tumors (e.g., pilocytic astrocytoma, ganglioglioma,

dysembryoplastic neuroepithelial tumor, and diffuse astrocytoma). These variants are highly associated with poor prognosis and intractable epilepsy. Existing BRAF inhibitors such as Vemurafenib and Dabrafenib are specific to BRAF V600E protein and have limited penetrance into the blood-brain barrier (BBB). Antisense oligonucleotide (ASO) therapy via intrathecal injection bypasses BBB and degrades the transcript of the target gene in the brain. Thus, it is a promising and effective therapeutic tool in neurological disorders with genetically and molecularly identified targets. We developed the genetically engineered mouse model of Braf-derived pediatric brain tumors with intractable epilepsy by introducing Braf p.V600E mutation into neural stem cells during embryonic brain development. These mice show a gradual increase in tumor size and epileptic seizures and a decrease in survival rate over time, thereby recapitulating BRAF-derived pediatric brain tumors with intractable epilepsy. We administrated the most effective ASO inhibiting mouse Braf RNA selected by *in silico* and *in vitro* screening. ASO was delivered by single bolus intracerebroventricular (i.c.v.) injection at 10 weeks after pre-monitoring of behavior seizure and tumor size. Oral administration of existing BRAF inhibitors could not significantly reduce seizures and tumor size in BRAF pediatric tumor models. Single ICV injection of Braf ASO successfully reduced the transcript and encoded protein in a dose-dependent manner and its knock-down effect lasted at least 3 months. Injected ASOs are well distributed to CD34-positive regions and tumor cells in Braf-derived neuro-glial tumors. The behavioral and electrographic seizure frequency is remarkably reduced after treatment of the ASO. The size of tumors and enlarged dysmorphic neurons are significantly reduced. The survival rate was significantly increased. Also, the bodyweight is rescued in Braf ASO treated group, compared to the vehicle-treated control group. No behavioral and molecular toxicity was found at two months after i.c.v. administration of ASO. In our study, ASO therapy targeting BRAF shows strong therapeutic effects on various aspects of BRAF-derived pediatric brain tumors, including the epileptic seizures, tumor size, survival rate as well as dysmorphic neurons. Therefore, ASO therapy targeting BRAF will be a promising and effect therapy in BRAF-derived pediatric brain tumors with intractable epilepsy.

Disclosures: S. Kim: None. **H. Jung:** None. **H. Koh:** None. **J. Lee:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.13

Title: WITHDRAWN

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.14

Topic: B.08. Epilepsy

Support: NRF-2019R1A6A3A01090600
NRF-2021R1A2C100447112

Title: Insulin-like growth factor-1 promotes synaptogenesis signaling, a major dysregulated pathway in a rat model of malformation of cortical development

Authors: *M. LEE[1], M.-J. KIM[2], M.-S. YUM[3], T.-S. KO[3];
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Abstract: Malformation of cortical development (MCD) is one of the main causes of intractable epilepsy and developmental delay in childhood. Using this MAM-induced MCD model which the pathologic findings observed in patients with MCD, we aimed to identify the most severely deteriorated canonical pathway in the early postnatal period. An infant rat model of methylazoxymethanol (MAM)-induced MCD was established by injecting MAM at gestational day 15. The offspring were sacrificed on postnatal day (P) 15 for proteomic analysis, which revealed significant downregulation in the synaptogenesis signaling pathway in the cortex of MCD rats. We explored a treatment based on molecular changes using the recombinant human insulin-growth factor-1 (rhIGF-1). Prenatally MAM-exposed rats were pretreated with rhIGF-1 (P12 to P14 twice daily) or vehicle (VEH, 0.1% BSA). rhIGF1 pretreatment significantly upregulated the expression of cortical synaptic proteins such as post-synaptic density protein 95 (PSD95), AMPA receptor 1 (AMPAR1), AMPAR4, N-methyl-D-aspartate receptor 1 (NMDAR1), and NMDAR2A ($p < 0.05$) in western blot analysis. Also, rhIGF-1 was injected from P12 to P14 twice daily and the effect of IGF1 on N-methyl-D-aspartate (NMDA)-induced spasms (15 mg/kg of NMDA, i.p.) was tested; the onset of P15 single spasm was significantly delayed ($p = 0.002$) and the number of spasms decreased ($p < 0.001$) in rhIGF1-pretreated rats ($n = 17$) as compared to those in VEH-treated rats ($n = 18$). Electroencephalographic monitoring during spasms showed significantly reduced spectral entropy and event-related spectral dynamics of fast oscillation in rhIGF-1 treated rats ($p < 0.001$, $n = 5$ each group). In experiments using multiple NMDA administrations, randomized rhIGF1 treatment after P12 spasms also significantly reduced the number of spasms on P15 NMDA-induced rats ($p = 0.016$, $n = 6$ each group). Thus, prenatal MAM exposure significantly downregulated the expression of synaptic transmission proteins in the cortex of infant rats. Early rhIGF-1 treatment could promote synaptic protein expression and effectively suppress NMDA-induced spasms. These findings suggest the possibility of early IGF1 treatment for patients with MCD-related epilepsy.

Disclosures: M. Lee: None. **M. Kim:** None. **M. Yum:** None. **T. Ko:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.15

Topic: B.08. Epilepsy

Title: Regulation of the activity and expression of NMDA receptor through of Probenecid in the kindling epilepsy model

Authors: E. LARA-GONZALEZ[1], E. GONZALEZ-GUEVARA[2], E. RENDON-OCHOA[1], A. LAVILLE[1], J. BARGAS[1], C. MIRANDA-NARVAEZ[2], ***J. MARTINEZ-LAZCANO**[2]; [1]UNAM, Mexico, Mexico; [2]INNyN MVS, Mexico D.F., Mexico

Abstract: The inhibitory effect of probenecid (PROB; an inhibitor of the activity and expression of some ATP Binding-Casette type transporters) on N-methyl-D-aspartate (NMDA) type receptors has been studied previously, finding unclear results, in addition to the mechanisms of action by which this inhibition occurs, they have not been able to explain this phenomenon. We propose that Probenecid, can modify the activity and expression of the NMDA receptor. To test our hypothesis, we used the kindling model of epilepsy. In male wistar rats implanted with electrodes in the basolateral amygdaloid nucleus and the sensory motor cortex, we quantified the amygdaloid afterdischarge duration (AD) and the behavioral state according to Racine's scale. Once obtained generalized seizures (stage 5), PROB was administered to two doses (100 and 300 mg/kg), in the hippocampal tissue to evaluate the expression of MDR1, MRP1, NR2B subunit of rNMDA and NOS isoforms expression. Also, we obtained cell dissociation of hippocampus, to perform voltage-clamp records of currents evoked by NMDA. PROB produces a reduction in the AD duration and the behavioral state, reduction in the expression of the NR2B, MDR1, MRP1, NR2B, nNOS and eNOS. In neurons derived from the hippocampus of the CA region of control rats, PROB produces a dose-dependent reduction in the current evoked by NMDA, in the case of neurons obtained from kindled rats, we observed that the NMDA current residuals were less compared against control neurons. In neurons from kindled rats the NMDA current was reduced compared to neurons from control rats in presence of 20 mM of PROB. PROB inhibits currents evoked by NMDA in dissociated neurons from control rats and kindled rats, from a mechanism that involving the inhibition of the ABC transporters.

Disclosures: E. Lara-Gonzalez: None. **E. Gonzalez-Guevara:** None. **E. Rendon-Ochoa:** None. **A. Laville:** None. **J. Bargas:** None. **C. Miranda-Narvaez:** None. **J. Martinez-Lazcano:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.16

Topic: B.08. Epilepsy

Support: NIH Grant R01NS084920
Good Samaritan Foundation of Legacy Health

Title: Sarcosine and epileptogenic changes to the hippocampal methylome

Authors: S. BAER[1], B. PENG[2], ***L. PHUNG**[1], R. GESESE[1], J. COOK[1], T. JI[3], H.-Y. SHEN[1]; [1]Legacy Res. Inst., Portland, OR; [2]Mol. Vision Lab., Hillsboro, OR; [3]Pediatric Neurol., Randall Children's Hospital, Legacy Emanuel Med. Ctr., Portland, OR

Abstract: Background: DNA methylation contributes to seizure development and epileptogenesis. We previously reported that sarcosine, a glycine transporter inhibitor effectively reduced epileptogenesis in a rat kindling model, accompanied by reversal effects on seizure-related DNA methylation in rat hippocampus. This study aims to further investigate the epigenetic mechanisms of sarcosine in epilepsy. Methods: Adult Sprague-Dawley rats were used for the kindling epileptogenesis model. Sarcosine (3g/kg. i.p.) vs saline vehicle were administrated to rats daily for five days during the kindling period. Reduced representation bisulfite sequencing (RRBS) and quantitative real-time PCR were used to quantify DNA methylation levels across the genome and to determine the mRNA levels of genes in epileptogenesis and sarcosine treatment. Differentially methylated regions (DMRs) were identified via bioinformatics analysis. Results: We demonstrated (i) A total of 516 DMRs in the hippocampus of kindled rats versus non-kindled controls; (ii) 341 DMRs were identified in the hippocampus of kindled rats with daily sarcosine treatment vs vehicle treatment; (iii) kindling epileptogenesis and sarcosine treatment produce substantial changes in 217 epiPathway and Gene Ontology; 13 pathways changes were identified under influences of epileptogenesis and sarcosine; (iv) The mRNA level of three genes, i.e., *HDAC9, Smad7, and FOS genes,* among 12 selected genes with significant changes in DMRs, were identified with significant changes in epileptogenesis and sarcosine treatment. Conclusion: Our finding demonstrated sarcosine-mediated epigenetic changes that affect the expression of epilepsy-associated genes.

Disclosures: S. Baer: None. **B. Peng:** None. **L. Phung:** None. **R. Gesese:** None. **J. Cook:** None. **T. Ji:** None. **H. Shen:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.17

Topic: B.08. Epilepsy

Support: Zogenix

Title: Chronic Dosing of Fenfluramine in Three Animal Species (Mice, Rats, and Dogs) Has No Structural Impact on Cardiac Valves

Authors: K. OKAMOTO[1], A. GAMMAITONI[2], ***B. BOYD**[1];
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Abstract: Fenfluramine (FFA), which is approved for the treatment of seizures in patients with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS), had previously been licensed as an appetite suppressant drug for use in obese adults. The drug was globally withdrawn in 1997 following reports of valvular heart disease (VHD) involving the mitral and/or aortic valves in some patients. Although serotonin and/or agonist activity at the 5-HT_{2B} receptor has been implicated in VHD, no conclusive evidence of this relationship has yet been reported. The risk of VHD during treatment with FFA was assessed as part of the nonclinical safety development program for FFA. A total of 344 mice were treated with FFA in 3 studies at 5-140 mg/kg/day for durations of 2 to 26 weeks; 866 rats were treated with FFA in 5 studies at 1-50 mg/kg/day for between 3 weeks and 2 years; and 60 dogs were treated with FFA at 2.5-25 mg/kg/day for 10 months. All vehicle and FFA doses were administered by oral gavage. Separate groups of animals were included in mouse or rat studies for estimation of pharmacokinetic (PK) parameters of FFA and its active metabolite nor-FFA by noncompartmental analysis (WinNonlin). At the end of the study, animals were euthanized; hearts were removed and fixed in 10% neutral buffered formalin. A longitudinal section of the heart 0.5 to 1.0 mm ventral to the pulmonary artery through both the right and left ventricles and including both the mitral and aortic valves was prepared, embedded in paraffin, and stained with H&E for microscopic evaluation. No microscopic changes were observed in mitral or aortic valves from any animal treated with FFA. The mean maximum plasma concentration (C_{max}) of FFA measured after the final dosing ranged from 507 to 2,935 ng/mL in all studies and the mean area under the plasma concentration-time curve ($AUC_{0\text{-}24hr}$) ranged from 6,455 to 28,000 hr•ng/mL. Similarly, the C_{max} of norfenfluramine (the metabolite of FFA) ranged from 483 to 2,380 ng/mL and the mean $AUC_{0\text{-}24hr}$ ranged from 7,865 to 38,550 hr•ng/mL. These studies were conducted in 3 different mammalian species, with dosing covering all ages of animal lifecycle. They were treated chronically with multiple dosing levels of FFA starting at ages between newborn and puberty, and progressing in the longest study to the end of their natural lifecycle. The consistent lack of changes in valve morphology contradict the widely accepted hypothesis that chronic dosing with FFA is a substantial risk factor for VHD. The animal study results do support the clinical cardiovascular safety of FFA used to treat DS and LGS, which now includes ≥550 patients treated for up to 6 years without echocardiographic evidence of VHD.

Disclosures: K. Okamoto: A. Employment/Salary (full or part-time):; UCB BioSciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UCB BioSciences. **A. Gammaitoni:** None. **B. Boyd:** A. Employment/Salary (full or part-time):; UCB BioSciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UCB BioSciences.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.18

Topic: B.08. Epilepsy

Support: SIP Grant 20211617

Title: Alcohol amides as anticonvulsants

Authors: *S. E. MEZA TOLEDO, L. M. MORALES-COUOH, A. L. AMBRIZ-HERNÁNDEZ, E. BURGUEÑO-TAPIA, G. MARCOS-CRUZ;
Bioquímica, Inst. Politécnico Nacional, Esc.Nac.Cien.Biol, Ciudad DE Mexico, Mexico

Abstract: In an effort to find new anticonvulsants several alcohol amides were prepared and studied their anticonvulsant activity against seizures induced by 4-aminopyridine (4-AP) and thiosemicarbazide (TSC) in mice. Compounds 3-hydroxy-3-(3',5'-bis(trifluoromethylphenyl)) butyramide (**1**), 3-hydroxy-3-(3'-trifluoromethylphenyl) butyramide (**2**) and 3-hydroxy-3-ethyl-3-phenylpropionamide (**3**) were prepared using condensation reactions and characterized through infrared spectrophotometry and nuclear magnetic resonance spectroscopy. Compounds **1** and **2** exhibited an anticonvulsant activity in mice greater than that of phenobarbital (PB), while the anticonvulsant activity of **3** was similar that of PB against seizures induced by 4-AP and TSC. The activation of gamma-aminobutyric acid mediated neurotransmission could be involved in the anticonvulsant activity of synthesized compounds. This study shows that alcohol amides represent a new class of anticonvulsant compounds worthy of further development for potential antiepileptic therapy.

Disclosures: S.E. Meza Toledo: None. **L.M. Morales-Couoh:** None. **A.L. Ambriz-Hernández:** None. **E. Burgueño-Tapia:** None. **G. Marcos-Cruz:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.19

Topic: B.08. Epilepsy

Support: PRONACES-CONACYT grant 194171
VIEP-BUAP 2021-2022 to CA in Neuroendocrinología (BUAP-CA-288)
Fellowship from CONACYT No. 952483

Title: Prolactin reduces potency of absence seizures in an animal model of H-ABC leukodystrophy: the taiep rat

Authors: *S. HERNANDEZ-ALVARADO[1], C. CORTES[2], J. R. EGUIBAR, Sr.[3];
[1]Behavioral Neurophysiol., Benemerita Univ. Autonoma de Puebla, Puebla. Pue., Mexico; [2]B. Univ. Autonoma de Puebla, Puebla, Mexico; [3]Behavioral Neurophysiol., Benemerita Univ. Autonoma De Puebla, Puebla, Pue., Mexico

Abstract: The *taiep* rat is a tubulin mutant derived from Sprague-Dawley strain. It is the unique animal model of the human leukodystrophy named hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC). *Taiep* had a mutation in the tubulin β4A and had a progressive myelin loss with ventriculomegaly in MRI analysis that are similar to H-ABC. They also had spike-wave discharges (SWDs) in electroencephalogram with a mean frequency of 6.25 Hz resembling absence seizures, in humans. Absence seizures are behaviorally characterized by sudden loss of consciousness, due to abnormal activation of the thalamo-cortical circuit that produced a synchronization of brain electrical activity. We previously demonstrate that acute central prolactin administration increased the mean duration of SWDs with no changes in their frequencies. The aim of this study was to analyze the power spectrum of spike-wave discharges after central administration of prolactin in adult female *taiep* rats. Six-month-old female *taiep* rats were implanted using stereotaxic surgery with stainless steel screw electrodes and a cannula to left lateral ventricle. 7 days later they were bilaterally ovariectomized and maintained in permanent estrus using s.c. injections of 17-β estradiol. After intracerebroventricular (i.c.v.) administration with artificial cerebrospinal fluid (a CSF), or with 0.5, 1 and 2 μg of rat prolactin. We did 8-hour EEG recordings, and fast Fourier transform analysis was realized. Our results showed that i.c.v. administration of prolactin reduced the potency of SWDs with respect to that obtained with aCSF. The 0.5 μg dose decreased the potency up to 65% (from 5.871 ± 0.66 μV to 9.335 ± 1.05 μV; P&lt0.001). With the 1 μg dose to 55% (from 5.145 ± 0.74 μV to 9.335 ± 1.05 μV; P&lt0.001); and the 2 μg dose reduced potency to 46% of the control values (from 4.299 ± 0.76 to 9.335 ± 1.05 μV; P&lt0.001). In conclusion, prolactin modifies the electrical activity of the thalamo-cortical circuit during SWDs in estrogenized female *taiep* rats that could be a useful tool to test in human beings with leukodystrophies. Partially supported by PRONACES-CONACYT grant 194171 and by VIEP-BUAP 2021-2022 to CA in Neuroendocrinología (BUAP-CA-288). SHA is PhD student on Physiological Sciences and fellowship from CONACYT No. 952483.

Disclosures: S. Hernandez-Alvarado: None. **C. Cortes:** None. **J.R. Eguibar:** None.

Poster

698. Epilepsy: Pharmacological and Gene Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 698.20

Topic: B.08. Epilepsy

Title: Preclinical Characterization of [^{18}F]T-008, a Novel PET Imaging Radioligand for Cholesterol 24-Hydroxylase (CH24H)

Authors: *T. KOIKE[1], C. C. CONSTANTINESCU[2], S. IKEDA[1], T. NISHI[1], E. SUNAHARA[1], M. MIYAMOTO[1], O. BARRET[2], D. ALAGILLE[2], G. TAMAGNAN[2], T. KUROITA[1]; [1]Takeda Pharmaceut. Co., Takeda Pharmaceut. Co., Kanagawa, Japan; [2]Invicro, LLC, New Heaven, CT

Abstract: Cholesterol 24-hydroxylase (CH24H also known as CYP46A1) is an enzyme responsible for the conversion of brain cholesterol into 24*S*-hydroxycholesterol (24HC). The selective CH24H inhibitor soticlestat (TAK-935) is being pursued as a drug for treatment of seizures in developmental and epileptic encephalopathies, and is currently in phase 3 for the treatment of Dravet syndrome [NCT04940624] and Lennox-Gastaut syndrome [NCT04938427]. In this study, we describe the discovery and preclinical validation of the novel radiolabeled CH24H ligand (3-[^{18}F]fluoroazetidin-1-yl){1-[4-(4-fluorophenyl)pyrimidin-5-yl]piperidin-4-yl}methanone), known as [^{18}F]T-008 or [^{18}F]MNI-792, and its tritiated analog, [^{3}H]T-008. *In vitro* autoradiography (ARG) studies in CH24H wild-type (WT) and knockout (KO) mouse brain sections were conducted using [^{3}H]T-008. Binding of [^{3}H]T-008 was specific to CH24H in the mouse brain sections, and was not observed in CH24H KO or in wild-type mice after pre-treatment with soticlestat. PET imaging was conducted in two adult rhesus macaques using [^{18}F]T-008. Each macaque received two test-retest baseline scans and two sequential blocking doses of soticlestat administered prior to [^{18}F]T-008 to determine CH24H enzyme occupancy. PET data were analyzed with Logan graphical analysis using plasma input. A Lassen plot was applied to estimate CH24H enzyme occupancy by soticlestat. The rank order of [^{18}F]T-008 uptake was striatum > cortical regions > cerebellum, which was consistent with CH24H distribution in the brain. Robust quantification of [^{18}F]T-008 in NHP could be achieved in the absence of a tissue reference region. Pre-blocking with soticlestat reduced the maximum uptake and increased the washout in all brain regions in a dose-dependent manner. Calculated global occupancy values for soticlestat at a dose of 0.89 mg/kg were 97%-98%, indicating maximum occupancy. These observations support the use of [^{18}F]T-008 for PET imaging of CH24H in healthy and epileptic conditions in humans and for *in vivo* evaluations of interactions between CH24H and candidate therapeutics.

Disclosures: T. Koike: None. **C.C. Constantinescu:** None. **S. Ikeda:** None. **T. Nishi:** None. **E. Sunahara:** None. **M. Miyamoto:** None. **O. Barret:** None. **D. Alagille:** None. **G. Tamagnan:** None. **T. Kuroita:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.01

Topic: C.01. Brain Wellness and Aging

Support: NIAAA R21AA027374
NIAAA R01AA023181

Title: Bt75, a novel rarα agonist, inhibits neuroinflammation in experimental models of alzheimer’s disease through akt/nf-κb pathway and m1-to-m2 phenotypic polarization of microglia

Authors: *X. ZHANG[1], S. SHIVAKUMAR[2], C. WILLIAMS[2], S. CANALS-BAKER[2], D. A. WILSON[2], B. C. DAS[3], M. SAITO[2];
[1]Nathan Kline Inst., [2]Nathan Kline Inst. for Psychiatric Res., Orangeburg, NY; [3]Pharmaceut. Sci., Long Island Univ., Brooklyn, NY

Abstract: Alzheimer's disease (AD), the most common form of dementia, is a terminal, progressive disorder leading to memory loss, personality changes and the inability to communicate. BT75, a boron-containing retinoid, is a novel retinoic acid receptor (RAR)**α** agonist synthesized by our research group. Previous studies indicate that activation of retinoic acid (RA) signaling pathway may attenuate progression of AD. Presently, we aim to examine the anti-inflammatory effect of BT75 using cell culture and AD mouse model. SIM-A9 (muse microglial cell line) cells were pretreated with different doses of BT75 (1μM - 25μM) and stimulated by LPS. Griess reaction method for the detection of Nitric Oxide (NO) and ELISA was applied for the detection of inflammatory factors. The cell viability was detected by MTT method. The target proteins involved in the cell signal pathway were determined by Western blot. Results showed that BT75 attenuated the cytotoxicity induced by high dose of LPS in SIM-A9 cells and suppressed the releases of nitric oxide (NO) and IL-1β in cell culture medium induced by LPS in SIM-A9 cells. BMS195614, a specific RARα antagonist blocked the inhibition of NO production of BT75, indicating that BT75 inhibited LPS-induced NO production at least partially through RARα signaling pathway. Moreover, BT75 inhibited p-AKT and p-NF-κB expression induced by LPS. In addition, BT75 promoted M1-to-M2 phenotypic polarization in microglia. For in vivo study, C57BL/6 mice were intracerebroventricularly injected with streptozotocin (STZ) at 3mg/kg body weight to induce AD-like icv-STZ model. BT75 (5mg/kg body weight) was given to icv-STZ mice with intraperitoneal injection for 3 weeks. Sham mice were intraperitoneally given vehicle or BT75 (5mg/kg body weight) separately. Immunofluorescence staining on mouse brain sections was performed for the detection of GFAP-positive astrocyte and Iba1-positive microglia. Western blot assay was done for the detection of target proteins like synaptophysin, nNOS and P-Tau. The results indicated that BT75 inhibited glial cell activation and p-Tau expression in the hippocampus of icv-STZ mice. BT75 also increased synaptophysin and decreased nNOS expression in the hippocampus of icv-STZ mice. Taken together, BT75-inhibited neuroinflammation may be mediated by AKT/NF-κB pathway and microglia polarization in LPS-stimulated SIM-A9 cells and BT75 possessed neuroprotective effects against the STZ-induced AD model mice via inhibition of glial cell activation. Thus, BT75 is a promising neuroprotective agent worthy of further development into AD treatment. Supported by NIAAA R21AA027374 and NIAAA R01AA023181.

Disclosures: X. Zhang: None. **S. Shivakumar:** None. **C. Williams:** None. **S. Canals-Baker:** None. **D.A. Wilson:** None. **B.C. Das:** None. **M. Saito:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.02

Topic: C.01. Brain Wellness and Aging

Support: Graduate Student Council award to ANQ
National Institutes of Health: R00 DA039791 (JJP)
R01 DA052851 (JJP and NMA)
R01 DA039044 (MJK)
administrative supplement from award P30 GM122733 (pilot project to JJP and MJK)

Title: Hormonal Intervention Combined with Allopregnanolone Alleviates Premature Age-Related Comorbidities in Female Mice Exposed to Ovarian Failure and HIV-1 Tat

Authors: *A. QRAREYA[1], F. MAHDI1[1], N. ASHPOLE[1], M. KAUFMAN[2], J. PARIS[1];
[1]Univ. of Mississippi, University, MS; [2]McLean Hosp., Belmont, MA

Abstract: In the U.S, ~50% of people living with HIV (PLWH) are aged 50 or older. However, age-related comorbidities occur frequently among PLWH compared to age-matched seronegative people. Women with HIV experience an earlier transition to post-menopause that is associated with a higher incidence of age-related comorbidities. Despite antiretroviral therapy, neurotoxic HIV proteins such as the trans-activator of transcription (Tat) persist within the central nervous system and may contribute to age-related comorbidities. We find that Tat is sufficient to dysregulate aspects of the neuroendocrine system in mice. However, the benefit of hormonal replacement therapy (HT) in HIV is unclear. Herein, we use 4-vinylcyclohexene diepoxide to achieve an ovary-intact peri- and post-menopause model in Tat-transgenic mice. We hypothesized that conditional Tat expression [Tat(+)] would exacerbate age-related comorbidities compared to age-matched controls [Tat(-)]. We anticipated HT would attenuate Tat/age-related comorbidities to a greater degree when intervention occurred in the peri-estropausal stage, as opposed to the post-estropausal stage. We also assessed the effects of the most commonly-prescribed HT, Prempro® (conjugated equine estrogens and medroxyprogesterone acetate), alone or in combination with a neuroprotective progesterone metabolite (allopregnanolone; AlloP). Overall, post-estropausal mice demonstrated greater anxiety- and depression-like behavior than did peri-estropausal mice. When exposure to Tat occurred in the peri-estropausal stage, mice exhibited little initial change in nociceptive sensitivity or neuromuscular function; however, as Tat exposure continued throughout the post-estropausal transition, mechanical nociceptive thresholds were increased. Neuromuscular function generally declined. This may suggest a reduction in mechano-sensitivity and muscle strength as exposure to Tat becomes chronic. Notably, if Tat exposure first occurred in the post-estropausal stage, mechanical pain responses were much greater. The anti-anxiety-like benefits of Prempro® were only observed when HT was initiated in the peri-estropausal stage. At this time, the inclusion of AlloP potentiated the benefits of Prempro®, but only among Tat(-) controls. Tat-induced cognitive deficits were not observed until mice transitioned to post-estropause. Prempro® alone did not improve cognition in Tat(+) mice, but did so when combined with AlloP. Similarly, co-administration with AlloP improved antinociception in post-estropause. Thus, combined Pempro® and AlloP provided the greatest benefit to post-estropausal mice exposed to HIV Tat.

Disclosures: A. Qrareya: None. **F. Mahdi1:** None. **N. Ashpole:** None. **M. Kaufman:** None. **J. Paris:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.03

Topic: C.01. Brain Wellness and Aging

Support: R21 AG056039
R01 AA025380

Title: Voluntary running is associated with enhanced acquisition of the 5-choice serial reaction time task in middle-aged female rats

Authors: *C. G. KENNEDY, J. L. LEASURE, S. P. RODGERS;
Psychology, Univ. of Houston, Houston, TX

Abstract: Midlife in women is a unique period characterized by a dramatic decline in ovarian hormones, which is associated with an increased risk of cognitive impairment in old age. Hormone therapy can be neuroprotective but is not recommended for preventing or treating cognitive impairment due to potential adverse side-effects. Physical exercise is a promising alternative strategy to promote female brain health and cognition but studies of its efficacy during midlife are lacking. We conducted a study to assess the impact of midlife aerobic exercise on executive function as there is some evidence in aging adults that aerobic exercise provides greater benefits to executive processes in women than men. We used a voluntary wheel running (VWR) model of exercise and the 5-Choice Serial Reaction Time Task (5-CSRTT) to evaluate executive function in female rats approaching reproductive senescence. Others have shown that midlife hormone therapy enhances performance on this task, and we have shown that VWR enhances performance in young males. We predicted that midlife VWR would enhance task performance in female rats. We randomly assigned 11-mo-old retired breeders to locked (sedentary, n=16) or unlocked (exercise, n=16) running wheels for 2h/d, Mon-Fri, for 9 wks. Next, we trained the rats on the 5-CSRTT for 10 wks. Training consisted of 8 stages of increasing difficulty. A median split analysis showed that rats in the exercise condition naturally diverged into a group of high runners (M=2.39±0.14 km/wk) and low runners (M=1.06±0.15 km/wk). This divergence was not due to estrous cyclicity as analysis of vaginal cytology showed no relationship between running distance and estrous stage (χ^2 (2)=1.42, p =.49). A Kruskal-Wallis test showed a significant effect of exercise on task acquisition (H(2)=8.17, p=. 017) with high runners reaching criterion performance in fewer sessions relative to low runners (z=2.52, p=.035) and sedentary rats (z=2.48, p=.039). Repeated measures ANOVA showed significant interactive effects between exercise and training stage on omission errors (F(12,156)=1.88, p=.04) and correct response times (F(12,156)=4.10, p<.0001) with high runners outperforming sedentary rats on certain stages. Current efforts are directed at analysis of synaptodendritic plasticity in prefrontal cortex regions known to underpin performance on the 5-CSRTT, to determine whether group differences in structural elements are associated with cognitive performance. Our results to date provide the first preclinical evidence for the potential of

voluntary aerobic exercise as a midlife lifestyle intervention to promote executive function in females.

Disclosures: C.G. Kennedy: None. **J.L. Leasure:** None. **S.P. Rodgers:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.04

Topic: C.01. Brain Wellness and Aging

Support: DoD W81XWH1910702
DoD W81XWH-21-1-0311
DoD W81XWH-21-1-0305
DoD W81XWH-21-1-0314

Title: Neuropathological and Behavioral Profile of a Chronic Experimental GWI Model Reminiscent of Neuropsychiatric Signs in Veterans

Authors: *X. WU, T. SINGH, M. NEFF, D. S. REDDY;
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Abstract: Gulf War Illness (GWI) is a chronic, multi-symptom illness affecting the brain and other systems, which is most diagnosed amongst veterans. Cognitive and mood impairments are among the primary symptoms in GWI veterans. Scientific evidence suggests that GWI in a significant fraction of veterans is linked to a combination of chemical exposures met by service personnel during the Gulf war. However, there is currently no effective therapy for GWI veterans. Investigation on the mechanisms of GWI symptoms will help designing therapies for GWI. Here, we investigated the chronic profile of an experimental model of GWI in rats with an emphasis on long-term (10-months) neuropathological changes, neuroimaging markers and behavioral deficits. Experimental GWI was induced in rats by 4 weeks of daily exposure to GWI related chemicals with mild restrained stress. To check neuronal damage, we performed histological analysis of brain sections stained with NeuN and PV. In stereological analysis, GWI-exposed rats showed a significant decrease in principal neurons and interneurons, showing a long-lasting neuronal damage and cell loss in several brain regions. To check neuroinflammation, we performed histological analysis of GFAP and IBA1 staining. A significant increase in astrocytes with hypertrophy and activated microglia were evident in GWI-exposed rats, confirming marked increase in inflammatory response in the brain. In the neuroimaging analysis, there were significant increases in lateral ventricle T2 relaxation times and significant differences in the volumes of hippocampus, thalamus, and lateral ventricle. These pathological changes were positively correlated with behavior deficits on anxiety, memory and depression panels. Overall, the GWI rat shows striking consistency in recapitulating major signs

of veteran GWI. This model helpful for assessing therapeutic interventions for GWI-related neuropsychiatric dysfunction.

Disclosures: **X. Wu:** None. **T. Singh:** None. **M. Neff:** None. **D.S. Reddy:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.05

Topic: C.01. Brain Wellness and Aging

Title: Novel adult brain processing method reveals age-, sex-, and species-dependent effects of pharmaceutical compounds on neuron survival and neuritogenesis

Authors: *A. SEFIANI[1], C. G. GEOFFROY[2];
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Abstract: Neurodegenerative diseases and neurotraumatic injuries are typically age-associated disorders that can reduce neuron survival, axon and neurite outgrowth, and synaptic plasticity leading to loss of cognitive capacity, executive function, and motor control. In pursuit of reducing the loss of said neurological functions, novel compounds must be identified that augment neuron survival, axon regeneration/neuritogenesis, and synaptic plasticity. However effective high-throughput *in vitro* screenings are at finding compounds, most screens use iPSC derived, embryonic, or post-natal neurons. This is a major issue as they are likely to have different characteristics than the targeted neurons in clinical settings. Indeed, the majority of the patients suffering from neurodegenerative diseases and neurotrauma are of middle-age and older. This dichotomy in age between the neurons used in drug screens and patients certainly impedes chances of translational success. It has been historically challenging to culture adult neurons let alone conduct screenings; therefore, age-appropriate drug screenings have previously not been plausible. Thus, we have developed a novel adult neuron processing method and created the first high content morphology-based screening system using age-appropriate adult cortical neurons. This novel method allows for rapid and economical mass processing of large mammalian brains to maximize neuron survival for increased screening capacity. After conducting targeted screens utilizing cortical neurons from 2-year-old adult sheep (equating to humans in their 20s) and mice, we have discovered age-, sex-, and species-dependent effects of compounds on neuritogenesis and neuron survival. Our screens are expected to 1) prevent the premature dismissal of compounds with no effect in iPSC/embryonic screens yet advantageous to adults, 2) reduce the false positivity rate by vetting compounds with no benefit to adults neurons, and 3) provide multi-species validation to better predict clinical success. Therefore, utilizing age-, sex-, and species-appropriate *in vitro* models to find novel compounds increasing neuron survival and neurite outgrowth, made possible by our novel neuron processing method, will greatly increase the probability of translational success.

Disclosures: **A. Sefiani:** None. **C.G. Geoffroy:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.06

Topic: C.01. Brain Wellness and Aging

Title: In vivo transient reprogramming has no effect on the choroid plexus

Authors: *J. AVILA LOPEZ, C. ABBOUD, M. IBRAHIM, J. ROCHA AHUMADA, M. AVINO, M. PLOURDE, C. BENTZINGER, B. LAURENT;
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Abstract: In vivo reprogramming of differentiated somatic cells to pluripotency using the transient expression of the Oct3/4, Sox2, Klf4 and c-Myc (OSKM) transcription factors can be used to induce tissue regeneration. A cyclic regime for short-term OSKM expression has been shown to promote regeneration of several organs (e.g. liver, muscle) however its impact on the brain remains largely unknown. We investigated the effects of a cyclic short-term OSKM expression on the choroid plexus (CP), an highly vascularized tissue found within the brain ventricles which is responsible for producing the cerebrospinal fluid (CSF). Transient reprogramming was done on 8-week-old male and female mice carrying the polycistronic OSKM cassette under tetracycline operator (tetO) and the reverse tetracycline-controlled transactivator (rtTA) (R26-rtTA;tetO-*OSKM*) (n=6) by putting doxycycline (1mg/ml) in drinking water for 3 days followed by 4 days of withdraw during a period of 3 weeks. Control male and female mice only carrying rtTA (R26-rtTA;+) (n=9) were also subjected to a similar induction. We first confirmed the transient OSKM expression by quantitative PCR and validated its impact on several organs. Reprogrammed mice showed accumulation of small regenerating fibers after skeletal muscle injury (injection of cardiotoxin) compared to their controls. Liver, spleen and kidneys of reprogrammed mice also exhibited the presence of some teratomas within the tissue, confirming the successful transient reprogramming. We then performed the analysis of the CP at cellular and molecular levels. No teratomas were observed within the brain but the morphological analysis of the CP tissue showed minor changes in the size of the cells. By immunofluorescence, no significant differences were observed for the integrity of the brain-CSF barrier and the CSF production between reprogrammed and control mice. A whole transcriptome analysis (RNA-seq) was also carried on the tissue and showed no difference in gene expression after the transient reprogramming. Our results indicate that the CP remains insensible to in vivo transient reprogramming and highlight that more tailored strategies need to be developed for exploring the potential of CP reprogramming in regenerative medicine.

Disclosures: **J. Avila Lopez:** None. **C. Abboud:** None. **M. Ibrahim:** None. **J. Rocha Ahumada:** None. **M. Avino:** None. **M. Plourde:** None. **C. Bentzinger:** None. **B. Laurent:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.07

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant GM103418
NIH grant DK-088940
NIH Grant P40OD021331

Title: Effects of intrinsic aerobic capacity on resistance exercise engagement and performance in aged rats

Authors: E. D. RENWICK[1], K. G. STANFORD[1], J. STOPPERAN[1], E. FEY[1], A. K. LEE[1], C. S. MCCOIN[1], L. G. KOCH[2], S. L. BRITTON[3], J. P. THYFAULT[1], J. W. PINKSTON[4], P. C. GEIGER[1], ***J. A. STANFORD**[1];
[1]Univ. Kansas Med. Ctr., Kansas City, KS; [2]Univ. of Toledo, Toledo, OH; [3]Univ. of Michigan, Ann Arbor, MI; [4]Western New England Univ., Springfield, MA

Abstract: Exercise can protect against functional decline in aging and disease. One potential barrier to engaging in exercise is low aerobic capacity. Controlled preclinical studies support a relationship between aerobic capacity and aerobic exercise. Associations between aerobic capacity and resistance exercise have not been studied in animal models, however. The goal of our study was to determine the extent to which aerobic capacity influences resistance exercise engagement and performance using rats that differ in intrinsic aerobic capacity. We trained middle-aged low aerobic capacity (LCR) and high aerobic capacity (HCR) rats to perform a voluntary unilateral forelimb isometric resistance exercise task. After rats learned to press and hold an isometric force-sensing disc, we increased the force requirements to compare performance between the two groups. We found that task engagement and time integral of force (a measure of "work") were similar between the two groups at the lower force requirements but were greater in the LCR rats at the higher force requirements. LCR rats maintained longer disc presses under all force requirements. We then measured bulbar function using a task that measures tongue force during licking. Unlike the forelimb task, engagement in the lick task was greater in HCR than in LCR rats and licking speed was greater in the HCR group. Peak tongue force was greater in the LCR rats during the initial sessions, but the HCR rats' values increased across sessions. Our results reveal that low aerobic capacity does not affect engagement in the forelimb resistance exercise in this model.

Disclosures: E.D. Renwick: None. **K.G. Stanford:** None. **J. Stopperan:** None. **E. Fey:** None. **A.K. Lee:** None. **C.S. McCoin:** None. **L.G. Koch:** None. **S.L. Britton:** None. **J.P. Thyfault:** None. **J.W. Pinkston:** None. **P.C. Geiger:** None. **J.A. Stanford:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.08

Topic: C.01. Brain Wellness and Aging

Support: DOD Research and Education Program
US Army Research Office and the xTech HBCU Program
UNC-Pembroke Faculty Research Grants

Title: Non-pharmacologic avenue targeting the autophagy-lysosomal system to support proteostasis leads to synaptic and cognitive benefits in experimental models

Authors: *M. F. ALMEIDA[1,2,4], K. M. RENTSCHLER[1], M. C. PAIT[1,3], R. T. LONG[1], M. H. GIANG[1], S. CLAYMAN[1], K. G. FARIZATTO[5], B. A. BAHR[1,2,3];
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Abstract: Diet and aging influence cognition and the autopha gy-lysosomal protein clearance pathway, a pathwaymanipulated by synaptic activity and important for memory (Kulkarni et al. 2021-J Cell Biol220:e202002084). Understanding protein clearance systems and their crosstalk are important to identifytherapeutic avenues for Alzheimer's disease (AD) and other proteinopathies (Farizatto et al. 2017-PLoSONE 12:e0182895; Boland et al. 2018-Nat Rev Drug Discov 17:660). Enhancing the lysosomal proteasecathepsin B (CatB) improves protein clearance and cognitive function in models of AD, α-synucleinopathy,and mild cognitive impairment (Mueller-Steiner et al. 2006-Neuron 51:703; Butler et al. 2011-PLoS ONE6:e20501; Hwang et al. 2019-Inter J Mol Sci 20:4432). Here, we tested whether the synapto-protectiveCatB effects elicited by pharmacological modulators are produced by plant extract treatment in brainorganotypic cultures. In our results, American ginseng and bacopa extracts enhanced the 30-kDa activeform of CatB over 3-fold in the hippocampal explants, whereas only small increases were produced byAsian ginseng and blueberry extracts. Interestingly, both pharmacological and non-pharmacologicalagents induced distinct associations between CatB substrate degradation, synaptic resilience indicators,and enhanced conversion of LC3I to LC3II, an indicator of autophagic activation. American ginseng alsoproduced correlative effects on CatB and synaptic protein levels, in addition to protecting synapticintegrity in hippocampal tissue subjected to proteostatic stress produced by the lysosomal inhibitorchloroquine. Next steps for the translational research phase of our study included a rodent model of mildcognitive impairment (MCI). Young adult (3 months) and middle-aged Fischer rats (12-14 months old)were assessed and confirmed to exhibit cognitive decline with age. A group of the middle-aged MCI ratswere then fed American ginseng-supplemented food pellets and the daily extract intake was determinedto be consistent across the 6-week treatment period before assessment with learning and memory tests.The specific American ginseng extract found to promote both the

autophagy-lysosomal pathway andsynaptic integrity also statistically improved cognitive abilities in the MCI rats, including improved memoryby 54% compared to MCI rats fed control food pellets. These results indicate that American ginseng hasthe ability support proteostasis and improve synaptic resilience, both key factors for cognitivemaintenance.

Disclosures: M.F. Almeida: None. **K.M. Rentschler:** None. **M.C. Pait:** None. **R.T. Long:** None. **M.H. Giang:** None. **S. Clayman:** None. **K.G. Farizatto:** None. **B.A. Bahr:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.09

Topic: C.01. Brain Wellness and Aging

Title: Identification of TFEB-associated drugs that ameliorate neurodegenerative disorders progression using a high-throughput screening platform

Authors: *Y. XIONG, M. SARDIELLO;
Pediatrics, Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Our previous work has established transcription factor EB (TFEB) as a master regulator of the autophagy-lysosomal pathway and has shown that activation of TFEB slows down disease progression in murine and cell models of neurodegenerative disorders, including neuronal ceroid lipofuscinoses (NCLs), Alzheimer's disease and Parkinson's disease. In *vivo*, activation of TFEB reduces neuroinflammation and neurodegeneration, and elongates the life span of affected mice. The activity of TFEB is negatively regulated by essential kinases including mTORC1 and AKT. Nevertheless, these kinases are not the ideal targets for long-term therapies based on their pharmacological inhibition. Hence, there is an unmet need for the identification of TFEB regulators that are suitable for prolonged pharmacological modulation. Here we present the development of a platform to identify drug modifiers of TFEB. This platform enables high-throughput screens on cells and is designed to infer the relevant biochemical signaling associated with each gene or drug hit. Thousands of cells treated with each drug are automatically evaluated and the nuclear translocation and stability of TFEB within each cell is measured. To achieve statistical significance and reproducibility, each drug is applied in three different doses and incubation times. Each sample is compared to both the negative control DMSO and the positive control Torin1, an mTORC1 inhibitor and a known TFEB activator. Using this platform, we have identified eleven novel drugs that modify TFEB nuclear translocation and/or stability. We subsequently assessed these drug modulators based on the level of TFEB phosphorylation and mTORC1 activity under the treatment with each drug. Some of these hits lead to notable TFEB dephosphorylation and nuclear translocation without markedly affecting mTORC1 activity, indicating that their mechanism of action is independent of mTORC1. Results from this pathway-centered screening paradigm inform about the most viable routes to develop treatments for neurodegenerative disorders through TFEB modulation.

Disclosures: **Y. Xiong:** None. **M. Sardiello:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.10

Topic: C.01. Brain Wellness and Aging

Title: Lta4h inhibition improves cognition by reducing plasma ltb4 levels and modulating multiple brain cell types

Authors: *S. RAINA, J. M. ADAMS, S. REGE, A. T. LIU, R. BRITTON, A. L. NGUYEN, N. V. VU, D. Y. KIRSHER, D. P. LEONE, R. HARISH, B. SZOKE, E. CZIRR, C. MILLWARD, M. K. CAMPBELL;
Alkahest, Inc., San Carlos, CA

Abstract: Leukotriene A4 Hydroxylase (LTA4H) is an enzyme that catalyzes the synthesis of LTB4, a pro-inflammatory factor. Previously we have shown that LTA4H is a detrimental factor in aging, as it is upregulated with age as well as with cognitive decline in Alzheimer's disease. Increased plasma levels of LTA4H correlate with worsening cognition measured by the mini-mental state exam (MMSE). This cognitive decline with age is a common issue, and is a symptom of many age-related diseases, currently without effective therapeutic options. We identified an LTA4H inhibitor, AKST1220, and developed an optimized protocol to measure target engagement in the plasma of both humans and mice, by assessing LTB4 levels following calcimycin stimulation *in vivo* and *ex vivo*. Using this assay, we defined the pharmacokinetic and pharmacodynamic profile of AKST1220, supporting clinical development. To understand the mechanism of LTA4H inhibition in an aging brain, we chronically dosed mice with AKST1220 and performed single cell RNA sequencing to identify major gene changes in neurons, brain endothelial cells, and astrocytes, which we hypothesize may all contribute to the improved cognition shown. All together, these molecular changes, along with the characterization of AKST1220 pharmacology, support its development as a new therapeutic candidate for age-related cognitive decline.

Disclosures: **S. Raina:** A. Employment/Salary (full or part-time):; Alkahest. **J.M. Adams:** A. Employment/Salary (full or part-time):; Alkahest. **S. Rege:** A. Employment/Salary (full or part-time):; Alkahest. **A.T. Liu:** A. Employment/Salary (full or part-time):; Alkahest. **R. Britton:** A. Employment/Salary (full or part-time):; Alkahest. **A.L. Nguyen:** A. Employment/Salary (full or part-time):; Alkahest. **N.V. Vu:** A. Employment/Salary (full or part-time):; Alkahest. **D.Y. Kirsher:** A. Employment/Salary (full or part-time):; Alkahest. **D.P. Leone:** A. Employment/Salary (full or part-time):; Alkahest. **R. Harish:** A. Employment/Salary (full or part-time):; Alkahest. **B. Szoke:** A. Employment/Salary (full or part-time):; Alkahest. **E. Czirr:** A. Employment/Salary (full or part-time):; Alkahest. **C. Millward:** A. Employment/Salary (full or part-time):; Alkahest. **M.K. Campbell:** A. Employment/Salary (full or part-time):; Alkahest.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.11

Topic: C.01. Brain Wellness and Aging

Title: Changes in brain structure and function in old mice following chronic exposure to smoked cannabis high in THC or CBD

Authors: *A. H. SADAKA[1], P. KULKARNI[1], S. IRIAH[1], M. FEBO[2], C. T. JOHNSON[3], H. B. BRADSHAW[3], R. J. ORTIZ[4], M. A. GITCHO[5], C. F. FERRIS[1];
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Abstract: There is compelling evidence in preclinical and clinical studies that chronic use of cannabis during adolescence and early adulthood can have detrimental effects on cognitive function and brain structure. However, there is evidence from 18-month-old mice of enhanced cognitive function and hippocampal structure given a continuous low dose of synthetic THC. There are also preliminary, albeit contradictory, findings in humans that exposure to cannabis in old age may enhance learning, memory, and quality of life. To explore this topic, 23 predominately female elderly mice (~20 months, 19F, 4M) received daily treatments of vaporized placebo or cannabis high in CBD or THC for 28 days. Changes in brain structure and function were recorded with multimodal MRI, and cognitive, anxiolytic, locomotive, and analgesic effects were tested using behavioral modalities. Imaging and behavior were recorded during chronic cannabis exposure and washout, i.e. 14-days after the cessation of drug exposure. Cognitive effects were assessed using novel object preference, anxiolytic and locomotive effects using open-field testing, and analgesic effects using hot-plate tail-flick. Changes in brain structure were assessed using voxel-based morphometry (VBM), alterations in white and gray matter microarchitecture using diffusion-weighted imaging, and functional coupling using connectomics. Images from each modality were registered and analyzed using a 3D MRI mouse atlas, providing site-specific data on 140 different brain areas. Cognitive decline ($p=0.017$), reduced anxiety ($p=0.023$), and increased locomotion (0.028) were observed after first-time exposure to high THC cannabis but not after 28 days or washout. Analgesic effects were significantly greater for THC mice after 28 days of inhalation ($p=0.038$), indicating that antinociceptive properties of inhaled THC may be immune to tolerance. The midbrain dopaminergic system was significantly affected by inhalation of high THC, with VBM indicating an initial decrease in volume ($p<0.001$) after 28 days, followed by an increase in the same regions ($p=0.002$) after a 2-week washout. Fractional anisotropy values were reduced in the same areas, indicating a reduction in gray matter volume. The absence of tolerance to analgesic effects suggests that cannabis high in THC may be an effective treatment for chronic pain. Meanwhile,

the effects on the dopaminergic system warrant more research to understand the underlying mechanism.

Disclosures: **A.H. Sadaka:** None. **P. Kulkarni:** None. **S. Iriah:** None. **M. Febo:** None. **C.T. Johnson:** None. **H.B. Bradshaw:** None. **R.J. Ortiz:** None. **M.A. Gitcho:** None. **C.F. Ferris:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.12

Topic: C.01. Brain Wellness and Aging

Support: South Carolina Honors College (to KEC)
University of South Carolina Office of Undergraduate Research (to KEC)
NIH Grant K01AT010348 (to RTE)
VISN7 Research Development Award (to FH)
NIH Grant P20GM103641 (to JAM, FH, and RTE)
NIH Grant K01AG061263 (to JAM)
University of South Carolina Office of the Vice-President of Research (to JAM)

Title: Beneficial Effects of Ketogenic Diet on Memory and Synaptic Mitochondria Differ Between Males and Females in Normal Aging

Authors: *K. E. COBB[1], T. J. COX[1], E. GORMAN-SANDLER[1], K. B. PATEL[1], R. T. ENOS[2], F. HOLLIS[1], J. A. MCQUAIL[1];
[1]Pharmacology, Physiol. and Neurosci., [2]Pathology, Microbiology, and Immunol., Univ. of South Carolina Sch. of Med., Columbia, SC

Abstract: The age-associated neurological disorder Alzheimer's disease (AD) is characterized by defective brain glucose utilization. Impaired neural activity, which relies heavily on glucose as the major cellular energy source to produce ATP, is an early sign of disease progress. Consequently, strategies to normalize glucose metabolism and replenish brain energy needs could prevent age-associated memory loss, normalize synaptic function, and reduce AD risk. Ketogenic diets enriched in medium-chain triglycerides (MCTs) but restricted in carbohydrates can attenuate blood glucose and increase circulating fat-derived ketone bodies, which are readily metabolized by the brain. The ketogenic diet is also well-known to regulate neural activity, as it is an effective intervention for drug-resistant epilepsy. Therefore, the ketogenic diet may be a suitable, diet-based intervention to remediate metabolic and cognitive symptoms of aging. To test this hypothesis, we assigned male and female Fischer 344 × Brown Norway F1 hybrid rats to consume calorie-matched control (70% calories from carbohydrates) or ketogenic diets (76% calories from MCTs) for 8 weeks beginning at 6 or 24 months (mo.) of age. Consumption of the ketogenic diet reliably attenuated blood glucose and significantly increased blood beta-

hydroxybutyrate (the dominant ketone body) regardless of sex or age. After 6 weeks on diet and verifying stable week-to-week measurements of blood metabolites, we assessed hippocampus-dependent learning in the Morris water maze to determine the effect of diet on spatial memory. We reliably detected cognitive impairment of 24 mo. vs. 6 mo. rats as well as better spatial learning in ketogenic diet-fed rats compared to control diet-fed rats. We further detected a sex-by-age-by-diet interaction and post hoc comparisons localized significant, improving effects of ketogenic diet on learning and memory to 24 mo. male rats and 6 mo. female rats; ketogenic diet did not influence learning in 6 mo. males or 24 mo. females. After 8 weeks on diet, we measured substrate-stimulated mitochondrial respirometry in isolated hippocampal synaptosomes and determined that ketogenic diet increased Complex I + II coupled respiration in 24 mo. female rats but reduced this same parameter in 6 mo. males. These results indicate that effects of a ketogenic diet on memory are sex- and age-dependent and dissociable from influences on brain mitochondria. In future work, we will seek to understand the loss of beneficial cognitive response to ketogenic diet in aging females and investigate diet effects at mid-life in a surgical model of menopause and estrogen supplementation.

Disclosures: K.E. Cobb: None. **T.J. Cox:** None. **E. Gorman-Sandler:** None. **K.B. Patel:** None. **R.T. Enos:** None. **F. Hollis:** None. **J.A. McQuail:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.13

Topic: C.01. Brain Wellness and Aging

Support: South Carolina Honors College (to NJH)
University of South Carolina Office of Undergraduate Research (to CHR)
NIH Grant K01AG061263 (to JAM)

Title: Effects of Chronic Stress on Working Memory Are Sex-Specific and Age-Dependent

Authors: *T. J. COX, N. J. HAMMOND, C. H. RYAN, H. A. DUFALA, J. A. MCQUAIL; Pharmacology, Physiology, and Neurosci., Univ. of South Carolina, Columbia, SC

Abstract: Normal aging is associated with varying degrees of memory loss coupled to changes in function of the hypothalamic-pituitary-adrenal (HPA) axis, the brain-body system involved in regulation of stress responses. Working memory, which depends on the prefrontal cortex (PFC), is susceptible to decline with age. Further, PFC neurons regulate HPA axis activity and undergo structural changes when challenged with prolonged exposure to stressful stimuli. Thus, we hypothesized that chronic stress would exacerbate age-related working memory impairment and reveal mechanisms by which HPA axis dysfunction contributes to brain aging. To test this hypothesis, we evaluated PFC-dependent working memory in male or female F344 rats at 6-, 14-, or 24-months (mo.) of age. Working memory accuracy was measured using a delayed match-to-

sample operant task and, while testing was ongoing, similar numbers of each sex and age were assigned to unstressed (UNS) or chronic variable stress (CVS) treatment. CVS entailed twice-daily exposure to stressors that included forced swims, physical restraint, predator urine, or cage-flood, presented in an unpredictable order for 21 days; UNS rats underwent daily testing but were not exposed to stressors. We observed that CVS interacted with age and sex to influence working memory accuracy. In males, CVS lowered accuracy of 6 mo. rats but increased accuracy of 14- and 24-mo. rats, compared to age-matched UNS. Choice accuracy of females was significantly greater compared to males and not observed to decline with age or stress. In parallel to effects on working memory accuracy, CVS reduced the number of trials completed per session, independent of sex or age. Importantly, lower trial completion was not accompanied by any change in response latencies, suggesting CVS rats remained motivated to obtain food rewards within each trial. CVS also reduced body weight and increased adrenal weight, typical stress-associated physiological changes, regardless of sex or age. These findings reveal that the effects of chronic stress on PFC-dependent working memory are highly dependent on biological sex and chronological age. New studies will determine the degree to which CVS effects on working memory depend upon stress and sex hormone signaling and quantify molecular changes in the PFC of stressed and aging rats. Collectively, these findings will lead to new interventions to normalize disrupted HPA axis function and improve memory over the full lifespan.

Disclosures: **T.J. Cox:** None. **N.J. Hammond:** None. **C.H. Ryan:** None. **H.A. Dufala:** None. **J.A. McQuail:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.14

Topic: C.01. Brain Wellness and Aging

Support: Office of the Associate Dean for Research and Graduate Education (to DJH)
South Carolina Honors College (to TAM)
University of South Carolina Office of the Vice-President of Research (to TAM)
University of South Carolina Office of Undergraduate Research (to TAM)
NIH Grant P20GM109091 (to JAM)
NIH Grant K01AG061263 (to JAM)

Title: Di- and Tri-Heteromeric NMDA Receptors in Age-Related Memory Loss

Authors: *D. J. HOROVITZ, M. A. TIEMAN, A. C. VILLAFUERTE, J. A. MCQUAIL; Pharmacology, Physiology, and Neurosci., Univ. of South Carolina, Columbia, SC

Abstract: NMDA receptor (NMDAR) dysfunction is implicated in age-associated memory loss and Alzheimer's disease (AD). NAMENDA, a non-selective NMDAR channel blocker, has FDA approval to treat symptoms of moderate-to-severe AD. NAMENDA may tonically inhibit extra-

synaptic NMDARs that gate excitotoxic Ca^{2+} influx and likely contain highly mobile GluN2B subunits. However, NAMENDA does not halt disease progression and may antagonize synaptic NMDARs required for memory that is sensitive to decline in brain aging and AD. Synaptic NMDARs are anchored in the post-synaptic density by GluN2A subunits that become more prevalent with age and after synaptic potentiation. However, complex interactions among GluN2 subunits and synaptic scaffolding proteins inhibit our ability to distinguish those NMDAR complexes that support normal learning and memory from others that contribute to age-related brain disorders. To address this gap, we characterized the naturalistic interactions among GluN2A and GluN2B subunits in the hippocampus of aging rats with behaviorally verified memory impairments. Male and female F344 rats were tested at 4-6 months or 22-24 months of age in the Morris water maze. Our behavioral data demonstrate that aging reliably impairs spatial learning, but individual differences of aged rats include some that perform similarly to young adults. Tissue from the behaviorally characterized rats was then immunoprecipitated or immunodepleted with GluN2A- and GluN2B-specific antibodies before Western Blot analysis to detect physical associations with other GluN1 and GluN2 subunits as well as PSD-95, the scaffolding protein that clusters NMDAR complexes in the post-synaptic density. Our findings suggest GluN2B and GluN2A abound in a tri-heteromeric NMDAR complex with GluN1. Further, GluN2B also forms detectable levels of di-heteromeric NMDAR with GluN1. Importantly, GluN1/GluN2/GluN2B tri-heteromeric NMDARs and GluN1/GluN2B di-heteromeric NMDARs both affiliate with PSD-95, strongly suggesting that either configuration is affiliated with the post-synaptic density. Interestingly, we also detected excess of free GluN2A subunits that were not associated with either GluN1 or PSD-95. Ongoing work will repeat these analytical and quantitative biochemical procedures in a larger cohort of behaviorally characterized aging rats with a wider range of memory performance. These forthcoming data will provide a clear picture for the naturally occurring configurations of NMDARs in the aging hippocampus that predict cognitive status and will be useful to tailor the design of new, more targeted approaches to rescue memory and prevent AD.

Disclosures: D.J. Horovitz: None. **M.A. Tieman:** None. **A.C. Villafuerte:** None. **J.A. McQuail:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.15

Topic: C.01. Brain Wellness and Aging

Support: South Carolina Honors College (to TAM)
University of South Carolina Office of the Vice-President of Research (to TAM)
University of South Carolina Office of Undergraduate Research (to TAM)
Office of the Associate Dean for Research and Graduate Education (to DJH)
NIH Grant P20GM109091 (to JAM)
NIH Grant K01AG061263 (to JAM)

Title: A D-Amino Acid Oxidase Inhibitor Reverses Age-Associated Memory Loss

Authors: *M. A. TIEMAN, D. J. HOROVITZ, A. C. VILLAFUERTE, J. A. MCQUAIL; Pharmacology, Physiology, and Neurosci., Univ. of South Carolina, Columbia, SC

Abstract: Normal aging is characterized by cognitive decline and an increased risk for age-associated neurological disorders, such as Alzheimer's disease (AD). NMDA receptors (NMDARs) are well-known to contribute to normal learning and memory and their loss in aging is observed to correlate with severity of memory impairment. At present, NAMENDA, an NMDAR channel blocker is prescribed for the treatment of moderate AD symptoms, where it is thought that extra-synaptic NMDAR activity contributes to excitotoxicity and neurodegeneration. However, NAMENDA's effects are limited, inconsistent, and temporary. Currently, no FDA-approved therapeutics target synaptic NMDARs whose activity is neuroprotective and supports memory. Serine, an NMDAR co-agonist, is concentrated within the synaptic cleft and is degraded by D-amino acid oxidase (DAAO). Therefore, we hypothesized that increasing the endogenous concentration of synaptic serine by inhibiting DAAO will lead to increased activation of synaptic NMDARs and improved spatial memory in aged rats. We first characterized naturally occurring age-associated memory deficits in 22-months old (mo.) male or female F344 rats on a hippocampus-dependent reference memory task in the Morris Water Maze (MWM) relative to 4-mo. controls. After the initial characterization we tested the effects of DAAO inhibitor, 3-methylpyrazole-5-carboxylic acid (MPC), using a Delayed Match-to-Place (DMTP) task, which relies upon hippocampal NMDARs and is suitable for repeated-testing. One hour before testing each day we injected rats with 0, 1, 3, or 10 mg/kg of MPC (in saline), with each rat receiving each dose according to a counterbalanced schedule. Under vehicle conditions, memory in the DMTP MWM was reliably correlated with individual differences in reference memory MWM testing, showing both tasks were equally sensitive to memory deficits in the same aging individuals. Escalating doses of MPC improved DMTP MWM memory performance and the 10 mg/kg MPC dose significantly improved memory compared to vehicle treatment. These behavioral results are consistent with our hypothesis that cognitive performance in aging may be enhanced through indirect potentiation of synaptic NMDAR activity. Forthcoming studies will use brain tissue from drug-treated rats to determine how memory-enhancing doses interact with hippocampal NMDAR signaling and normalize neuronal activity that are dysregulated in aging. These findings will lead to new, more targeted NMDAR therapeutics to prevent age-related memory loss and AD.

Disclosures: M.A. Tieman: None. **D.J. Horovitz:** None. **A.C. Villafuerte:** None. **J.A. McQuail:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.16

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Masupirdine (SUVN-502): A Pure 5-HT_6 Receptor Antagonist for the Treatment of Agitation/Aggression and Psychosis

Authors: *R. NIROGI, R. MEDAPATI, N. GANUGA, V. GRANDHI, R. ABRAHAM, P. JAYARAJAN, R. BADANGE, K. BOJJA, S. MANCHINEELLA;
Suven Life Sci. Ltd., Hyderabad, India

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder with decline in memory and cognitive function. In addition, most patients experience neuropsychiatric symptoms (NPS) like apathy, sleep disorders, mood disorders, anxiety, agitation/aggression, and psychosis which affects their quality of life and adds burden to the caregivers. Antipsychotics are the first line drugs generally prescribed to treat agitation/aggression or psychosis. However, they are associated with modest efficacy and side effects. Therefore, novel, efficacious and safe therapeutic agents need to be developed to treat NPS. The serotonin-6 (5-HT_6) receptors are G-protein coupled receptors widely expressed in cerebral cortex, hippocampus and striatum of the brain which are important for cognition and mood regulation. Masupirdine is a 5-HT_6 receptor antagonist which was evaluated for its anti-aggressive like activity in preclinical animal models like dominant-submissive assay (DSA) and resident-intruder task (RIT). In DSA, dominant animals were treated with masupirdine and submissive animals were treated with vehicle. In the masupirdine treatment group, dominance levels decreased significantly from the 3rd week of the treatment. In RIT, male CD1 mice were used to assess the effects on aggression. Masupirdine significantly decreased the aggressive behavior of resident animals towards intruders at all tested doses. After masupirdine was found to be safe and tolerated in healthy humans and has achieved efficacious concentrations, it was evaluated for its cognitive effects in patients with moderate Alzheimer's disease in a multicenter, randomized, double-blind, parallel group, 26-week, placebo-controlled Phase-2 study (NCT02580305). In a subgroup analysis, treatment with masupirdine at 50 mg and 100 mg significantly decreased the agitation/aggression score from Week 13 to Week 26. A significant decrease in psychosis symptoms was also observed at Week 4 and Week 13. Further exploration is warranted to confirm the beneficial effects of masupirdine in AD patients. Masupirdine is currently being evaluated as a monotherapy in a Phase-3 study for the potential treatment of agitation in participants with dementia of Alzheimer's type (NCT05397639).

Disclosures: R. Nirogi: None. **R. Medapati:** None. **N. Ganuga:** None. **V. Grandhi:** None. **R. Abraham:** None. **P. Jayarajan:** None. **R. Badange:** None. **K. Bojja:** None. **S. Manchineella:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's association

Title: Phase 2 study reveals adequate PK/PD relationshipofbosutinibin Dementia withLewyBodiesand clearsthe path for larger Phase 2/3 investigations

Authors: *M. HEBRON[1], C. MOUSSA[2];
[1]Georgetown university, Clinton, MD; [2]Georgetown Univ., Washington, DC

Abstract: Backgrounds: Bosutinib (Bosulif, Pfizer) is a potenttyrosine kinase (Abl/SRC) inhibitor that is FDA-approved at 500mg oral daily dose for leukemia. The effects of bosutinib were investigated in Dementia with Lewy Bodies (DLB). We investigated bosutinib, 100mg, which is equivalent to the lowest effective intraperitoneal daily dose (5mg/kg) in pre-clinical studies. Bosutinib was investigated in several models of neurodegeneration and it was shown to facilitate clearance of alpha-synuclein and other neurotoxic proteins via autophagy, protect dopaminergic neurons and improve motor and cognitive behavior in animals. ObjectivesTo investigate safety, pharmacokinetics (PK), pharmacodynamics (PD) and biomarkers effects of the lowest effective dose of Bosutinib in Dementia with LewyBodies (DLB) MethodsA single center, Phase 2, randomized, double-blind, placebo-controlled study primarily investigated safety and PK/PD relationship of 12-week oral treatment of bosutinib,100mg. Biomarkers and clinical outcomes were exploratory. ResultsApproximately 120 subjects were approached, 39 were screened, 13 did not meet inclusion criteria and 26 were randomized and included male and female (12:1) in bosutinib and male (13) in placebo with average age 72.94±8.8 (year±SD). There was no serious adverse events (SAEs) and no difference in AEs and no dropouts. Bosutinib, 100mg, was detected in the cerebrospinal fluid (CSF) and inhibited both Abl and Src. Bosutinibsignificantly reduced CSF alpha-synuclein (p=0.023) and the ratio of oligomeric/total alpha-synuclein (p=0.045) compared to placebo. There was also significant decrease in plasma oligomeric alpha-synuclein (p=0.04) and ptau181/Aβ42 (p=0.03). Bosutinib significantly (p=0.034) improved activities of daily living (ADCS-ADL-MCI) compared to placebo. ConclusionThis study showed that bosutinib is safe and enters the brain. Bosutinib, 100mg, inhibited Abl/Src indicting dual target engagement, reduced brain alpha-synuclein and improved activities of daily living, suggesting that this is lowest effective dose (100mg) in DLB. This study is underpowered (by design) but the data will guide adequately powered future studies of a higher dose range of bosutinib (100-400mg) over longer time (6 months) in DLB. FundingThis work was supported by the Alzheimer's Association Part the Cloud grant PTC-19-604235 to Charbel Moussa. DisclosuresCharbel Moussa is an inventor on a Georgetown University (GU) US and International Patent to use Bosutinib in neurodegenerative diseases, including alpha-synucleinopathies. GU exclusively licensed Bosutinib use patent to KeiffeRx.

Disclosures: M. Hebron: None. **C. Moussa:** None.

Poster

699. Neurodegenerative Disorders and Injury: Therapies

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 699.18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA grant R01AG060718 to GT

Title: Reduced Prevalence of Dementia in Patients Treated with Calcineurin Inhibitors

Authors: *J. SILVA, D. JUPITER, G. TAGLIALATELA;
Univ. of Texas Med. Br., Galveston, TX

Abstract: Background: There are currently no efficacious treatments for dementia. However, evidence suggests that patients treated with the immunosuppressive calcineurin inhibitor (CNI) tacrolimus have a lower prevalence of dementia, including of the Alzheimer type (AD), compared to the general population. Whether the observed effects are due to general immunosuppression or specifically to calcineurin inhibition remains unresolved. To address this important question, we interrogated the cutting-edge TriNetX database, comparing dementia prevalence in patients treated with the CNI tacrolimus to patients treated with the non-CNI immunosuppressive drug sirolimus.
Methods: A retrospective cohort study was conducted utilizing the TriNetX health research network. The TriNetX network contains data from 92 healthcare organizations across the US and was searched on June 14, 2022. Patients currently over age 60 were included based on prescription of tacrolimus or sirolimus. Patients with a history of dermatitis or who were prescribed both drugs were excluded. Patients prescribed tacrolimus were propensity-score matched, by age, race, ethnicity, and sex to those prescribed sirolimus, in a one-to-one ratio. The outcomes examined were diagnosis of unspecified dementia at least thirty days following earliest recorded drug treatment.
Results: Of the 9,166 patients in each of the two groups, 134 (1.47%) of those prescribed tacrolimus and 177 (1.94%) of those prescribed sirolimus were later diagnosed with dementia. Tacrolimus treatment was associated with a lower risk of developing dementia (relative risk of 0.76 of dementia in tacrolimus vs. sirolimus, $p < 0.05$).
Conclusion: The results suggest calcineurin inhibition lowers the risk of developing dementia, relative to general immunosuppression. These data encourage clinical evaluation of CNI drugs at non-immunosuppressive regimens as viable therapeutics for treatment of dementia, including AD.

Disclosures: J. Silva: None. **D. Jupiter:** None. **G. Taglialatela:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.01

Topic: C.01. Brain Wellness and Aging

Support: Valley Research Partnership P1A-5012
NIH-R15HL145646
NIH-R01NS100793

Title: The fibrillin-1 mutated mouse model presents accelerated cerebrovascular aging and vulnerability to mild traumatic brain injury

Authors: *T. CURRY[1], M.-E. BARRAMEDA[2], C. BROMBERG[1], M. SABER[1], R. K. ROWE[3], R. GONZALES[1], M. ESFANDIAREI[2], T. C. THOMAS[1];
[1]Univ. of Arizona Col. of Medicine-Phoenix, Phoenix, AZ; [2]Biomed. Sci., Midwestern Univ., Glendale, AZ; [3]Integrative Physiol., Univ. of Colorado Boulder, Boulder, CO

Abstract: Age presents a significant risk for prolonged morbidity and mortality after traumatic brain injury (TBI), yet mechanisms associated with age-related cerebrovascular vulnerability following TBI remain unclear. Age induces transforming growth factor-β (TGF-β) upregulation, implicated in cerebrovascular dysfunction, loss of blood-brain barrier (BBB) integrity, and increased neuroinflammation. Fibrillin-1 (*Fbn1*) mutation increases TGF-β availability and signaling in mice, inducing peripheral vascular dysfunction by 6-months (6M) of age. Patients suffering from *Fbn1* mutation have increased risk of cerebrovascular complications such as stroke, aneurysm, and more severe outcomes after TBI, yet the effect on cerebrovascular function is unknown. This study utilized male and female 6 and 12M old *Fbn1*$^{+/-}$ and C57BL/6 wildtype (WT) mice to investigate the effect of *Fbn1* mutation on accelerated vascular aging, cerebrovascular integrity, BBB permeability, and vulnerability to TBI. We hypothesized that *Fbn1* mutation accelerates cerebrovascular aging, leaving the brain vulnerable to mild TBI (mTBI). Ultrasound imaging demonstrated that increased aortic root diameters and exacerbated aortic wall stiffness in *Fbn1*$^{+/-}$ mice were associated with decreased posterior cerebral artery (PCA) blood flow compared to WT mice, similarly to 12M WT mice, which correlates with impaired PCA wall strength measured using isometric wire myography. To evaluate vulnerability to mTBI, fluid percussion injury was performed, where *Fbn1*$^{+/-}$ mice required a 15% lower pressure to induce mTBI righting reflex times (5-10 minutes) compared to WT. Fluorescent microscopy of Evans blue extravasation, as well as bright-field imaging of ImmunoglobulinG staining demonstrated exacerbated BBB permeability in the hippocampus of 6M *Fbn1*$^{+/-}$ mice compared to WT mice that were comparable to 12M WT and WT 1 day post injury (DPI) mice. This finding was further associated with increased iba-1 staining, suggesting elevated microglial activation. Matrix metalloproteinase-9, a TGF-β signaling product, was upregulated in the hippocampus of 6M *Fbn1*$^{+/-}$ mice, providing a potential mechanism for neuroinflammation. Higher neurological severity scale scores seen in 6M *Fbn1*$^{+/-}$ mice suggests neurobehavioral alterations that were more like 12M WT and WT 1DPI mice. These novel findings indicate that *Fbn1* mutation and potentially its associated increase in TGF-β signaling accelerates vascular aging and alters cerebrovascular vulnerability to mTBI, where age-related modulation could be neuroprotective.

Disclosures: T. Curry: None. **M. Barrameda:** None. **C. Bromberg:** None. **M. Saber:** None. **R.K. Rowe:** None. **R. Gonzales:** None. **M. Esfandiarei:** None. **T.C. Thomas:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.02

Title: WITHDRAWN

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.03

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant NS37853
Leon Levy Fellowship in Neuroscience

Title: Calcium transients in nNOS neurons underlie distinct phases of the neurovascular response to barrel cortex activation in awake mice

Authors: *S. AHN, A. ANFRAY, J. ANRATHER, C. IADECOLA;
Weill Cornell Med., New York, NY

Abstract: Neuronal nitric oxide (NO) synthase (nNOS), a calcium-dependent enzyme, is expressed by distinct populations of neocortical neurons. Although neuronal NO is well known to contribute to the blood flow increase evoked by neural activity, the functional relationships between nNOS neurons and local vascular response remains unclear. We sought to examine how nNOS neuron activity relates to local arteriolar dilation during neocortical activation. To this end, we used 2-photon microscopy to image the barrel cortex in awake, head-fixed mice through a chronically-implanted cranial window (509x509 μm^2). To express the calcium indicator GCaMP7f selectively in nNOS neurons we used adenoviral gene transfer (AAV PHP.eB Syn-FLEX-GCaMP7f, i.v.) in $NOS1^{cre}$ mice. We found that 96±3% (mean±SD) of nNOS-immunoreactive neurons (n=2,744 in 5 mice) co-express GCaMP7f while 99.6±0.5% of GCaMP7f-positive neurons co-express nNOS. After localizing the barrel cortex by Laser-speckle contrast during contralateral whisker stimulation, Texas red-conjugated dextran was injected i.v. to label microvessels, and the barrel cortex was imaged (layer 2/3). The barrel cortex was activated either by short (5 sec) or long (30 sec) air puff trains directed at the contralateral whiskers. Air puffs induced calcium transients in 34.9 ± 14.5 % of nNOS neurons and evoked local arteriolar dilation (9.6 ± 2.0 %; diameter: 14-18 μm). Correlation analysis between calcium transients in individual nNOS neurons (n = 253 in 6 movies from 3 mice) and local arteriolar dilation showed various degrees of correlation, with a mean Pearson's correlation coefficient of 0.27±0.19. A stronger correlation (0.66 ± 0.04) was observed if the activity of the whole ensemble of nNOS neurons was correlated with arteriolar responses. Analysis of the timing of air puff-evoked calcium transients of individual neurons relative to local arteriolar dilatation

revealed that selected nNOS neurons became active immediately prior to arteriolar dilation, while others after the dilatation. This trend was best observed during 30 sec air puffs and such early or delayed pattern of activation was conserved in the same neuron during repeated stimulation. Our data suggest that the contribution of nNOS neurons to functional hyperemia is best represented by the activity of the whole nNOS neural network and not by a selected nNOS subpopulation targeting NO to local arterioles. However, nNOS neuron subsets may specifically contribute either to the initiation or to the maintenance of the vascular response, suggesting a previously unappreciated temporal specificity to the role of NO in neurovascular coupling.

Disclosures: S. Ahn: None. **A. Anfray:** None. **J. Anrather:** None. **C. Iadecola:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.04

Topic: C.01. Brain Wellness and Aging

Support: National Institute on Aging K01AG068353
National Institute on Aging R01AG053555
National Institute on Aging F31AG074703
American Academy of Sleep Medicine Foundation SRA-1818

Title: Obstructive sleep apnea and cerebrovascular pathology in older adults

Authors: *D. E. BERISHA[1], B. RIZVI[1], M. CHAPPEL-FARLEY[1], I. Y. CHEN[1], N. SATTARI[1], A. DAVE[1], K. VINCES[1], N. J. MEZA[1], K. K. LUI[2], A. B. NEIKRUG[1], R. M. BENCA[3], M. A. YASSA[1], B. A. MANDER[1];
[1]Univ. of California, Irvine, IRVINE, CA; [2]UCSD, San Diego, CA; [3]Wake Forest Univ., Winston-Salem, NC

Abstract: Introduction: Alzheimer's disease (AD) is a neurodegenerative disorder that involves the accumulation of β-amyloid (Aβ) plaques and tau neurofibrillary tangles. Obstructive sleep apnea (OSA) increases risk for AD and has been associated with Aβ and tau pathologies. Mechanisms linking OSA and AD remain unknown. A potential mechanism is cerebrovascular pathology, likely exacerbated by two features of OSA: intermittent hypoxia and sleep fragmentation. White matter hyperintensities (WMH), an index of cerebrovascular pathology, increase in prevalence with age and AD. Here, we test the hypothesis that OSA severity is associated with WMH volumes in older adults. Materials and Methods: Thirty older adults (72.7±5.4 years; 18 female) with a full spectrum of OSA severity (AHI=15.7±19.4) were evaluated with overnight polysomnography (PSG). OSA severity was quantified using the Apnea-Hypopnea Index (AHI), Respiratory Disturbance Index (RDI), and blood oxygen desaturation (number, duration, frequency of ≥4% desaturations, and desaturation nadir) stratified by REM and NREM sleep stages. T1-MPRAGE and T2-FLAIR scans were acquired at

3 Tesla. Total and lobar WMH volumes were derived using a semi-automated tool and square-root-transformed. Results:REM Obstructive Total Hypopnea Index was significantly associated with total, frontal and parietal WMH volume. Similar relationships were detected with minutes spent in 70-80% oxygen saturation range and REM minimum oxygen saturation, all of which were significantly associated with total, frontal, and parietal WMH volume. Minimum sleep oxygen saturation, regardless of sleep stage, was significantly associated with frontal and parietal WMH volume. In all cases, these relationships persisted after adjustment for sex and age in regression models. No other significant relationships were observed. Conclusions: These findings suggest that OSA-related hypoxemia, particularly during REM sleep is associated with lobar and global WMH volumes. The specificity of findings to REM sleep indicates that hypoxia occurring in REM may confer a heightened vulnerability to cerebrovascular pathology. Future studies should utilize OSA treatment to determine if reducing hypoxemia and sleep fragmentation can reduce cerebrovascular risk for AD.

Disclosures: D.E. Berisha: None. **B. Rizvi:** None. **M. Chappel-Farley:** None. **I.Y. Chen:** None. **N. Sattari:** None. **A. Dave:** None. **K. Vinces:** None. **N.J. Meza:** None. **K.K. Lui:** None. **A.B. Neikrug:** None. **R.M. Benca:** None. **M.A. Yassa:** None. **B.A. Mander:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.05

Topic: C.01. Brain Wellness and Aging

Support: CAPES (processo 88881.504749/2020-01. 9951-Programa Estratégico Emergencial de Prevenção e Combate a Surtos. Endemias. Epidemias e Pandemias Edital de Seleção Emergencial I - Prevenção e Combate a Surtos. Endemias. Epidemias e Pandemias). Brazil
FAPEMIG (APQ-00735-19)
DMM, MARS, DQ, GB are research fellows of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)-Brazil

Title: Visuoconstructional impairment following mild COVID-19

Authors: *M. A. ROMANO-SILVA[1], J. J. PAULA[2], R. PAIVA[1], N. SOUZA E SILVA[1], D. V. F. ROSA[1], R. COIMBRA[3], F. DURAN[4], D. QUEIROZ[1], G. BUSATTO[4], D. M. MIRANDA[1]; [1]Univ. Federal De Minas Gerais, Belo Horizonte, Brazil; [2]Univ. Federal de Minas Gerais, Belo Horizonte, Brazil; [3]Inst. René Rachou, FIOCRUZ, Belo Horizonte, Brazil; [4]Univ. de São Paulo, São Paulo, Brazil

Abstract: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection disease (COVID-19) reached pandemic proportions in 2020 and brought long-term negative consequences to health and society. People recovered from COVID-19 may still present

complications including respiratory and neurological sequelae. In other viral infections, cognitive impairment occurs due to brain damage or dysfunction caused by vascular lesions and inflammatory processes. Persistent cognitive impairment compromises daily activities and psychosocial adaptation. Some level of neurological and psychiatric consequences were expected and described in severe cases of COVID-19. However, it is debatable whether neuropsychiatric complications are related to COVID-19 or to unfolding from a severe infection. Nevertheless, the majority of cases recorded worldwide were mild to moderate self-limited illness in non-hospitalized people. Thus, it is important to understand what are the implications of mild COVID-19, which is the largest and understudied pool of COVID-19 cases. We aimed to investigate adults at least four months after recovering from mild COVID-19, which were assessed by neuropsychological, ocular and neurological tests, immune markers assay, and by structural MRI and 18FDG-PET neuroimaging to shed light on putative brain changes and clinical correlations. In approximately one-quarter of mild-COVID-19 individuals, we detected a specific visuoconstructive deficit, which was associated with changes in molecular and structural brain imaging, and correlated with upregulation of peripheral immune markers. Our findings provide evidence of neuroinflammatory burden causing cognitive deficit, in an already large and growing fraction of the world population.

Disclosures: **M.A. Romano-Silva:** None. **J.J. Paula:** None. **R. Paiva:** None. **N. Souza e Silva:** None. **D.V.F. Rosa:** None. **R. Coimbra:** None. **F. Duran:** None. **D. Queiroz:** None. **G. Busatto:** None. **D.M. Miranda:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.06

Topic: C.01. Brain Wellness and Aging

Support: Translational & Clinical Innovation Awards, Stanford University
VA Palo Alto Health Care System

Title: Neuronal functions, dietary protein levels and uremic toxins in a mouse model of chronic kidney disease

Authors: A. SUZAKI[1,2,3], J. SUL[1,2,3], H. DAY[1,2,3], E. HAN[3,2], C. SAWEY[3,2], L. GOBA[2], *T.-T. HUANG[3,2];
[1]PAVIR, Palo Alto, CA; [2]Grecc, VA Palo Alto Hlth. Care Syst., Palo Alto, CA; [3]Neurol. and Neurolog. Sci., Stanford Univ., Palo Alto, CA

Abstract: Chronic kidney disease (CKD) is characterized by a progressive loss of renal function that leads to an accumulation of uremic toxins in circulation. A low protein diet is commonly prescribed to CKD patients as a means to delay the progression to end stage kidney failure. Uremic toxins can cross the blood brain barrier and cause neuroinflammation. Consequently,

patients with CKD experience various cognitive symptoms, including fatigue and impaired cognitive functions. How a low protein diet regimen impacts cognitive symptoms in CKD patients, on the other hand, is not well understood. To examine the pathogenic mechanism of uremic toxicity and the impact of low protein diet in the development of cognitive impairments in CKD, we used a partial nephrectomy (PNx) mouse model as the experimental system. Sham and PNx mice were maintained on regular or low protein diet for 14-16 weeks. The mice were examined for glomerular filtration rate (GFR), motor and cognitive functions, and neuronal activities. Plasma and brains were also collected for metabolomic analysis. Regardless of protein levels in the diet, kidney function, as measured by GFR, was reduced by 40% in PNx mice, which corresponded to a 65% reduction in kidney mass. Despite reduced kidney function, PNx mice performed equally well as sham controls in ambulatory activities and working spatial memory. However, in the Puzzle Box paradigm, in which mice were tested for problem solving skills over multiple days with increasingly difficult tasks, PNx mice on average took longer to overcome the obstacle in the most difficult task. Moreover, all mice performed well in novel object recognition test with 1-hour interval between training and testing. However, PNx mice on regular protein diet failed to distinguish between novel and familiar objects when the interval was extended to 24 hours. Examination of neuronal activities following exposure to a novel environment revealed a 30% reduction in c-Fos positive neurons in the hippocampal dentate gyrus in PNx mice on regular protein diet, but no reduction was observed in PNx mice on low protein diet. Consistent with impaired cognitive performance and reduced neuronal activities in PNx mice on regular protein diet and improvements when switched to low protein diet, metabolomic analysis showed similar changes in uremic toxins and markers for inflammation and redox homeostasis in the plasma and the brain. Taken together, the data support a correlation between elevated levels of uremic toxins and reduced neuronal activities and impaired cognitive performance in PNx mice. Furthermore, reduced dietary protein intake can effectively reduce uremic toxins and improve neuronal functions.

Disclosures: **A. Suzaki:** None. **J. Sul:** None. **H. Day:** None. **E. Han:** None. **C. Sawey:** None. **L. Goba:** None. **T. Huang:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.07

Topic: C.01. Brain Wellness and Aging

Support: KAKENHI 16K13054
KAKENHI 21H03363

Title: Amyloid-positive particles in pin1 KO mice are resemble with eosinophilic thalamic body in human.

Authors: *H. OHTAKI[1,2], K. ONO[3], M. TANAKA[1], Y. SETOGUCHI[1], A. HAYASHI[1], A. YOSHIKAWA[4], D. KANG[2], K. HONDA[2], A. KAKITA[5], T. UCHIDA[6];
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Abstract: Pin1 is a ubiquitous peptidyl-prolyl *cis/trans* isomerase (PPIase) and has been shown to be necessary for cell growth and apoptosis. Pin1 gene deficient (-/-) mice have been suggested the contribution of the age-dependent neurodegeneration. However, it is still unclear the pathological relationship between human diseases. We recently determined the pin1 (-/-) mice were impaired spatial cognitive and social communicating functions. The purpose of the present is to examine histological features in the pin1 (-/-) and the wild-type littermates with aging. The mice at 150, 300 and 600 days of age under anesthesia were perfused 10% neutral formalin following 0.9% NaCl for fixation and prepared thin-coronal brain sections after the embedding with paraffin. The brains were stained with toluidine blue (TB) and thioflavin S. While the stainability of thioflavin S was slightly greater in the entorhinal and piriform cortexes, there are obvious differenced between the genotypes. By the immunostaining such as tau, amyloid, and TDP-43 antibodies, we found an amyloid positive deposit in the thalamus. To characterize the neuropathological features of the deposits, the brains were stained with HE and Lxsol Fast Blue-Cresyl Violet (LFB-CV) to observe morphological changes, and Congo Red (CR) and Direct Fast Scarlet 4BS (DFS) diagnostic for amyloidosis. The particles were localized in the cytoplasmic regions in the neuronal cells and stained eosinophilic with HE staining and light blue similar with myelin. However, the particles were no stained with TB, CR, and DFS. The particles also did not stain apple green birefringence under polarized light on CR and DFS stain. These morphological features are suggested to resemble the eosinophilic thalamic body in human brain.

Disclosures: H. Ohtaki: None. **K. Ono:** None. **M. Tanaka:** None. **Y. Setoguchi:** None. **A. Hayashi:** None. **A. Yoshikawa:** None. **D. Kang:** None. **K. Honda:** None. **A. Kakita:** None. **T. Uchida:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.08

Topic: C.01. Brain Wellness and Aging

Support: NIMH K01 MH117343
NIGMS P20 GM109036
NIGMS P20 GM103629
NINDS RO1 NS114286

NIA R01 AG074489
Infectious Disease Society of America

Title: Intermittent infection with cytomegalovirus induces cognitive deficits and alters neurobiological energy metabolism in adult mice

Authors: *E. ENGLER-CHIURAZZI, H. WANG, K. O. MCDONALD, M. A. A. HARRISON, R. S. FREITAS, I. A. PURSELL, S. S. V. P. SAKAMURI, C. H. MONK, K. J. ZWEZDARYK;
Tulane Univ., New Orleans, LA

Abstract: Alzheimer's disease (AD) is the most common cause of dementia. The growing appreciation of a microbial etiology has revealed new horizons for improved understanding of the mechanisms underlying AD. Negative cognitive and neurobiological impacts of acute infection are known, and often potentiated by age. Though long-term consequences of cumulative infection exposure are inadequately studied, emerging evidence suggests that a higher lifetime infection burden impairs cognition and is associated with a faster rate of cognitive decline. Whether brain penetrance is necessary for these effects is not yet known. Our aim with this project line was to evaluate cognitive and neurobiological consequences of intermittent cytomegalovirus (CMV) exposure during aging and elucidate cellular energy metabolism mechanisms underlying these changes. We hypothesized that increased severity of cognitive impairment and neurological deficits would occur with increasing numbers of CMV exposures. Female BalbC mice were initially exposed i.p. to CMV (Smith strain, $1x10^5$ PFU) or mock (murine salivary gland extract in PBS) infection at 8 weeks of age. This CMV model largely does not enter brain parenchyma. Viral latency using this model is achieved after 14 days and CMV was readministered every 13 weeks until tissue collection at 8 or 14 months of age. Cognition was measured with the Y-maze and passive avoidance tasks, AD pathological markers via immunohistology, and brain microvascular bioenergetics via the Seahorse XFe Bioanalyzer, immunometabolic T cell phenotyping by flow cytometry and cytokine levels using Bioplex. At eight months of age, mice initially infected with CMV and then re-exposed displayed no evidence of an ongoing systemic inflammatory state , as circulating cytokine levels did not differ between the groups. T cell profiles were shifted, with CMV experience being associated with elevated levels of circulating CD3+ and T central memory cell subsets but diminished splenic T regulatory cell counts. These mice also exhibited spontaneous alternation deficits as well as increased mitochondrial respiration among brain microvasculature; additional behavioral, neurobiological, electrophysiological, and immunological analyses of the 8 and 14 month old cohorts are currently underway. Findings suggest that recurrent, intermittent viral infection may accelerate cognitive aging and foster a pro-dementia trajectory.

Disclosures: E. Engler-Chiurazzi: None. **H. Wang:** None. **K.O. McDonald:** None. **M.A.A. Harrison:** None. **R.S. Freitas:** None. **I.A. Pursell:** None. **S.S.V.P. Sakamuri:** None. **C.H. Monk:** None. **K.J. Zwezdaryk:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.09

Topic: C.01. Brain Wellness and Aging

Support: UNSW Scientia PhD Grant

Title: Delayed Respiratory-Related Evoked Potentials in COPD and healthy ageing

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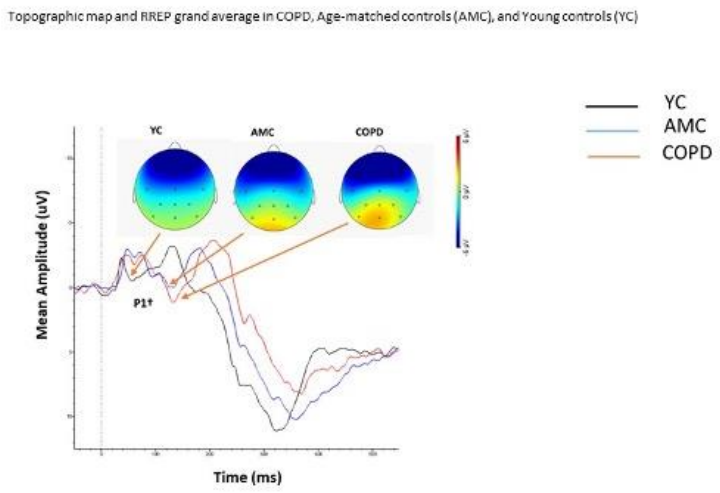
Abstract: Chronic Obstructive Pulmonary Disease (COPD) patients usually have high neural drive, and anxiety, which could modulate their neural responses to respiratory sensations. Increased neural processing and perception of respiratory sensations has been reported in COPD [i], however in that study, the COPD group had a 73% bigger mouth pressure than the controls, and they did not recruit a younger control group.
Methods: I measured respiratory-related evoked potentials elicited by brief airway occlusions in participants with moderate-to-severe COPD, healthy age-matched controls and healthy young controls, with a mouth pressure target to produce a similar stimulus across groups. Mean age was 76 years for COPD and age-matched controls, and 30 years for the young control group.
Results: The latencies of P1, P2 and P3 were delayed in COPD and age-matched control groups compared to the YC group P=0.028, 0.019 and 0.010 respectively. The P1 peak looked bigger in the COPD group Fig 1, but P1 amplitude was similar across groups, P= 0.295. N1 amplitude was greater in the young control group than in COPD and age-matched control groups (P=0.034).
Conclusion: Both COPD and age-matched control groups showed delayed neural responses to the airway occlusion which may indicate impaired processing of respiratory sensory inputs in both COPD and healthy age-matched control groups. The young control group had higher cognitive processing of respiratory inputs than the COPD group and the elderly control group with a greater N1 amplitude.
Reference i. Reijnders T, et al Brain Activations to Dyspnea in Patients With COPD. *Front Physiol* 2020: 11: 7



Disclosures: **I. Epiu:** A. Employment/Salary (full or part-time):; UNSW Scientia PhD Scholarship.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.10

Topic: C.01. Brain Wellness and Aging

Support: Merit Scholarship from Fonds de recherché du Quebec Nature et technologies
Discovery Grant from the Natural Sciences and Engineering Research Council of Canada (NSERC)

Title: Ovariectomy induces mitochondrial dysfunction and synaptic degeneration in the entorhinal cortex

Authors: *O. J. OLAJIDE[1], A. A. BATALLÁN BURROWES[1], A. BERGDAHL[2], C. A. CHAPMAN[1];
[1]Dept. of Psychology, Ctr. for Studies in Behavioral Neurobio., Concordia Univ., Montreal, QC, Canada; [2]Dept. of Health, Kinesiology & Applied Physiol., Concordia Univ., Montréal, QC, Canada

Abstract: Increasing evidence suggests that reductions in systemic estrogens may alter memory and cognitive functions that are mediated by medial temporal lobe structures including the hippocampus and entorhinal cortex (EC). Impairments in cognition and memory can be induced by perturbations in mitochondrial functions and degradation of synaptic proteins, and although

the EC is particularly susceptible to neurodegeneration and synaptic alterations, previous studies examining the roles of reduced circulating estrogens on cognitive deficits have focused mainly on cellular changes within the hippocampus. The present study therefore assessed the impacts of ovariectomy on entorhinal mitochondrial respiration and the immunoexpression of key synaptic components at multiple time points following ovariectomy. Rats were ovariectomized on postnatal day (PD) 63 with or without subdermal 17-β estradiol (E2) implants to maintain constant levels of circulating E2. Compared to animals that received sham surgery, high-resolution respirometry analysis using the Oroboros Oxygraph revealed reductions in mean mitochondrial respiratory measurements in EC samples obtained two weeks (on PD77 to 79) and four weeks (on PD91 to 93) following ovariectomy, but no notable change in oxygen consumption relative to control was recorded after eight weeks (on PD119 to 121). In addition, protein immunoblotting revealed marked reductions in the expression of both presynaptic marker synaptophysin and postsynaptic protein PSD95 four and eight weeks following ovariectomy. The reductions in mitochondrial respiration and synaptic proteins were prevented by chronic replacement of 17-β estradiol following ovariectomy, indicating that these effects were caused by the loss of estrogen. These results suggest that cognitive changes following ovariectomy may be due in part to an impairment in mitochondrial function following reductions in circulating 17-β estradiol.

Disclosures: O.J. Olajide: None. **A.A. Batallán Burrowes:** None. **A. Bergdahl:** None. **C.A. Chapman:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.11

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 AG054533

Title: High-fat diet impairs learning and memory and potentiates inflammation in aged mice

Authors: *A. K. EVANS[1], L. M. VIDANO[1], C. E. WOODS[1], N. L. SAW[1], C. READING[2], M. SHAMLOO[1];
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Abstract: A high-fat diet (HFD) is associated with disorders like obesity, diabetes, and cardiovascular disease. HFD has also been shown to result in increased neuroinflammation, impaired learning and memory and an increase in anxiety-related behavior in mice and rats. Aging is another factor associated with changes in neuroinflammation and behavior although the extent to which diet interacts with age-related changes in neuroinflammation and learning and memory is not well established. This study was designed to examine the effects of Aging and HFD on behavior and neuroinflammation in mice. Twelve-month-old C57BL/6J mice were

provided either a normal diet (ND; 18% fat, 58% carbohydrate, 24% protein) or a high-fat diet (HFD; 60% fat, 20% carbohydrate, 20% protein) for five months. A two month-old control group was provided with normal diet in parallel. Mice were tested in Activity Chamber, Y-maze, Novel Place Recognition and Novel Object Recognition, Elevated Plus Maze, Open Field, Morris Water Maze, and Fear Conditioning. Inflammatory cytokine levels in the plasma and hippocampus were assessed via Luminex assay. Effects of HFD and aging on the hypothalamic proteome were assessed. Immunohistochemistry was used to evaluate microglial proliferation and neurodegeneration in the locus coeruleus (LC). Here we show that consumption of a HFD for 5 months resulted in an increase in body weight and lipid profile (cholesterol, HDL, and LDL) in the blood and a decrease in distance moved compared to age-matched control mice and young mice provided with a normal diet. Effects of Age were limited to activity chamber and cued fear conditioning, whereas HFD resulted in an increase in anxiety-like behavior and impaired learning and memory. These behavioral changes were accompanied by an increase in neuroinflammation (eotaxin) and an increase in systemic inflammatory markers (MIP1B/CCL4, MCP1/CCL2, TNFA, IL6 and IP10). Proteomic analyses revealed changes in proteins related to energy metabolism. Our findings suggest that HFD leads to potentiation of inflammation associated with cognitive deficits. The HFD mouse model provides valuable insight into the impact of diet on cognition and the pathophysiology of aging and neurocognitive disorders.

Disclosures: **A.K. Evans:** None. **L.M. Vidano:** None. **C.E. Woods:** None. **N.L. Saw:** None. **C. Reading:** None. **M. Shamloo:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.12

Topic: C.01. Brain Wellness and Aging

Title: Comparative Analysis of Cerebrovascular Dysfunction in Inducible Mouse Models Identifies Key Pathways for Therapeutic Discovery

Authors: *C. WANDER, R. BRITTON, J. SIN, I. GALLAGER, R. ALCANTARA-LEE, C. YANG;
Alkahest, Inc, San Carlos, CA

Abstract: Cerebrovascular dysfunction is an age-related co-morbidity of many prevalent age-related neurological diseases, including Alzheimer's disease and cerebral small vessel disease. It is characterized by brain endothelial cell stress, blood-brain barrier (BBB) and cognitive dysfunction, and neuroinflammation. Cerebrovascular dysfunction therefore represents a key risk modifier for age-related neurological diseases. To identify animal models with the highest translational potential for neurological disease therapeutic discovery, we compared key phenotypes relevant to neurological diseases in multiple models of cerebrovascular dysfunction. We selected the Angiotensin-II and diet-induced Hyperhomocysteinemia models based on BBB

disruption, translational potential, and scalable inducibility in C57BL/6J male mice. In each model, we observed differential alterations in plasma pro-inflammatory factors, markers of BBB dysfunction and neuroinflammation, and cognitive deficits. Correlation analysis of these phenotypes highlighted key mechanistic pathways linking systemic inflammation to cerebrovascular dysfunction and neuroinflammation. These novel insights from scalable, translational models of cerebrovascular dysfunction will guide efforts in therapeutic discovery for age-related neurodegenerative diseases.

Disclosures: **C. Wander:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **R. Britton:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **J. Sin:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **I. Gallager:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **R. Alcantara-Lee:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **C. Yang:** A. Employment/Salary (full or part-time):; Alkahest, Inc.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.13

Topic: C.01. Brain Wellness and Aging

Support: NASA 80NSSC17K0461

Title: Predicted brain age increases with human spaceflight and remains affected months after return

Authors: ***T. WANG**[1], T. D. FETTROW[2], K. E. HUPFELD[3], J. J. BLOOMBERG[4], S. J. WOOD[4], A. P. MULAVARA[5], Y. E. DE DIOS[5], N. E. BELTRAN[5], P. A. REUTER-LORENZ[6], R. D. SEIDLER[1];
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Abstract: With the evolving plans for manned deep space exploration and space travel, more investigation into the impact of microgravity on human physiology is essential for the security and sustainability of future space missions. Magnetic resonance imaging (MRI) scans have been used to track the structural changes of the human brain from before launch to the International Space Station (ISS) to several months after return from the ISS. Our group and other teams have consistently reported the pre- to post-flight brain changes including an upward shift of the brain, enlarged ventricles, and the narrowed central sulcus. The emergence of machine learning has opened a new dimension to analyze MRI data of human brains. Trained by thousands of T_1-weighted scans of healthy populations and their chronological ages, open-source models like DeepBrainNet can detect subtle patterns of aging and pathological alterations in the brain and can indicate how “old” a brain appears to be. Here we estimated the brain age with

DeepBrainNet and calculated the brain-predicted age difference (brain-PAD) by subtracting the chronological age from the predicted age. The pre- to post-flight change of brain-PAD was used to quantify the impact of spaceflight on the human brain structure. We found that after 190-days (SD=57) missions to the ISS (n=13), the astronauts exhibited 1.03 years (SE= 0.69) on average of brain aging compared with pre-flight on the top of natural aging. Their brain-PAD continued to increase up to 30 days after return (linear mixed effect model p=0.039). We also found the astronauts' brain ages are always smaller than their chronological ages. Even in the scans after return, the average brain-PAD of astronauts is negative (-2.9 years, SD= 2.78). This may reflect neural reserve based on the typically higher education, fitness level, and training of astronauts in comparison to the overall population. No sex difference was observed. We did not find that astronauts with longer mission durations exhibited greater accumulated brain aging. Forthcoming analyses will include more crewmembers from retrospective datasets, which will allow us to further examine the potential effects of past mission experiences and flight duration on brain ages. In conclusion, the present work is the first to introduce the brain age to measure the impact of spaceflight. The increased brain ages during space flight could reflect a potentially detrimental impact of microgravity on the human brain. Also, the larger reserve (i.e., negative brain-PAD values) may be a protective factor for astronauts.

Disclosures: T. Wang: None. **T.D. Fettrow:** None. **K.E. Hupfeld:** None. **J.J. Bloomberg:** None. **S.J. Wood:** None. **A.P. Mulavara:** None. **Y.E. De Dios:** None. **N.E. Beltran:** None. **P.A. Reuter-Lorenz:** None. **R.D. Seidler:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.14

Topic: C.01. Brain Wellness and Aging

Support: Margaretha af Ugglas Stiftelse
Stohnes Stiftelse
Gamla Tjänarinnor

Title: Polypharmacy treatments differentially affect functional and cognitive outcomes in a mouse model of Alzheimer´s Disease depending on sex and multiple-drug combination

Authors: *F. EROLI, C. TSAGKOGIANNI, S. ZERIAL, F. ANDERSSON, M. LATORRE-LEAL, J. WASTESSON, A. CEDAZO-MINGUEZ, K. JOHNELL, S. MAIOLI;
NVS, Karolinska Inst., Stockholm, Sweden

Abstract: Background. Epidemiological studies associate the concurrent use of five or more drugs (polypharmacy) with a greater risk of developing adverse events and cognitive decline in older people. A target group that is particularly sensitive to unexpected events secondary to polypharmacy is people with dementia. In this category, the presence of comorbidities together

with cognitive deficits can further complicate the treatment. Despite this, there are few experimental data about the effects of chronic polypharmacy. We recently showed that the concurrent administration of five drugs affected cognitive functions and distinct hippocampal/cortical pathways in adult male and female wild-type mice. Gaining knowledge of the benefits and harms associated with multiple-drug use, with a focus on sex, will help in designing more customized therapies in the future. Aim. Here we investigate the effects of long-term administration of two different polypharmacy regimens in the APP^{NL-G-F} knock-in (APP KI) mouse model of Alzheimer´s Disease (AD), and whether this could affect the disease progression at early stages. Methods. APP KI male and female mice were fed for 2 months with a control or polypharmacy diet (combination #1: metoprolol, simvastatin, paracetamol, low-dose aspirin, citalopram; or #2: enalapril, atorvastatin, paracetamol, low-dose aspirin, citalopram) based on the most used medications by older adults in Sweden. Animals were assessed for locomotion, cognition, and anxiety through a complete battery of behavioral tests. At the end of the treatment brain tissues were collected for molecular biology experiments. The health status of the mice was monitored over the study period through body weight, food, and water intake measurement, together with the analysis of serum protein levels. Results. The treatments were both well tolerated by the animals. We found that polypharmacy in AD mice differentially affected essential functions such as locomotion, and distinct types of memory, depending on sex and multiple-drug combination. Interestingly, combination #1 improved spatial and fear-associated memory in male APP KI mice but not in females. Following these findings, we also discovered reduced levels of cortical Aß plaques in treated APP KI male mice. On the contrary, combination #2 didn´t exert a positive effect on cognitive abilities. Conclusions. Here we show that multi-medication therapies may impact the progression of AD pathophysiology, highlighting the need of understanding mechanisms of polypharmacy that can contribute towards the development of more tailored therapies in aging and AD, with sex being a key factor to consider.

Disclosures: F. Eroli: None. **C. Tsagkogianni:** None. **S. Zerial:** None. **F. Andersson:** None. **M. Latorre-Leal:** None. **J. Wastesson:** None. **A. Cedazo-Minguez:** None. **K. Johnell:** None. **S. Maioli:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.15

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant AG070077
NIH Grant TR002541

Title: Brain glutamate, cortical plasticity, atrophy, and cognition in the aging diabetic brain

Authors: *P. J. FRIED[1], A. NORTHROP[1], C. MORSE[1], D. MANNING[1], V. ZENG[2], S. R. BARATONO[1], R. OZDEMIR[1], S. S. BUSS[1], M. MUNSHI[3,4], M. SHAFI[1], N. R. BOLO[2];

[1]Neurol., [2]Psychiatry, [3]Gerontology, Beth Israel Deaconess Med. Ctr., Boston, MA; [4]Joslin Diabetes Ctr., Boston, MA

Abstract: Background. Type-2 diabetes mellitus (T2DM) affects the aging brain and is associated with reduced cognitive function and increased risk of Alzheimer's disease (AD). Using transcranial magnetic stimulation, our group and others have shown that older adults with T2DM and patients with early AD show similar alterations in the mechanisms of glutamate-mediated NMDA receptor (NMDAR)-dependent long-term potentiation (LTP)-like cortical plasticity. Furthermore, in T2DM, the amount of cortical plasticity was correlated with both cortical glutamate levels and NMDAR-dependent measures of short-term and working memory. We hypothesize that cognitive dysfunction in T2DM results in part from altered glutamatergic neurotransmission secondary to disruptions in brain glutamate homeostasis and that these changes may occur in individuals with pre-diabetes (pre-DM).
Objective. The objective of this study is to compare measures of cognition, cortical plasticity, brain glutamate levels, and cortical atrophy in older adults with T2DM, pre-DM, and non-diabetic (non-DM) controls.
Methods. Data were obtained from 15 participants (age range 58-79 y, 4 females; T2DM=4, pre-DM=4, non-DM=7) as part of an ongoing study. Cortical plasticity was evaluated from the motor cortex (M1) by comparing the average amplitude of motor evoked potentials before and after intermittent theta-burst stimulation. Cortical glutamate levels and age-adjusted cortical thickness (a surrogate measure of atrophy) were assessed from the same M1 region by magnetic resonance spectroscopy and imaging, respectively. Structured neuropsychological testing was used to assess cognition across the domains of global cognition, memory, and executive functions. Analyses of variance compared these variables across T2DM, pre-DM, and non-DM groups.
Results. Effect sizes (and pairwise relations) are reported in lieu of p-values due to the small sample sizes and preliminary nature of the analyses. There was a very-large effect for global cognition and memory composites across groups (R^2s $\geq$.35; T2DM < pre-DM < non-DM) and a large effect for executive functions (R^2=.17; pre-DM < T2DM < non-DM). There were also large effects for M1 glutamate levels (R^2=.22; pre-DM < non-DM < T2DM), M1 thickness (R^2=.27; T2DM < pre-DM, non-DM), and M1 plasticity (R^2=.29; pre-DM < T2DM < non-DM).
Conclusion. Compared to non-DM controls, older adults with either T2DM or pre-DM demonstrated reduced cognitive function, cortical thickness, and LTP-like plasticity. Glutamate tended to be higher in the T2DM group than either pre-DM or T2DM, possibly reflecting disruptions in glutamate homeostasis secondary to chronic hyperglycemia.

Disclosures: P.J. Fried: None. **A. Northrop:** None. **C. Morse:** None. **D. Manning:** None. **V. Zeng:** None. **S.R. Baratono:** None. **R. Ozdemir:** None. **S.S. Buss:** None. **M. Munshi:** None. **M. Shafi:** None. **N.R. Bolo:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.16

Topic: C.01. Brain Wellness and Aging

Support: 2018R1C1B6008884

Title: The effect of Aquaporin 4 deletion on aging and neurodegeneration

Authors: *S. KIM[1,2], H.-J. KIM[1,2], W. SHIN[2], L. CHOI[2], E.-J. LEE[1,2];
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[2]Asan Med. Inst. of Convergence Sci. and Technol., Seoul, Korea, Republic of

Abstract: Aquaporin 4 (AQP4) protein is a water channel expressed on astrocytic endfeet in the brain. The role of AQP4 has been studied in healthy and a range of pathological conditions. Emerging data suggest that AQP4 may also be implicated in the glymphatic system and may be involved in the clearance of waste proteins. Aging is a risk factor for the development of neurodegenerative diseases including Alzheimer's disease. The role of AQP4 in clearing waste proteins may become substantially important with age. However, there have yet to be studied showing the effect of AQP4 function in the aging process and neurodegeneration. Here we show that mice lacking AQP4 (AQP4(-/-)), which have normal neurological function during young age, exhibit reduced learning ability and accumulation of waste proteins during old age. Young AQP4(-/-) mice (8 weeks old) showed no significant difference from AQP4(+/+) mice in behavioral tests while older AQP4(-/-) mice (34 weeks old) demonstrated lower cognitive performance than AQP4(+/+) mice in learning ability during Barnes maze test. Other behaviors including locomotion did not significantly differ between the AQP4(-/-) and AQP4(+/+) mice in both age periods. At the protein level, waste protein such as PHF-1 and inflammatory markers were accumulated in the hippocampus of older AQP4(-/-) mice, as compared to older AQP4(+/+) mice. Taken together, although AQP4 deletion does not significantly affect neuronal function at a young age, it negatively affects cognitive function with age, accompanied by increased levels of waste protein and inflammatory markers. These findings suggest that AQP4 protein may be important in aging and neurodegeneration by dealing with waste clearance and inflammatory processes, which warrants future confirming studies.

Disclosures: S. Kim: None. **H. Kim:** None. **W. Shin:** None. **L. Choi:** None. **E. Lee:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.17

Topic: C.01. Brain Wellness and Aging

Support: NRF grand 2018R1C1B6008884

Title: Phosphodiesterase-5 inhibitor for cognitive impairment in a mouse model of chemobrain induced by paclitaxel

Authors: *H.-J. KIM[1,2], S. KIM[1,2], W. SHIN[2], L. CHOI[2], E.-J. LEE[1,2];
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Abstract: As the lifespan of cancer patients increases, treatment-related problems that decrease quality of life are becoming important. Cancer survivors often report cognitive impairment after chemotherapy (chemobrain), especially in hippocampus-dependent memories. In particular, more than 90% of patients with breast cancer liver longer than 5 years, and upto 70% of these patients experience chemotherapy-induced cognitive impairment. However, no treatment for chemobrain is currently available in clinical practice. Here we report a therapeutic potential of phosphodiesterase-5 inhibitor that activates NO synthase for improving cognitive impairment in a mouse model of chemobrain induced by paclitaxel (PTX) that constitutes main chemotherapy regimen in patients with breast cancer. We treated adult C57Bl/6 mice with 20 mg/kg PTX (3 times/week, for 4 weeks) to induce chemobrain according to the previous protocol. Mice treated with PTX demonstrated a weak phenotype of cognitive impairment, mimicking symptoms of human chemobrain: slightly decreased cognitive impairment in Morris water maze (MWM) test, while no abnormalities during other behavior assays including Open filed test and Novel object recognition test. Simultaneous treatment of mice with phosphodiesterase-5 inhibitor (3 mg/kg, daily for 4 weeks) alleviated PTX-induced cognitive impairment in MWM test, while it did not significantly affect other behavior assays including locomotion. Phosphodiestrase-5 inhibitor decreased expression levels of inflammatory (interleukin-6) and oxidative stress (nitrotyrosine) markers in the hippocampus. In summary, phosphodiesterase-5 inhibitor restored cognitive function in a mouse model of chemobrain induced by PTX through decreasing inflammatory and oxidative stress pathways. These findings suggest that treatment of phosphodiestratse-5 inhibitor may be useful for alleviating cognitive impairment induced by chemotherapy, which warrants future confirming studies.

Disclosures: H. Kim: None. **S. Kim:** None. **W. Shin:** None. **L. Choi:** None. **E. Lee:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.18

Topic: D.06. Vision

Support: University of Oklahoma Vice President for Research and Partnerships

Title: The pattern electroretinogram as an indirect measure of central dopamine status in the context of human iron deficiency

Authors: *M. WENGER, S. NEWBOLDS, L. BOOZARY, A. BARNETT;
Univ. of Oklahoma Cell. and Behavioral Neurobio., Norman, OK

Abstract: Iron deficiency (ID) is the most prevalent nutrient deficiency in the world. It can be found at high rates in both developing and developed countries, particularly among infants, adolescents, and women of reproductive age. ID has negative effects on physical performance and work productivity. Critically, there is accumulating evidence that ID, without anemia, has a range of negative effects on cognition and brain function. Animal models of ID have consistently indicated effects of ID on learning and memory by way of its effects on the neurotransmitter dopamine (DA) and its associated transporter protein. These results with animal models are suggestive, but these hypotheses have not been tested in humans, because standard research measures of dopamine status require either spinal puncture or exposure to radiation. The present project sought to determine whether electroretinography (ERG) could provide an indirect measure of central dopaminergic status. A total of 20 iron deficient non-anemic women and 20 iron sufficient women (matched on age and race/ethnicity) completed four tasks while concurrent electroencephalography (EEG) data were acquired. The first task was a pattern ERG task in which high contrast checkerboard and square wave patterns were alternated; the ERG was recorded from two skin electrodes positioned just below the lower lid of each eye. The second task involved fixating on a central character on the computer screen for five min during which spontaneous eye blinks were recorded. The third task was a contrast detection threshold task and the fourth task was a probabilistic selection task. We concentrate here on the ERG and the spontaneous blink rate data given the known relationship between blink rates and levels of dopamine. We observed a significant positive relationship between blink rate and the blood measure of serum ferritin, suggesting a relationship between serum ferritin and dopamine. Further, we observed a significant negative relationship between serum ferritin and both the amplitude and the latency of the ERG a-wave, with a trending positive relationship between serum ferritin and the amplitude of the ERG b-wave. Finally, we observed a significant negative relationship between blink rate and the amplitude of the ERG a-wave, further suggesting a relationship between the ERG measure and dopamine. The results as a whole suggest the potential utility of using ERG to test mechanistic hypotheses regarding the role of dopamine in ID in humans.

Disclosures: **M. Wenger:** None. **S. Newbolds:** None. **L. Boozary:** None. **A. Barnett:** None.

Poster

700. Systemic Factors That Affect Brain Functions in Normal, Aging, Diseased Brains

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 700.19

Topic: F.03. Stress and the Brain

Support: US Department of Defense W81XWH1910560

Title: Does offset analgesia vary as a function of adverse childhood events and resilience?

Authors: *C. E. LUNDE[1,3], E. SZABO[1], Z. WU[1], K. D. KARUNAKARAN[4], A. KIM[1], S. A. HOLMES[2], D. BORSOOK[4], C. SIEBERG[1,5];

[1]Dept. of Psychiatry and Behavioral Sci., [2]Boston Childrens Hosp., Boston, MA; [3]Nuffield Dept. of Women's and Reproductive Hlth., Univ. of Oxford, Oxford, United Kingdom; [4]Massachusetts Gen. Hosp., Boston, MA; [5]Havard Med. Sch., Boston, MA

Abstract: Background & Aims. Endometriosis is one of the most common chronic gynecological diseases affecting 10-15% of women in their reproductive years and 70% of people with chronic pelvic pain. Approximately 62% of adults in the US report at least one childhood trauma, which is associated with an increased risk of chronic pain and gynecological complications in adulthood. The neural mechanisms associated with stress-related psychopathology are expected to differ significantly from those associated with resilience. This study aimed to explore the role of childhood traumatic events and resilience on descending pain inhibition in people with EAP using functional near-infrared spectroscopy (fNIRS). **Methods**. A 3-temperature offset analgesia (OA) paradigm, a form of endogenous pain inhibition using heat stimuli, was applied to the left forearm (*ΔOA=pain score max - pain score min during offset trial*). At the same time, hemodynamic signals were measured bilaterally over the frontal and somatosensory cortex. Participants completed the Childhood Traumatic Events Scale (CTES) and the Connor-Davidson Resilience Scale (CD-RISC). fNIRS data processing is in progress. Resting-state and OA response functional connectivity will be computed using pair-wise Pearson's r correlation of regions of interest. T-tests will be used to assess statistically significant differences in hemodynamic responses during resting state and OA. fNIRS and behavioral data will be compared using a partial correlation analysis, controlling for CTES burden score and resilience. The research plan was approved by the Ethical Committee of Boston Children's Hospital. **Results.** 14 females with surgically confirmed endometriosis (mean age = 26.7 years, SD = 5.4) and 14 pain-free females (mean age = 22.6 years, SD = 4.2) have been recruited. T-tests showed participants with EAP showed an attenuated OA response, median: 77.1% vs. 43.8%, *(t(25) =.484, p=.05*) and statistically significant difference in average CTES burden score: 22.6 (4.2) vs 26.7 (5.4) (*t(25) =-1.7, p=.05*). No significant difference between groups were found for the measure of resilience (CD-RISC). **Conclusion**. Results may help describe the role of the prefrontal and somatosensory cortex during OA, and the impact of adverse events and resilience during development on the OA response in people with and without EAP. This new approach may allow for identifying meaningful subgroups of patients with EAP, developing better preclinical models, and thus ultimately lead to more effective treatment.

Disclosures: C.E. Lunde: None. **E. Szabo:** None. **Z. Wu:** None. **K.D. Karunakaran:** None. **A. Kim:** None. **S.A. Holmes:** None. **D. Borsook:** None. **C. Sieberg:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant NS085171 (JC)
NIH grants AG065290 (JC)

Title: Effects of age on the distribution of epileptiform spikes across sleep-wake states in amyloid precursor protein transgenic mice

Authors: *M. SILVA-PÉREZ, J. PARK, J. CHIN;
Baylor Col. of Med., Baylor Col. of Med., Houston, TX

Abstract: In Alzheimer's disease (AD) patients and mice, there is an increased incidence of seizures and epileptiform activity, which may be underestimated due to the prevalence of nonconvulsive seizures, and the observation that seizures and epileptiform spikes primarily occur during sleep. In AD patients, epileptiform spikes are non-uniformly distributed across sleep-wake states and occur predominantly during nonrapid eye movement (NREM) sleep. The mechanisms that give rise to epileptiform spikes, and their preferential occurrence during NREM sleep, are not clear. Several mouse lines that express human amyloid precursor protein (APP) containing AD-linked mutations also exhibit epileptiform spikes primarily during sleep. In APP mice from Line Tg2576, epileptiform spikes occur only during rapid eye movement (REM) sleep at early stages of disease but invade NREM sleep as disease and age progress. APP mice from Line J20 have been found to also exhibit epileptiform spikes primarily during REM sleep at early stages of disease. However, whether the occurrence of epileptiform spikes shifts to other brain states as disease and age progress in J20 mice is unclear. Determining if the occurrence of epileptiform spikes in specific sleep states is similar between patients and mice is necessary for assessing the extent to which insights gained from mouse models can be translated to the human disease. To investigate whether the distribution of epileptiform spikes across sleep-wake states changes with age in J20 APP mice, we performed video-EEG monitoring of mice at different stages of disease progression. In young mice at early stages of disease, half of the total daily epileptiform spikes occurred during REM sleep, even though REM sleep typically makes up less than 10% of the sleep-wake cycle. At later stages of disease, the proportion of epileptiform spikes during NREM sleep increased, demonstrating a shift in prevalence with age. This shift from REM to NREM sleep indicates that the epileptiform activity exhibited by aged APP mice reflects that observed in AD patients more closely than the epileptiform activity in young APP mice. These results also suggest that identifying the mechanisms in APP mice that give rise to epileptiform spikes, and underlie the shift from REM to NREM sleep, may provide novel insights into the basis of epileptiform activity in AD patients.

Disclosures: M. Silva-Pérez: None. **J. Park:** None. **J. Chin:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RF1AG069378
NIH RF1AG072727

Title: Microbial community analysis demonstrated sex and disease-selective metabolic differences in the fecal microbiome of a mouse model of Alzheimer's Disease

Authors: *A. M. FLODEN, C. K. COMBS;
Univ. of North Dakota, Grand Forks, ND

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder displaying many symptoms, including memory loss and cognitive decline. Advanced stages of AD can include diarrhea or constipation, suggesting that the gut is also affected by AD changes. We previously observed disease-related changes, including fecal Aβ and inflammatory changes in the intestines of both humans and rodent models of disease, supporting the idea of a gut-brain connection during disease. Our prior work demonstrated fecal and oral microbiome differences between the AD mouse model, *App* $^{NL\text{-}G\text{-}F}$, and control mice. Based on this gastrointestinal dysbiosis, we hypothesized that significant metabolic differences exist between the disease and healthy microbiomes. To test this idea, we collected feces from 6 month old male and female C57BL/6 wild type and $App^{NL\text{-}G\text{-}F}$ mice. Fecal bacteria were cultured in the absence or presence of Aβ 1-40 and Aβ 1-42 to simulate the intraluminal intestinal environment. Microbial community analysis was examined by quantifying the metabolism of 31 different carbon sources. Although the presence of Aβ 1-40 or Aβ 1-42 did not affect metabolism, both male and female $App^{NL\text{-}G\text{-}F}$ mice had significantly reduced metabolism of 2-hydroxybenzoic acid compared to wild type mice. In addition, female $App^{NL\text{-}G\text{-}F}$ mice demonstrated significantly reduced metabolism of pyruvic acid methyl ester, d-galacturonic acid, Tween 40, Tween 80, L-phenylalanine, α-cyclodextrin, glycogen, itaconic acid, glucose 1-phosphate, phenylethylamine, and putrescine compared to C57BL/6 controls. These data demonstrate significantly compromised metabolic activity of the intestinal microbiome of $App^{NL\text{-}G\text{-}F}$ mice with a more robust deficiency associated with the females. Our findings support the notion of intestinal microbiome changes in AD and highlight functional outcomes of this dysbiosis.

Disclosures: A.M. Floden: None. **C.K. Combs:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: U01 AG032969
R56 AG061869
R56 AG072599
R01 AG067598

P01 AG014449
P01 AG017617
R01 AG074004

Title: Illuminating epichaperomes: tools and methods to study epichaperomes in cells and tissues

Authors: *S. BAY[1], A. SANTHASEELA[1], C. DIGWAL[1], S. SHARMA[1], A. ALAM[1], S. JOSHI[1], A. RODINA[1], P. PANCHAL[1], K. MANOVA-TODOROVA[1,2], O. ARANCIO[4,5,6,7], S. GINSBERG[8,9,10], G. CHIOSIS[1,3];
[1]MEMORIAL SLOAN KETTERING CANCER CENTER, Sloan-Kettering Inst., NEW YORK, NY; [2]Mol. Cytology Core, [3]Dept. of Med., Sloan Kettering Inst., New york, NY; [4]Columbia Univ., NEW YORK, NY; [5]Dept. of Pathology and Cell Biol., [6]Taub Inst. for Res. on Alzheimer's Dis. and the Aging Brain, [7]Dept. of Med., Columbia Univ., New york, NY; [8]New York Univ., NEW YORK, NY; [9]Ctr. for Dementia Research, Nathan Kline Inst., [10]Departments of Psychiatry, Neurosci. & Physiology, and the NYU Neurosci. Inst., New York Univ., New york, NY

Abstract: Optimal functioning of neuronal networks is critical to the complex cognitive processes of memory and executive function that deteriorate in Alzheimer’s disease (AD). AD-related stressors mediate global disturbances in dynamic intra- and inter-neuronal networks through pathologic epichaperomes, long-lived oligomeric structures with pathologic scaffolding function (Inda et al. Nature Communications 2020). Epichaperomes negatively impact protein networks important for neuronal function, such as synaptic plasticity, cell-to-cell communication, protein translation, cell cycle re-entry, axon guidance, metabolic processes and inflammation, leading to network-wide dysfunction and cognitive decline - the higher the epichaperome levels, the higher the number of proteins negatively impacted upon, and in turn, the higher the severity of perturbation to the complex network of molecular interactions in affected cells. These are all biological functions known to decline in AD suggesting epichaperome inhibition as a viable target for reversal of functional imbalances associated with AD. Indeed, as proof-of-principle we showed synaptic protein network connectivity and in turn cognitive function revert to normal levels upon treatment with small molecules, such as PU-AD, that dismantle epichaperomes into individual, normal, folding chaperones, providing a therapeutic channel not optimally exploited to date. We discovered both epichaperome drugs, as well as diagnostics for precision application of epichaperome drugs, and translated them to human studies in AD and other CNS disorders. To advance our understanding of epichaperomes in Alzheimer’s disease and learn important mechanistic insights into context-dependent epichaperome composition, structure, and function, we developed chemical probes and methods for use in confocal and single molecule super-resolution imaging approaches. Here we present probe synthesis, characterization, and specificity. We provide examples in the use of these probes on cellular models as well as in human brain tissues and provide proof-of-principle in how these probes can be utilized to address key questions related to the context-dependent composition of the epichaperomes, their cellular localization and localization change in response to and during distinct intra- and extra-cellular events and/or stressors. In sum, these preliminary studies propose our imaging probes as unique and important reagents to study the biology of an emerging AD target.

Disclosures: **S. Bay:** None. **A. Santhaseela:** None. **C. Digwal:** None. **S. Sharma:** None. **A. Alam:** None. **S. Joshi:** None. **A. Rodina:** None. **P. Panchal:** None. **K. Manova-Todorova:** None. **O. Arancio:** None. **S. Ginsberg:** None. **G. Chiosis:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: TL1TR001431
ARCS MWC Scholarship
NINDS 1R01NS097762-05S1
NINDS 1R01NS097762

Title: Epilepsy-Alzheimer's disease interactions in the tgf344-Alzheimer's Disease rat model.

Authors: *D. D. PALMER, P. A. FORCELLI;
Dept of Pharmacol., Georgetown Univ., Washington, DC

Abstract: Among the multitude of comorbidities arising from Alzheimer's Disease (AD), the heightened risk of seizures is increasingly recognized. Epilepsy influences disease progression and cognitive decline in AD patients while AD pathology may exacerbate seizure burden; thus, developing strategies to suppress seizures is necessary. The TgF344-AD rat, expressing both mutant human APP and PSEN1, shows non-convulsive spike and wave discharges (SWD). We have previously reported that optogenetic activation of the deep and intermediate layers of the superior colliculus (DLSC) suppress SWDs in "pure" epilepsy models. Thus, we aimed to determine if activation of DLSC would suppress seizures in the TgF344-AD model. Second, we examined the interaction between *status epilepticus* (SE) and AD pathology in the same model. Adult male and female TgF344-AD rats were used. We injected virus coding for channelrhodopsin-2 (ChR2) into the DLSC of rats, implanted fiber optics, and cortical EEG electrodes. We then compared continuous neuromodulation to that of on-demand neuromodulation (real time detection of seizures) paradigms across three frequencies (5,20,100Hz). For our second aim, male and female TgF344-AD rats and wild-type littermates were used and split into 4 groups [AD-Saline, AD-SE, WT-Saline, WT-SE]. Pilocarpine or saline was injected at 4.5 months of age. 6 months after SE, spatial memory was tested using the Morris Water Maze. Additionally, cortical EEG screws were implanted and all rats underwent 48hrs of chronic EEG monitoring. We unexpectedly found that discharges in the TgF344-AD rat differed from SWDs observed in typical absence epilepsy models. We identified two types of SWDs - Type I had typical generalized, bilaterally synchronous onset and offset. Type II had unilateral onset, occasional periods of bilateral synchronization, and periods of only unilateral activity. Activation of the DLSC produced indeterminant effects, but ongoing analysis assessing the impact on Type I vs. Type II seizures may reveal a different pattern. Behavioral deficits were

evident in the MWM. As expected, SE resulted in deficits. Likewise, AD genotype resulted in subtle deficits. No genotype by SE interaction was found, likely due to an SE derived floor effect. 48hr chronic EEG recordings also revealed Type I and Type II seizures, and emergence (as expected) of limbic seizures after SE. In conclusion, TgF344-AD rats display novel seizure types, each of which may be targetable through optogenetic activation of the DLSC. Additionally, SE induction exacerbates cognitive decline in both AD and WT rats, finding ways to treat both seizure types may reverse deficits and pathological severity.

Disclosures: D.D. Palmer: None. **P.A. Forcelli:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BBSRC EASTBIO, 2096645

Title: Short- and long-term associative memory impairments in 5XFAD Alzheimer's disease mouse model

Authors: *V. AMBROZOVA, J. A. AINGE;
Univ. of St Andrews, St Andrews, United Kingdom

Abstract: Studying the neurobiological mechanisms of Alzheimer's disease (AD) and the resulting cognitive decline is essential for informing AD treatment strategies. The amyloid cascade hypothesis postulates that AD stems from deposition of amyloid-beta in the brain. The 5XFAD mouse model accumulates intraneuronal AB42 in the brain from 1.5 months of age before the formation of amyloid deposits occurs at 2 months (Oakley et al., 2006). This study aimed to examine the effects of amyloid pathology on short- and long-term memory in 5XFAD mouse model (n = 10; F=6, M=4) and C57 controls (n = 10, F=6, M=4) at 3 months of age. The mice were trained on an associative odour-context task until they reached a criterion and could determine a correct odour based on a particular context cue. After a two-week delay, their ability to recall previously learned odour-context pairings was tested. During the two delay weeks mice were administered four spontaneous recognition tasks: novel object recognition (NOR), object-place recognition (OP), object-context recognition (OC) and object-place-context recognition (OPC). These tasks tested the short-term non-associative (NOR) and associative (OP, OC, OPC) memory of mice for encountered objects and their configurations with places and contexts. On the odour-context task the 5XFAD mice needed similar amount of time as controls to encode odour-context pairings and reach the criterion (80% correct trials on average on two consecutive days) but compared to controls the accuracy of the 5XFAD mice was worse. At recall the performance of the 5XFAD mice was impaired in comparison to controls but remained above chance level overall. On the object recognition tasks, unlike controls, the 5XFAD mice did not

show any evidence of remembering familiar OP, OC and OPC configurations. However, their performance on non-associative NOR task was unaffected. Together, these findings show that the 5XFAD mouse model suffers from short- and long-term associative but not non-associative memory deficits at 3 months of age and the associative memory impairments arise from diminished memory encoding and retrieval. Characterization of these early deficits in learning and memory can be beneficial in the assessment of AD therapeutic strategies in preclinical stages.

Disclosures: V. Ambrozova: None. **J.A. Ainge:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Department of Biotechnology, New Delhi, India

Title: Comparative analysis of cellular and molecular therapeutic approach for amyloidβ induced memory loss

Authors: *P. BALI[1], B. NEHRU[2], A. ANAND[3];
[1]Biol. Sci., Indian Inst. of Sci. Educ. and Research-Mohali, Chandigarh, India; [2]Dept. of Biophysics, Panjab Univ., Chandigarh, India; [3]Dept. of Neurol., Post Grad. Inst. of Med. Educ. and Res., Chandigarh, India

Abstract: Background: Neurodegenerative disorders like Alzheimer's disease (AD) is one of the untreatable, which severely hampers the lifestyle of the patient. The available therapies are only giving symptomatic relief without targeting the cause of the disease. The increasing failure of clinical trials in two decades indicates the need to explore the potential of alternative therapies for targeting the pathophysiology of the disease along with the symptomatic relief.**Methods**: We comparatively tested the efficacy of lineage negative stem cells (Lin-ve SC) and recombinant brain derived neurotrophic factor (R-BDNF) to rescue the amyloid-β induced memory loss after taking the required ethical approvals. The oligomers of amyloid-β were injected bilateral intra-hippocampal using stereotaxic surgery and Lin-ve SC were transplanted t the site of injury. The Lin-ve SC were isolated from human umbilical cord blood derived mononuclear cells after newborn delivery using magnetic assisted cell sorter. Similary, 1uM R-BDNF was injected at the site of hippocampal injury. Neurobehavioral parameters i.e. Morris water maze and passive avoidance was analysed to test the behavioral outcomes of these two therapies. Further, molecular expression was studies by Real-time PCR and immunohistochemistry using in brain tissues. **Results**: The transplantation of Lin-ve SC and administration of R-BDNF led to amelioration of memory loss associated with reduction of amyloid deposition from the hippocampus. The expression of neurotrophic factors i.e. glial derived neurotrophic factor

(GDNF), ciliary derived neurotrophic factor (CNTF) and Brain-derived neurotrophic factor (BDNF) were significantly enhanced in both the therapies as compared to injury group. The administration of ANA-12, a TrkB inhibitor, reversed the behavioral and molecular effects of R-BDNF as well as Lin-ve SC indicating involvement of BDNF-TrkB pathway in the rescue of hippocampal injury.
Conclusion: Our results showed that both the therapies are comparative in rescuing the memory loss induced by the amyloid-β. The therapies are effectively reducing the amyloid-β by activation of astrocytes because of the paracrine effects by regulating the neurotrophic factors resulting in anti-apoptotic effects.

Disclosures: P. Bali: None. **B. Nehru:** None. **A. Anand:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Using human iPSC-derived neurons and astrocytes produced by transcription factor-based differentiation protocols for the study of Alzheimer's Disease in vitro

Authors: *M. KILANDER[1], Y. CHEHREGHANIANZABI[1], A. SAMRA[1], T. TANAKA[1], N. HEMMI[2], M. OGIHARA[2], M. KO[1];
[1]Elixirgen Scientific, Inc., Baltimore, MD; [2]Ricoh Co., Ltd., Kawasaki, Japan

Abstract: Alzheimer's disease (AD) is the most prevalent form of dementia, and with an estimated 35 million people affected worldwide, there is an urgent need for therapeutic strategies to alleviate the severe suffering experienced by AD patients and their families. Despite many decades of research into the neuropathological mechanisms of AD, to date, there is still no cure. Thus, technologies and models that can provide new insights into the progression and treatment of AD are in high demand. In this regard, *in vitro* models generated from the differentiation of human induced pluripotent stem cells (hiPSC), holds the potential to provide a more accurate and ethical alternative to animal-based systems for the investigation of neurological diseases. Consequently, using hiPSCs derived from diseased patient material, neurons and astrocytes can be differentiated to generate a biological platform that mimics the neuropathological processes occurring in the AD-affected brain. Employing Elixirgen Scientific's proprietary Quick-Tissue™ technology, we established an iPSC-based AD model to investigate the disease phenotype and to evaluate potential pharmaceutical interventions. Our rapid and robust transcription factor-mediated differentiation protocols are reproducible, applicable to iPSC lines from both healthy and diseased donors and, does not leave any genetic footprint. Within less than 2 weeks from the start of differentiation, our human iPSC-derived excitatory neurons show high expression of neuronal and excitatory markers such as TUBB3 and VGLUT1. Assessment by an ELISA demonstrated elevated expression of Aβ1-42 peptides and p-Tau proteins in our AD patient

iPSC-derived neuron cultures compared to neurons generated from healthy donor iPSCs. Subsequently, decreased levels of Aβ1-40 and Aβ1-42 peptides were observed when the cultures were treated with beta secretase inhibitors. After 6 weeks of differentiation, our hiPSC-derived astrocytes display a gene expression profile akin to human primary astrocytes and express several characteristic astrocyte markers, such as ALDH1L1, CD49f, GFAP, S100β and CD44. Interestingly, we observed that astrocytes differentiated from AD donor iPSCs displayed a more fibroblast-like morphology than cells generated from a healthy control line. Since this type of morphology has been linked to brain inflammation and is moreover indicative of the 'reactive' astrocyte state, our finding implies that a pathological phenotype can be detected in AD patient iPSC-derived astrocyte cultures. In conclusion, Elixirgen Scientific's Quick-Tissue™ technology can generate models relevant for neurodegenerative disease research.

Disclosures: **M. Kilander:** A. Employment/Salary (full or part-time):; Elixirgen Scientific, Inc. **Y. Chehreghanianzabi:** A. Employment/Salary (full or part-time):; Elixirgen Scientific, Inc. **A. Samra:** A. Employment/Salary (full or part-time):; Elixirgen Scientific, Inc. **T. Tanaka:** A. Employment/Salary (full or part-time):; Elixirgen Scientific, Inc. **N. Hemmi:** A. Employment/Salary (full or part-time):; Ricoh Co., Ltd. **M. Ogihara:** A. Employment/Salary (full or part-time):; Ricoh Co., Ltd. **M. Ko:** F. Consulting Fees (e.g., advisory boards); Elixirgen Scientific, Inc..

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH NIEHS SBIR Grant 1R43ES029898-01A1
NIH NIEHS SBIR Grant 1R43ES029897-01
NIH NIEHS SBIR Grant 2R44ES029897-01
NIH Grant 1R43ES029897-01S1

Title: Modeling Neuroinflammation induced by Amyloid Beta Oligomers in Cultured Human iPSC-Derived Neural Organoids on Synthetic Hydrogels

Authors: *J. KULAS, P. FAVREAU, W. RICHARDS, K. GREUEL, K. PARHAM, J. ZIMMERMANN, C. LEBAKKEN;
Stem Pharm, Inc., Madison, WI

Abstract: While much of what is known about neuroinflammation comes from rodent studies, recent research has revealed striking differences in the biology of animal disease models compared to human patient samples. Induced pluripotent stem cell (iPSC) technology offers a potential solution to address the growing need for more physiologically relevant models to study disease and test novel therapeutic approaches. We have developed human iPSC-derived neural

organoids incorporating microglial cells seeded on chemically defined synthetic hydrogels to study neuroinflammation. Single-cell transcriptional analysis demonstrates that the organoids are cell-type diverse, containing multiple neuronal subtypes, astrocytes, microglia, and endothelial cells. Bulk and single-cell RNA sequencing analyses demonstrate high intraclass correlation and low coefficients of variation between biological replicates. Incorporated microglia are distributed throughout the organoids, display ramified morphology resembling *in vivo* morphology, and demonstrate a gene signature that strongly correlates with *in vivo* microglia expression. We compared two inflammatory stimuli, Amyloid Beta oligomers or LPS paired with IFNγ, for their ability to induce inflammatory changes. Both stimuli drove rapid changes in transcription with a significant increase in IL1α transcript detected at 8 hours. Cytokine levels in cell culture media increased as a function of time. iPSC-derived microglia, seeded on synthetic hydrogels, phagocytosed Amyloid Beta oligomers which were detected within CD68-positive compartments. We conclude that human iPSC-derived organoid models may serve as a complementary approach to traditional animal models to examine microglial activation and inflammatory signaling.

Disclosures: **J. Kulas:** A. Employment/Salary (full or part-time):; Stem Pharm, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm, Inc. **P. Favreau:** A. Employment/Salary (full or part-time):; Stem Pharm, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm, Inc. **W. Richards:** A. Employment/Salary (full or part-time):; Stem Pharm, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm, Inc. **K. Greuel:** A. Employment/Salary (full or part-time):; Stem Pharm, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm, Inc. **K. Parham:** A. Employment/Salary (full or part-time):; Stem Pharm, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm, Inc. **J. Zimmermann:** A. Employment/Salary (full or part-time):; Stem Pharm, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm, Inc. **C. Lebakken:** A. Employment/Salary (full or part-time):; Stem Pharm, Inc.. 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.; Stem Pharm, Inc.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Stem Pharm, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm, Inc..

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: John E. and Sarah M. McGinty Foundation
Campbell Foundation
Neurodar
Brigham Young University, College of Life Sciences, Mentoring Environment Grant
Brigham Young University, School of Family Life, Gerontology Program
Brigham Young University, Magnetic Resonance Imaging Research Facility, Seed Grant
Brigham Young University Neuroscience Experiential Learning Fund

Title: Age, genotype, and diet effects on an ApoE mouse model

Authors: *E. BLACK[1], A. RASCH[2], T. WIMMER[4], A. LI[2], S. CIESLAK[4], K. STEED[5], R. ADHIKARI[3], J. J. WISCO[6], B. HUTCHINSON[4];
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Abstract: Current theories regarding accumulation of Alzheimer's Disease-related deposits of abnormal intra- and extracellular proteins include reactions to oxidative stress and mitochondrial dysfunction. These accumulations are also known to be affected by genotype and age. How these factors may affect the individual hippocampal subfields is unknown and published data are limited. In this study we explored whether oxidative stress reactions, age, and genotype have a greater effect on dysregulatory protein accumulation in any particular subfield of the hippocampus. We stained for ferritin, ferroportin, hyper-phosphorylated tau, and β-amyloid proteins in the hippocampal region of 111 Apolipoprotein E2 (ApoE2), ApoE3, or ApoE4 mice fed a control diet or an oxidative stress-inducing homocysteine diet and euthanized at 3, 6, 9, or 12 months. We analyzed stains based on hippocampal subfield and compared the protein accumulation levels within each group. All study investigators were blinded. We found a significant effect of genotype on the CA1 and HI regions in ferritin expression. Genotype and age were associated with a statistically significant effect on the HI region in ferroportin expression. Additionally, though not reaching significance in all subfields, we found trends of decreased ferritin and ferroportin expression in ApoE4 mice in all hippocampal subfields. There was also a significant effect on hyper-phosphorylated tau protein levels based upon a given mouse genotype and diet interaction, with none of the subfields alone accounting for the amount of protein. There were also non-significant trends in each hippocampal subfield of increasing ferroportin and hyper-phosphorylated tau after 6 months of age, and decreasing β-amyloid and ferritin with age. This study identified that there are changes in iron regulatory molecules based on genotype globally within the hippocampus, without regard to subfield. Our findings also suggest a diet-genotype interaction which affects levels of specific Alzheimer's Disease biomarkers globally in the hippocampus. Additionally, we identified a trend toward increased ability to clear β-amyloid, and decreased ability to clear hyper-phosphorylated tau with age in all subfields, in addition to evidence of increasing iron load with time.

Disclosures: **E. Black:** None. **A. Rasch:** None. **T. Wimmer:** None. **A. Li:** None. **S. Cieslak:** None. **K. Steed:** None. **R. Adhikari:** None. **J.J. Wisco:** None. **B. Hutchinson:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The role of APP-like in the development and aging of the motor network of Drosophila melanogaster

Authors: *S. HARRAZ[1], F. VONHOFF[2], J. GUEVARRA[2], C. GUALTIERI[2], Z. SMITH[2]; [2]Biol. sciences, [1]Univ. Maryland, Baltimore, Baltimore, MD

Abstract: Alzheimer's disease (AD) neuropathology has been associated with cleavage of the Amyloid Precursor Protein (APP) and the accumulation of amyloid-beta aggregates. APP is a highly conserved protein that is expressed in all neurons during embryonic stages. Numerous studies have examined the role of APP in degeneration and memory decline in aging organisms. However, recent studies show that some of the hallmarks of AD pathology can also be observed in children and young adults, suggesting that developmental mechanisms may play a critical role in AD onset. This hypothesis is supported by studies showing a role of APP in various developmental processes. However, the molecular mechanisms underlying APP function during development are still not fully understood. APP is a highly conserved protein that is expressed in all neurons during embryonic stages, but the molecular mechanisms underlying APP function during development are poorly understood. The fruit fly, Drosophila melanogaster, possesses an Amyloid precursor protein (APP) homologue called APP-Like (APPL) that has similar functions and characteristics of human APP. Therefore, we explored the role of APPL in brain and motor network function in flies mutant for appl. We use fluorescence imaging in dendrites and flight performance assays to determine the role of APPL during network development and degeneration at the cellular and behavioral levels. Flight performance of control and appl- mutant flies was measured at various ages (2, 10, and 30 days old). Compared to same age controls, young 2d old appl- flies show a significantly decreased flight performance by 13%, whereas 30d old appl- flies show a significantly enhanced decline in performance by 50%. This suggests that appl- flies may be affected by developmental defects as well as enhanced aging-dependent degeneration. To counter the effects of neurodegeneration, we are now testing increased physical exercise as well as nutraceutical supplementation as possible treatment options to ameliorate the APPL-dependent phenotypes.

Disclosures: **S. Harraz:** None. **F. Vonhoff:** None. **J. Guevarra:** None. **C. Gualtieri:** None. **Z. Smith:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CONACYT Grant A1-S-7540
DGAPA Grant IG200521

Title: Amyloid beta and tau pathology induced alterations on spatial memory and hippocampal physiology can be reversed by a microtubule stabilizer

Authors: *A. A. ROBLES-GÓMEZ, F. PEÑA-ORTEGA;
Inst. de Neurobiología, Inst. de Neurobiología, Querétaro, Mexico

Abstract: Amyloid-β (Aβ) and abnormal tau protein are not just the principal Alzheimer disease (AD) markers, but also have been hypothesized to act synergically in most of the deficits in neuronal function and cognition related to this disease. However, the physiological mechanisms and consequences of Aβ-tau interactions are a matter of debate. Aberrant cytoskeletal dynamics are thought to be a principal factor for the pathological actions of both peptides. Therefore, it has been suggested that microtubule stabilizing agents (MSAs) could be used to counteract the effects of each peptide or the pathological conditions induced by their combination. Here, we analyzed the spatial memory with the Hebb-Williams maze (H-WM) and the intrinsic and synaptic properties of CA1 pyramidal neurons (CA1-PN) with whole-cell recordings of WT and rTg4510 mice in the presence or absence of Aβ and a MSA (epothilone D). Both, Aβ and tau impaired retrieval in the H-WM but produced divergent effects on CA1-PN excitability (hypoexcitability and hyperexcitability, respectively). When Aβ and abnormal tau were combined, there was a net increase in hippocampal excitability without worsening of the retrieval deficit. Interestingly, epothilone-D prevented the alterations induced by both peptides. However, it produced minor changes in learning and hippocampal excitability by itself. Overall, Aβ and hyperphosphorylated tau produce divergent effects on intrinsic and synaptic properties that are, nevertheless, associated with memory retrieval deficits. Moreover, we showed that despite MSAs can prevent the deleterious effects of Aβ and tau, which further supports its use to treat AD, it must be acknowledged that they can produce negative effects on behavior and brain function, highlighting the need for more research of their potential clinical use.

Disclosures: A.A. Robles-Gómez: None. **F. Peña-Ortega:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Wenner Gren Stiftelserna
O. E. och Edla Johanssons vetenskapliga stiftelse
Gun och Bertil Stohnes stiftelse
Alzheimers Fonden

Title: Early CA3-CA1 synapse mistuning in APP^{NL-F}mice model of Alzheimer's disease.

Authors: *B. PORTAL, M. LINDSKOG;
Uppsala Univ., Uppsala Univ., Uppsala, Sweden

Abstract: Amyloid-beta (Aβ) depositions and neurofibrillary tangles are hallmarks for Alzheimer's disease (AD) and have been associated with memory loss. Despite hundred years of research, there are today no treatments for this neurodegenerative disorder. Well described in the late phases, early stages of AD remain yet to be explored, although changes in synaptic transmission and plasticity has been reported before plaques and tangles are detectable. AIM: This study is using a APP knock-in (APP^{NL-F}) mice model of AD, carrying two disease-causing mutations, to investigate synaptic impairement at an early stage of the disease. METHODS: Acute hippocampal slices of six-months old mice were used for electrophysiological recordings. Field recordings in the CA1 area after Schaffer collateral stimulations was used to investigate synaptic plasticity and patch-clamp recordings of pyramidal cells in the CA1 area to study synaptic transmission. Western-blot and immunohistochemistry were used to understand molecular changes. RESULTS: Six-months old APP^{NL-F} mice display an overall synaptic mistuning in the hippocampus, compared to wild-type controls. The frequency of spontaneous miniature synaptic potentials (mEPSP) was significantly reduced, with no change in amplitude of the events. Moreover, the threshold for long term potentiation (LTP) was reduced: a LTP inducing protocol that was sub-thresholded in slices from wild-type mice could still evoke LTP in slices from APP^{NL-F} mice. In line with synaptic mistuning, APP^{NL-F} mice had increased levels of NMDA receptors and ERK in the hippocampus, compared to wild-type. Interestingly, preliminary data show that ketamine 5mg/kg i.p delivered 24h prior recording, restores part of the synaptic activity and reduces the long term potentiation. CONCLUSION: In this study, we show a synaptic mistuning at early stages of the AD pathology, associated with an increase in NMDA receptors and the intracellular signaling protein ERK. Both of these proteins are well known to be important for synaptic tuning and plasticity. Interestingly, such mistuning is partly corrected by non anesthetic low-dose of ketamine administered 24h prior recording. However, further studies are required to better understand behavioral consequences the observed neuronal impairments and the consequences of the ketamine treatment.

Disclosures: B. Portal: None. **M. Lindskog:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH 3HL059658-17S1

Title: Sex-differences in sleep phenotype severity in mouse knock-in models of familial Alzheimer's disease

Authors: *R. TISDALE[1], S. MILLER[2], J. HEU[1], T. SAITO[3], T. C. SAIDO[4], D. XIA[5], P. E. SANCHEZ[5], J. J. PALOP[2], T. S. KILDUFF[1];
[1]SRI Intl., SRI Intl., Menlo Park, CA; [2]Gladstone Insititute of Neurolog. Dis., San Francisco, CA; [3]Dept. of Neurocognitive Sci., Nagoya City Univ. Grad. Sch. of Med. Sci., Nagoya, Japan; [4]Lab. of Proteolytic Neurosci., RIKEN Ctr. for Brain Sci., Wako-shi, Japan; [5]Denali Therapeutics, Inc., South San Francisco, CA

Abstract: Poor sleep quality and reduced sleep duration are associated with Alzheimer's disease (AD)-related β-amyloid (Aβ) pathologies. Clinically, women exhibit faster rates of brain atrophy and more rapid cognitive decline in AD than males, although clinical biomarkers of amyloid pathologies appear similar between sexes. To better understand how Aβ contribute to AD-related sleep symptomatology, we studied electrophysiologically-defined sleep in male (M) and female (F) *App*^{SAA} (5M/5F; 19.4±0.16 months), *App*$^{NL-G-F}$ (5M/3F; 20.7±0.63 months) and their wildtype (WT) age-matched littermates controls (WT^{SAA}: 3M/3F; 19.0±0.34 months; WT^{NL-G-F}: 4M/3F; 20.0±0.68 months). *App*^{SAA} and *App*$^{NL-G-F}$ knock-in (KI) mouse strains express humanized Aβ and familial AD mutations in the murine *App* gene. In comparison to their wildtype (WT) age-matched littermates , KI mice from both strains exhibited significantly more wakefulness (*App*^{SAA}: $F_{(1,336)}$=7.79; p=0.006; *App*$^{NL-G-F}$: $F_{(1,312)}$=26.22; p<0.001) and activity (*App*^{SAA}: $F_{(1,336)}$=4.64; p=0.032; *App*$^{NL-G-F}$: $F_{(1,312)}$=50.76; p<0.001), particularly during the dark phase, an effect that was more pronounced in females than males. KI mice exhibited longer wake bouts (*App*^{SAA}: $F_{(1,336)}$=23.43; p<0.001; *App*$^{NL-G-F}$: $F_{(1,312)}$=34.23; p<0.001) and fewer episodes of wake (*App*^{SAA}: $F_{(1,336)}$=8.81; p=0.003; *App*$^{NL-G-F}$: $F_{(1,312)}$=119.8; p<0.001), NREM (*App*^{SAA}: $F_{(1,336)}$=12.41; p<0.001; *App*$^{NL-G-F}$: $F_{(1,312)}$=124.9; p<0.001) and REM sleep (*App*^{SAA}: $F_{(1,336)}$=12.41; p<0.001; *App*$^{NL-G-F}$: $F_{(1,312)}$=33.2; p<0.001), indicating a disturbed sleep architecture due to the impaired ability to exhibit normal state transitions. Female KI mice exhibited a more pronounced phenotype in all measures; condition effects in the *App*^{SAA} strain were mostly driven by females, as sleep architecture in males was distinguishable from WT littermates only by fewer REM bouts ($F_{(1,336)}$=26.66; p<0.001). In response to a 6-h sleep deprivation, *App*$^{NL-G-F}$ mice exhibited a sleep rebound comparable to WT littermates. While sleep homeostatic function thus appears to be intact in *App*$^{NL-G-F}$ mice, both KI strains exhibit a decreased need for sleep, largely foregoing sleep during the dark phase, while not increasing sleep amount or sleep bout duration during the light period. Our results indicate females may display a more pronounced Aβ-related sleep phenotype, suggesting sleep as a clinical biomarker that could be assessed for sex differences.Acknowledgements: Research supported by NIH 3HL059658-17S1.

Disclosures: **R. Tisdale:** None. **S. Miller:** None. **J. Heu:** None. **T. Saito:** None. **T.C. Saido:** None. **D. Xia:** None. **P.E. Sanchez:** None. **J.J. Palop:** None. **T.S. Kilduff:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01 AG064066
BrightFocus Foundation Grant A2019382F

Title: Investigation of neuronal hyperactivity and stability of spatial coding in aged App $^{NL\text{-}G\text{-}F}$ mice

Authors: *G. A. RODRIGUEZ[1], E. F. ROTHENBERG[1], S. V. VAJRAM[1], S. A. HUSSAINI[1,2];
[1]Taub Inst. for Res. on Alzheimer's Dis. and the Aging Brain, [2]Dept. of Pathology and Cell Biol., Columbia Univ. Med. Ctr., New York, NY

Abstract: The progressive accumulation of amyloid beta (Aβ) pathology in the brain has been associated with aberrant neuronal network activity and poor cognitive performance in preclinical mouse models of Alzheimer's disease. Here, we assessed the impact of advanced Aβ pathology on the stability of spatial coding in the medial entorhinal cortex (MEC) upon short- and long-term exposures to a familiar environment, and the dynamic ability of MEC ensembles to initiate spatial coding in a novel context. Single-unit recordings were collected in the MEC of 18-month *App* $^{NL\text{-}G\text{-}F}$ mice and age-matched C57BL/6J controls as they explored contextually novel and familiar open field arenas. Recording sequences consisted of 'recording blocks' made up of four individual recording sessions spread over two consecutive days, with two recording sessions performed each day. The inter-session interval per day was ~4-6 hr and the time interval between days was ~16-18 hr. We did not find group differences in the average running speed or total distance traveled in our recording sessions, or in the percentage of open field coverage, suggesting that there was no effect of APP genotype on motivated foraging behavior in our paradigm. To determine the general activity state of MEC neurons in 18-month mice, we examined the average firing rates of ~600 single-units collected across Session 1 recordings taken from several recording blocks (*App* $^{NL\text{-}G\text{-}F}$, n=329 single-units; n=4 mice; Control, n=293 single-units; n=5 mice). Initial analysis showed a significantly higher proportion of hyperactive MEC neurons in *App* $^{NL\text{-}G\text{-}F}$ mice (~30%) versus Control mice (~15%), and again when cells were divided into Narrow Spiking and Wide Spiking neuronal populations (*App* $^{NL\text{-}G\text{-}F}$ vs Control: NS, 39% vs 27%; WS, 26% vs 10%). To determine if hyperactive neurons contribute to spatial coding and stability in novel and familiar contexts, we first identified spatially modulated cell types (*e.g.*, grid, head direction, border, *etc.*) in our mice and examined their firing rates and spatial tuning properties across recording sessions. We found evidence for strong, stable head-

directional tuning in both 18-month *App* $^{NL-G-F}$ mice and Control mice. In contrast, impaired spatial periodicity in grid cells featured predominantly in *App* $^{NL-G-F}$ mice versus Controls, supporting a previous investigation in younger *App* $^{NL-G-F}$ mice. Border cells were also found to be impaired in 18-month *App* $^{NL-G-F}$ mice. Characterization of neuronal activity patterns for spatial cells and non-spatial cells across sessions is ongoing, with the goal of identifying how hyperactive neurons contribute to functional or dysfunctional encoding of spatial representations.

Disclosures: G.A. Rodriguez: None. **E.F. Rothenberg:** None. **S.V. Vajram:** None. **S.A. Hussaini:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSF 1944247
2018-AARGD-591014

Title: Comparing aggregate effects of interacting Alzheimer's Disease transgenic mouse etiologies on cognitive function

Authors: *C. HEARD[1], B. NELSON[2], A. SINGH[1], V. MURTHY[1], C. S. MITCHELL[1];
[1]Georgia Inst. of Technol., [2]Georgia Inst. of Technol., Atlanta, GA

Abstract: The heterogeneity among study results makes it difficult to assess and compare effects of various Alzheimer's Disease (AD) etiologies in transgenic mice. Discerning these aggregate effect sizes is pivotal for prioritizing future etiological and therapeutic research. This study aggregates data across experimental AD transgenic mouse model studies examining varying AD-related etiologies to estimate the effect size of each experimental etiology on mouse cognitive function as measured via normalized Morris Water Maze (MWM) escape latency. Etiologies assessed include amyloid beta accumulation and amyloid ratio (40/42); beta-secretase (BACE), an enzyme that cleaves the amyloid precursor protein APP; apolipoprotein E (APOE, including APOE 2, 3, 4, and APOE knock-out), which is known to increase risk of clinical AD; and tauopathy, especially phosphorylated tau (p-tau). Statistical analysis was performed on a curated experimental database of over 3,000 Alzheimer's mouse model peer-reviewed articles. Normalized escape latency of Morris Water Maze was measured across studies using pooled sample size and standard deviation. Mean escape latency was divided into groups as a function of mouse etiology type (amyloid beta, BACE, tau, APOE) and modulatory treatment type (no external treatment; treatment to increase impact of etiology; treatment meant to decrease impact of the etiology). Statistical analysis with ANOVA was performed followed by hypothesis testing with Bonferroni correction for multiple comparisons (family-wise alpha = 0.05). Machine learning models were used to assess relative feature weights of each etiology as a secondary

validation. Results illustrated significant differences between AD etiologies and/or their interactions that can be exploited to prioritize future preclinical and clinical AD research. In particular, non-amyloid etiologies illustrate a greater impact on cognition as measured via MWM. Given most amyloid accumulation appears prior to functional onset of symptoms in clinical AD, leveraging effects of other etiologies or their interaction with amyloid beta provide a promising avenue for therapeutics aimed at prolonging cognitive function.

Disclosures: C. Heard: None. **B. Nelson:** None. **A. Singh:** None. **V. Murthy:** None. **C.S. Mitchell:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MR/N013867/1
R01 R01AG050425
R01 R01AG064066

Title: Investigating high-frequency oscillations in the EC-Tau/hAPP mouse model of Alzheimer's disease and human APOE-targeted replacement mice apoε3 and apoε4

Authors: *A. L. PETRACHE, S. A. HUSSAINI;
Columbia Univ., New York, NY

Abstract: Alzheimer's disease (AD) is characterised by accumulation of amyloid beta and tau pathology in the entorhinal cortex and the hippocampus leading to progressive decline in cognitive function. Specifically, the lateral entorhinal cortex (LEC) is known to be one of the earliest regions to be affected by this pathology. To identify the earliest changes in the LEC, we recorded network activity from its neurons. Brain waves that occur with a frequency over 80 Hz are termed high-frequency oscillations (HFOs). Ripples (80Hz-250Hz) are implicated in memory formation, and fast ripples (250Hz-500Hz) are pathological and implicated in epileptogenic activity. The aim was to identify whether mice exhibiting genes linked with a high genetic risk factor of AD or that modelled AD pathology showed a changed HFO pattern compared to age-matched wild-type C57BL/6 control mice, specifically, whether they exhibited more fast ripples. As the AD mouse model is expected to present with reduced cognitive capacity and as ripples are important for memory consolidation and negatively impacted in AD, we hypothesised that recordings from the AD model will show fewer ripples and indeed a larger number of fast, pathological, ripples.The following four genotypes were utilised: human APOE-targeted replacement mice *apoε3* and *apoε4*, AD mouse model EC-Tau/hAP, which models amyloid-β and tau, and age-matched C57BL/6 controls. All were males with a mean age of 20 months. Recordings ranging between 600s and 1000s were performed in the LEC at a depth of between

3.1 and 3.3 mm, and the number of EoIs normalised by the recording length. A minimum of 3 in-vivo recordings were performed in the awake mice while freely exploring an open arena, with minimum 4 animals for each of the four groups. To visualise and analyse HFOs, we utilised a python-based interface termed “High Frequency Oscillations Graphic User Interface” (hfoGUI), based on Stockwell’s transformation. Data analysis was performed blind.A minimum of 20 recordings were randomly chosen and checked at random points in the recording to see whether the algorithm was identifying events correctly. In all verified cases the interface was correct.Early data visualisation and analysis via hfoGUI and GraphPad Prism suggests an increase in the number of fast ripples in the EC-Tau/hAPP mice compared to age-matched wild-type mice. The data set is already being scaled up and although the results are preliminary, the work is important as it can inform our knowledge of abnormal brain wave patterns in AD. Detecting these changes could inform cognitive decline detection in AD animal models and potentially play a role in informing future diagnosis techniques in AD patients.

Disclosures: **A.L. Petrache:** None. **S.A. Hussaini:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.17

Topic: C.02. Alzheimer’s Disease and Other Dementias

Support: NIA R01-AG057767
NIA R01-AG061937
NIA R21-AG062985
1-19-IBS-126

Title: Effects of prolonged oral senolytic drug treatments on APP/PS1 mice

Authors: ***Y. FANG**[1], D. MEDINA[2], K. QUINN[1], M. R. PECK[1], R. STOCKWELL[2], S. MCFADDEN[1], A. BARTKE[2], K. N. HASCUP[1], E. R. HASCUP[1];
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Abstract: The accumulation of senescent cells was causally linked with cognition-associated neuronal loss. Genetic or pharmacological deletion of senescent cells in the mouse brain led to functional improvements in tau transgenic mouse models of Alzheimer’s disease (AD). We have previously shown that oral administration of senolytic drugs have sex-dependent effects on cognitive performance in normal aging C57BL/6 mice. However, the effects of the prolonged oral senolytic treatment in young double-mutant transgenic APP/PS1 mice, an amyloid-based mouse model of AD, is unknown. To study the effects of prolonged senolytic drug treatments, Fisetin (100 mg/kg BW), or Dasatinib (5 mg/kg BW) plus Quercetin (50 mg/kg BW) (D+Q) or vehicle control were orally administered to APP/PS1 male and female mice starting at 4 months of age. The treatments were carried out once/month for 8 months. The results revealed that

prolonged oral Fisetin affected insulin sensitivity measured by insulin tolerance test (ITT) in APP/PS1 mice in a sex-dependent pattern. Fisetin treatments significantly improved insulin sensitivity in male APP/PS1 mice, while insulin sensitivity was impaired in female mice. Fisetin did not affect body composition, energy metabolism (indirect calorimetry), or cognitive function (Morris water maze; MWM). The response of APP/PS1 mice to prolonged oral D+Q treatment also showed sexually dimorphic effects. In female APP/PS1 mice, D+Q treatments reduced white adipose tissues (WAT) including subcutaneous, gonadal and perirenal fat depots, and elevated fasting glucose levels without significant change in energy metabolism or cognitive function. In male APP/PS1 mice, D+Q treatments led to decreased interscapular brown adipose tissue (BAT) and gonadal fat depot without significant effects on energy metabolism. Surprisingly, prolonged oral D+Q treatments in male APP/PS1 increased the area under the curve for cumulative distance and corrected integrated path length (CIPL) from platform during 5-day training in MWM. Decreased platform entry during the probe challenge support long-term impaired spatial memory. In summary, Fisetin affected glucose metabolism in a sex-dependent pattern. D+Q also showed sexually dimorphic changes of fat depots and cognitive functions measured by MWM, in which D+Q treatments impaired spatial memory in male APP/PS1 mice.

Disclosures: **Y. Fang:** None. **D. Medina:** None. **K. Quinn:** None. **M.R. Peck:** None. **R. Stockwell:** None. **S. McFadden:** None. **A. Bartke:** None. **K.N. Hascup:** None. **E.R. Hascup:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association Grant 2016-NIRG-369-583

Title: The impact of tau humanization on gene expression, AD-like pathology, synaptic function and cognitive performance in AD mice

Authors: *H. CYNIS[1], S. BARENDRECHT[1], A. SCHREURS[2], S. GEISSLER[1], V. ILSE[1], V. SABANOV[2], S. WUSSOW[1], R. PANDEY[3], G. W. CARTER[3], M. HOLZER[4], S. ROSSNER[4], S. SCHILLING[1], C. PREUSS[3], D. BALSCHUN[2];
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Abstract: Modeling Alzheimer's disease (AD) in mice has been critical for understanding the contribution of genes and mechanisms involved in disease development. Thereby, hyperphosphorylation and intraneuronal aggregation of the microtubule-associated protein tau is a major pathological hallmark of AD. The second principle finding in AD brain is amyloid-beta (Abeta), which is extracellularly deposited in plaques. Although abnormal deposition of both

proteins is found in AD brain, their relation is not well understood. Therefore, we have generated and characterized a novel human tau knock-in (htau-KI) mouse model and cross-bred them with 5xFAD mice to study the effect of cerebral amyloid-beta deposition on human tau pathology. We studied 5xFADxhtau-KI mice in terms of correlation of gene expression data with human brain regions, development of Alzheimer's-like pathology, synaptic transmission and behavior. Our main findings are antagonistic effects of human beta-amyloid and human tau in 5xFADxhtau-KI observed at transcriptional level and corroborated by electrophysiology and histopathology. The comparison of gene expression data of the 5xFADxhtau-KI mouse model to 5xFAD, control mice and to human AD patients revealed changes in pathways related to mitochondria biology, extracellular matrix- and immune function. These changes were accompanied by plaque-associated MC1-positive pathological tau that required the htau-KI background. LTP deficits were noted in 5xFAD and htau-KI mice in contrast to signs of rescue in 5xFADxhtau-KI mice. Increased frequencies of miniature EPSCs and miniature IPSCs indicated an upregulated presynaptic function in 5xFADxhtau-KI. Finally, we characterized these mice in terms of spatial learning using Morris Water Maze and exploratory and anxiety-like behavior using the Elevated Plus Maze. There, we found in 12 months old mice differences in exploratory and anxiety-like behavior and a better spatial learning ability in tau-KI and 5xFADxtau-KI compared to 5xFAD mice. In conclusion, the replacement of mouse tau by human tau causes a variety of pathological findings under progressive amyloidosis. Probing further into these pathological circuits is expected to provide new insights into the tau and Abeta interplay during AD development.

Disclosures: H. Cynis: None. **S. Barendrecht:** None. **A. Schreurs:** None. **S. Geissler:** None. **V. Ilse:** None. **V. Sabanov:** None. **S. Wussow:** None. **R. Pandey:** None. **G.W. Carter:** None. **M. Holzer:** None. **S. Rossner:** None. **S. Schilling:** None. **C. Preuss:** None. **D. Balschun:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.19

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AMED 21dm0207073h003

Title: Detection of seed-competent, high-molecular-weight Abetaoligomers in the cerebrovasculature in Alzheimer's disease

Authors: *T. HASHIMOTO[1], H. UCHIGAMI[1,2,3], M. KASHIWAGI-HAKOZAKI[2], T. MATSUBARA[4], S. MURAYAMA[4], Y. SAITO[4], T. TODA[3], T. IWATSUBO[2];
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Abstract: Mounting evidence suggests that the deposition and spreading of amyloid beta peptide (Abeta) in the brain is an early and central event in the pathogenesis of Alzheimer's disease (AD). We found that high-molecular-weight (~200-300 kDa, HMW), Tris-buffered saline (TBS)-soluble Abeta oligomers derived from brains of Abeta-laden APP transgenic (Tg) mice or AD patients have a potency to induce beta-amyloidosis in the brains of APP Tg mice; however, it is still unclear how the HMW Abeta oligomers spread throughout the brain and induce beta-amyloidosis. Recently, circulation and clearance of Abeta along the perivascular space via the perivascular drainage pathway has been revealed, and raised the possibility that the HMW Abeta oligomers may also extend in the brain through the perivascular route. Here, we first found that the HMW Abeta oligomers were detected in the TBS-soluble fraction of the meninges isolated from the brains of AD patients. To examine whether the meningeal HMW Abeta oligomers are capable of inducing beta-amyloidosis *in vivo*, we inoculated the meningeal HMW Abeta oligomers into the hippocampus of plaque-free APP Tg mice. After four months, we found that the meningeal HMW Abeta oligomers induced a robust Abeta deposition in the hippocampus, suggesting that the HMW Abeta oligomers derived from meninges of AD patients are seed-competent Abeta species. We next examined whether cerebral amyloid angiopathy (CAA) impacts the HMW Abeta oligomers in the brain. We extracted TBS-soluble fractions from the brains of six CAA-rich AD cases and five CAA-minimal AD cases, and purified the HMW Abeta oligomers by size-exclusion chromatography. We found that the levels of the HMW Abeta oligomers in the brains of CAA-rich AD cases were higher than those of CAA-minimal AD cases, whereas the levels of SDS-insoluble and formic-acid-soluble Abeta species were comparable between CAA-rich and minimal AD cases, suggesting that the seed-competent HMW Abeta oligomers may accumulate in the CAA in the brains of AD patients. These observations indicate that CAA may play a role as a reservoir of Abeta seeds for beta-amyloidosis in the AD brains.

Disclosures: T. Hashimoto: None. **H. Uchigami:** None. **M. Kashiwagi-Hakozaki:** None. **T. Matsubara:** None. **S. Murayama:** None. **Y. Saito:** None. **T. Toda:** None. **T. Iwatsubo:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.20

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R61NS115161

Title: Generation and characterization of a mouse model for Mixed Etiology Dementia

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Abstract: Alzheimer's disease (AD)-Related Dementias is a group of progressive neurodegenerative disorders with mid to late life onset, including Lewy body dementia, frontotemporal dementia (FTD) or mixed etiology dementia (MED) such as AD exhibiting TDP-43 pathology. In efforts to clarify disease mechanisms and identifying therapeutic targets for this challenging disorder, a critical need is the availability of new multi-dimensional mouse models that replicate combinations of co-occurring pathological features of human dementias. Recent studies indicate that TDP-43 proteinopathy, initially associated with amyotrophic lateral sclerosis and FTD, is also found in 30-60% of AD cases and correlates with worsened neurodegeneration and cognitive functions. How TDP-43 pathology contributes to neuron loss and cognitive deficits remains elusive. Our previous work supporting the view that loss of TDP-43 splicing repression of cryptic exons underlies neurodegeneration lead us to hypothesize that in MED, loss of such TDP-43 function exacerbates AD pathologies and/or neuron loss. To address this question, we generated a mouse model for MED (*APPswe/PS1ΔE9;Tau4R;CaMKIIα^{ER};TDP-43$^{F/F}$*) by a crossbreeding strategy with our previously characterized inducible model lacking TDP-43 in forebrain neurons (*CaMKIIα^{ER};TDP-43$^{F/F}$*) and inducible tau (*Tau4R*) and β-amyloidosis (*APPswe/PS1ΔE9*) mouse models. To test the influence of TDP-43 on tauopathy-dependent neurodegeneration, we deleted TDP-43 temporally in excitatory hippocampal neurons by oral administration of tamoxifen citrate for 4 weeks in 6 month-old "MED" mice as well as *CaMKIIα^{ER};TDP-43$^{F/F}$* and *APPswe/PS1ΔE9;Tau4R* control littermates and these mice were subsequently sacrificed and analyzed at 14-month of age. As expected for *CaMKIIα^{ER};TDP-43$^{F/F}$*, we observed selective vulnerability of CA3/2 neurons. However, such vulnerability is exacerbated in the MED model. Surprisingly, we also found a marked loss of granule neurons in the dentate gyrus of MED mice but not age-matched control littermates. Further characterization molecularly and pathologically of this MED model will be presented. To date, these intriguing observations are consistent with the idea that loss of TDP-43 function accelerates tauopathy-dependent neuron loss in AD exhibiting TDP-43 pathology and this novel mouse model hold promise as a faithful mimic for this type of MED.

Disclosures: M.S. Baghel: None. **T. Li:** None. **P.C. Wong:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.21

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RF1AG072727
NIH RF1AG069378
NIH R01AG048993
NIH P20GM113123
NIH U54GM128729

Title: Alzheimers disease-related APP mutations alter colitis-associated colon cancer in a sex-selective fashion

Authors: *T. ISHIDA-TAKAKU, M. SOHRABI, S. CHANDRASEKARAN, C. K. COMBS; Dept. of Biomed. Sci., Univ. of North Dakota Sch. of Med. and Hlth. Sci., Grand Forks, ND

Abstract: Cancer and Alzheimer's disease (AD) are common age-associated diseases and leading causes of death in the United States. Multiple epidemiologic studies have shown inverse associations between cancer and AD. However, the molecular mechanisms underlying this negative correlation are largely unknown. In both cancer and AD, sex differences are thought to be potential causes of disease heterogeneity. Two-thirds of AD patients in the US are women. In contrast, the incidence and mortality rates of some cancers, such as colorectal cancer, are higher in males. Several studies have reported elevated levels of amyloid precursor protein (APP) or its N-terminal fragment, sAPP, in cancers supporting the idea that a mechanistic relationship may exist between APP biology and cancer progression. In this study, we attempted to recapitulate the inverse relationship between AD and cancer using a mutant APP amyloidosis line with an azoxymethane (AOM)/dextran sodium sulfate (DSS) colitis-associated colon cancer model to contrast the progression of both diseases. We compared male and female C57BL/6 wild type, App^{NL-G-F}, and $App^{-/-}$ mice treated with or without an IP injection of AOM and 1 week of oral DSS followed by recovery for a total time of 17 weeks. Immunohistochemistry demonstrated APP expression in normal and cancerous epithelium as well as enteric neurons in the colons of wild type and App^{NL-G-F} mice. Immunoreactivities for β-secretase (BACE1) and Aβ peptide were also observed in normal and cancerous epithelium of App^{NL-G-F} mice, suggesting that APP processing occurs in these cells. The mortality rate of $App^{-/-}$ male mice was dramatically increased by AOM/DSS-induced colon cancer compared to the other lines. This increased mortality rate was not obvious in the female $App^{-/-}$ mice. Despite the mortality differences, there were no significant differences in tumor number or area in $App^{-/-}$ male mice compared to wild types. However, male App^{NL-G-F} mice demonstrated a significant increase in tumor number and area compared to wild type mice. In contrast, female App^{NL-G-F} mice demonstrated nearly complete protection from colon cancer with significantly reduced tumor number and area compared to wild type controls. These data support a sex-selective relationship between AD and colon cancer, with AD-associated APP mutations potentiating and attenuating cancer in males and females, respectively.

Disclosures: T. Ishida-Takaku: None. **M. Sohrabi:** None. **S. Chandrasekaran:** None. **C.K. Combs:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.22

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Advantageous role of BDNF in reducing Aβ in 3D culture model of Alzheimer's disease

Authors: *G. BAKIASI, M. PANIER, B. GONG, R. E. TANZI, S. CHOI;
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Abstract: Alzheimer's disease (AD) is an irreversible, progressive neurological disorder characterized by memory loss and cognitive disturbance. Two pathological hallmarks of AD are amyloid plaque and neurofibrillary tangle. Amyloid plaques are primarily composed of amyloid-β (Aβ) which is derived from the amyloid precursor protein (APP) via serial cleavage of β- and γ-secretase. Neurofibrillary tangles are composed of filamentous accumulations of aggregated hyperphosphorylated tau (pTau). Brain-derived neurotrophic factor (BDNF) is a member of the nerve growth factor family and has been the focus of intense interest in AD research. Current literature shows that BDNF has an important role in modulating cognitive function as well as synaptic and neuronal dysfunction. Yet, the direct roles of BDNF on Aβ and tau pathologies are unknown or inconclusive.We previously developed a three-dimensional (3D) "human" neural cell culture model of AD which displays robust Aβ deposits and tauopathy (referred as 3D cultures; *Choi et al.,* Nature 2014). Here, we found that BDNF treatment significantly reduced the levels of Aβ40 and Aβ42 as well as Aβ42/Aβ40 ratio in the conditioned media of 3D cultures that harbor APP Swedish/London mutations. BDNF also reduced the levels of APP C-terminal fragment α and β (APP-CTFα and APP-CTFβ, respectively). This insight to the mechanism of beneficial role of BDNF can impact the use of BDNF in clinical settings, thus, further mechanism study is warranted

Disclosures: G. Bakiasi: None. **M. Panier:** None. **B. Gong:** None. **R.E. Tanzi:** None. **S. Choi:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.23

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 NS086965
NIH R01 NS085171

Title: Secreted frizzled-related protein 3 (sFRP3) mediates seizure-induced impairment in spatial discrimination in an Alzheimer's disease transgenic mouse model

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Abstract: Alzheimer's disease (AD) is associated with hippocampal dysfunction, and one contributing factor may be the dysregulation of adult hippocampal neurogenesis. Neurogenesis in the adult dentate gyrus (DG) is important for cognition and mood, both of which are affected in AD. Using an amyloid precursor protein (APP) transgenic mouse model, we previously showed that the spontaneous seizure activity that develops in APP mice aberrantly increases the proliferation, and consequently accelerates the depletion, of a finite pool of neural stem cells (NSCs) in the DG. APP mice also exhibited impaired spatial discrimination, a behavior that relies on adult-born neurons. These alterations were prevented by treatment with an anti-seizure drug. However, the exact molecular mechanisms that drive seizure-induced activation and depletion of NSCs is unclear. Here, we used RNA-sequencing to look for regulators of neurogenesis that are differentially expressed between the DGs of APP mice and their nontransgenic (NTG) littermates. We focused on the Wnt signaling pathway, which is critically involved in neurogenesis in both development and adulthood. Surprisingly, few Wnt components were differentially expressed, of which secreted frizzled-related protein 3 (sFRP3) stood out. sFRP3 is an inhibitor of the Wnt signaling pathway, and thus acts as a "brake" on neurogenesis. We found decreased sFRP3 expression in APP mice that was restored after treatment with an anti-seizure drug, suggesting that seizures suppress sFRP3 expression in APP mice. In addition, we found that sFRP3 may be epigenetically regulated by seizure-induced transcription factors. We hypothesized that seizure activity in APP mice recruits such transcription factors to suppress sFRP3 expression, thus accelerating the use and depletion of the NSCs and impairing spatial discrimination. To test this hypothesis, we designed an adeno-associated virus (AAV) to express sFRP3 in DGCs of APP and NTG mice. We found that long-term viral-mediated expression of sFRP3 improved spatial discrimination in APP mice. Our results suggest that sFRP3 may mediate seizure-driven impairment in cognition, in APP mice and perhaps also in AD.

Disclosures: C. Fu: None. **J. Park:** None. **U. Tosi:** None. **X. Zhang:** None. **Y. Zheng:** None. **J. Chin:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.24

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Weston Brain Institute (TR192003, C.L.W., D.J.V., B.A.K.)
Canada Research Chait (B.A.K)

Title: Investigating sleep disturbance induced by repetitive concussion using a closed-head TBI method in APP knock-in mouse models

Authors: *J. YUE[1], M. L. KELLY[2], T. YILDIRIM[2], S. SAW[2], W. H. CHENG[3], D. J. VOCADLO[1], C. L. WELLINGTON[3], B. A. KENT[2];

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Abstract: Sleep disturbance is a common symptom of mild traumatic brain injury (mTBI) associated with a higher risk of cognitive decline and accumulation of the peptide beta-amyloid (Aβ), which is a pathogenic driver of Alzheimer's disease (AD). The APP/PS1 mouse strain, overexpressing amyloid precursor protein (APP) mutant, has been widely used to model AD pathology due to elevated $A\beta_{42}$ peptide deposition in the brain, yet its heavily overexpressed APP and correlated physiological artifacts suggest deviation from an accurate recapitulation of human AD. A recent AD model, the APP^{NL-F} strain, carrying the knock-in APP mutant, expresses elevated $A\beta_{42}$ peptides and progressive cognitive decline with no major artifacts, hence stimulating our interest in testing its utility for concussion research. Previously, several transgenic APP mice models were characterized with changes in brain activity frequencies across various sleep stages relative to wild type littermates using electroencephalography (EEG) analysis. Using a similar approach, in this study we sought to evaluate the effects of repetitive concussion on sleep one-month post-injury, and compare Aβ accumulation between APP^{NL-F} and APP/PS1 mouse models. Immediately following each concussion using a closed-head impact model of engineered rotational acceleration (CHIMERA) TBI method, both male and female APP^{NL-F} mice (n = 4-6) demonstrate physiological injury responses by extended duration of loss of righting reflex (sham = 74 sec vs TBI = 386 sec; p = 0.0031) and temporary acute pain scores (from severe to mild or no pain: sham < 5 min vs TBI = 65 min). However, one-month post-TBI EEG analysis reveals no significant change in the duration of sleep. Power spectra analysis also does not show significant changes in dominating frequencies across sleep stages. Immunohistochemistry will be used to quantify deposition of Aβ in the hypothalamus, hippocampus and cortex. Current results echo those published in other CHIMERA TBI studies where neuroinflammatory markers return to basal levels one-month after mild-TBI prior to chronic upregulation. We, therefore, strive to optimize the TBI paradigm and choice of AD mouse strain to be used in future TBI studies. Our ultimate goal is to study the fundamental connection between AD and sleep loss following concussion in an AD mouse strain that models human disease.

Disclosures: J. Yue: None. **M.L. Kelly:** None. **T. Yildirim:** None. **S. Saw:** None. **W.H. Cheng:** None. **D.J. Vocadlo:** None. **C.L. Wellington:** None. **B.A. Kent:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.25

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BFU2017-82494-P
PID2020-115823-GB100

Margarita Salas Postdoctoral Research Fellow funded by European Union NextGenerationEU/PRTR.

Title: Spatial memory training reverses Aβ modulation of GirK channels in the hippocampus of transgenic $APP_{Sw,Ind}$ Alzheimer's disease mice model

Authors: L. JIMENEZ-DIAZ[1], S. TEMPRANO-CARAZO[1], A. CONTRERAS[1], C. A. SAURA[2], ***J. NAVARRO-LOPEZ**[1];
[1]Univ. of Castilla-La Mancha, Ciudad Real, Spain; [2]Univ. Autònoma de Barcelona, Bellaterra (Barcelona), Spain

Abstract: Alzheimer's disease (AD) is a dementia characterized by progressive memory decline and neurodegeneration by the accumulation of amyloid-β (Aβ) and the hyperphosphorylation of *tau*. The hippocampus, responsible for learning and memory processes, is one of the most susceptible brain areas to Aβ. Last findings point to an imbalance between excitatory and inhibitory neurotransmission as the initial impairment in early stages (Jeremic et al., 2021). The G-protein-gated inwardly rectifying potassium (GirK) channel decreases excitability and contributes to inhibitory neurotransmission. Therefore, it has been proposed as a potential target to restore excitatory/inhibitory balance in amyloidosis models. Indeed, GirK channel has been related to AD since its modulation could reverse LTP and memory deficits induces by Aβ (Sánchez-Rodríguez et al., 2017). Furthermore, it is well stablished that periodic cognitive training on a hippocampal-dependent memory task mitigates early AD memory deficits (Parra-Damas et al., 2014), although its effect on GirK channels remain unknown. Here, the effects of genotype, age and training in a hippocampal-dependent memory task on the protein expression of GirK subunits and modulators were studied using male $APP_{Sw/Ind}$ mice. Results showed that Aβ caused a reduction of GirK2 expression as well as an increase of GIRK-modulator SNX27 expression in 6-months-old transgenic mice. Additionally, there was a developmental effect, exhibiting a down-regulation of GirK2 and an up-regulation of Girk3 in older mice compared to young ones, regardless the genotype. Finally, training in a hippocampal-dependent memory task, such as the Morris Water Maze, restored GirK2 and SNX27 levels in 6-month-old $APP_{Sw/Ind}$ mice. Thus, the effect of Aβ on GirK2, a subunit essential for the proper inhibitory function of GirK channels, could partially account for the excitatory/inhibitory unbalance transmission found in AD models, and training in a cognitive hippocampal-dependent task reverses this effect and lessens early Aβ dependent-AD's deficits.
References 1. D. Jeremic, L. Jiménez-Díaz, J. D. Navarro-López, Past, present and future of therapeutic strategies against amyloid-β peptides in Alzheimer's disease: a systematic review. Ageing Res Rev 72, 101496 (2021). 2. I. Sánchez-Rodríguez et al., Activation of G-protein-gated inwardly rectifying potassium (Kir3/GirK) channels rescues hippocampal functions in a mouse model of early amyloid-β pathology. Sci Rep 7, 14658 (2017). 3. A. Parra-Damas et al., Crtc1 activates a transcriptional program deregulated at early Alzheimer's disease-related stages. J Neurosci 34, 5776-5787 (2014).

Disclosures: L. Jimenez-Diaz: None. **S. Temprano-Carazo:** None. **A. Contreras:** None. **C.A. Saura:** None. **J. Navarro-Lopez:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.26

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant NS085171 (JC)
NIH Grant AG065290 (JC)

Title: Gene expression pathways of resilience in a mouse model of Alzheimer's Disease

Authors: *C. ST. ROMAIN, C.-H. FU, T. PUNNEN, J. CHIN;
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Alzheimer's Disease (AD) is a heterogeneous disease, but all patients with AD exhibit the neuropathological hallmarks of disease including amyloid plaques and neurofibrillary tangles. However, not all individuals with neuropathology are cognitively impaired. Identification of factors underlying the resiliency of the latter group could reveal potential therapeutic targets for AD. To approach this question, we studied transgenic mice that express mutant human amyloid precursor protein (APP mice, Line J20), in which we found that ~30% of mice appear to be "resilient". Resilient APP mice produce amyloid β (Aβ) and develop plaques with the same time course as susceptible APP mice in this line. In addition, they develop spontaneous seizure activity with the same time course as susceptible APP mice; however, around 3 months of age, resilient APP mice stop having seizures and epileptiform activity and exhibit normal spatial memory. This resilience develops despite the mice having similar levels of Aβ and history of seizures comparable to susceptible APP littermates with progressively worsening memory and continued seizure activity. To investigate differences between resilient and susceptible APP mice, we examined an RNA-seq dataset generated using dentate gyrus samples from resilient APP mice, susceptible APP mice, and nontransgenic (NTG) littermate controls. We predicted that genes that were differentially expressed in resilient APP mice compared to susceptible or NTG mice might be candidate "resilience" genes. Of the genes we identified, we further investigated oxytocin receptor (Oxtr), which was decreased in the resilient group compared to both susceptible and NTG groups. Because Oxtr expression is typically decreased when oxytocin levels are high, we hypothesized that resilient mice might have higher levels of oxytocin. Using immunohistochemistry, we confirmed resilient mice exhibited higher numbers of oxytocin-expressing cells in hypothalamic areas. Moreover, susceptible APP mice with the lowest numbers of oxytocin-expressing cells exhibit the highest degree of ΔFosB expression, a seizure-induced transcription factor that negatively regulates spatial memory in APP mice. Notably, oxytocin is a neuromodulator with key roles in social behavior and maternal-bonding, and APP mice exhibit deficits in social interaction and maternal caretaking. In humans, social isolation is a risk factor for development of AD, whereas frequent social interaction can delay AD onset and help mitigate cognitive decline. Together, these findings suggest that oxytocin pathways could contribute to resilience-conferring gene expression programs in AD.

Disclosures: C. St. Romain: None. **C. Fu:** None. **T. Punnen:** None. **J. Chin:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.27

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 5T32NS041218

Title: Tyrosine kinase inhibition as a therapeutic strategy for Alzheimer's Disease

Authors: *M. STEVENSON[1], M. HEBRON[1], B. KALUVU[2], R. VARGHESE[3], C. WOLF[2], C. MOUSSA[1];
[1]Neurol., [2]Chem., [3]Biostatistics, Georgetown Univ., Washington DC, DC

Abstract: Alzheimer's Disease (AD) is a neurodegenerative disease of aging marked by extensive neuron death and subsequent cognitive decline. The main pathological hallmarks of AD are amyloid-beta plaques composed of improperly cleaved amyloid precursor protein (APP) and neurofibrillary tangles composed of hyperphosphorylated tau (pTau) filaments, which are believed to interact and result in subsequent neurodegeneration. While the exact cause of toxic protein accumulation is unclear, one observed feature of AD is impaired autophagy, the process by which a cell identifies unnecessary or unwanted components for degradation. However, whether neuronal autophagy is implicated in AD pathogenesis and the accumulation of amyloid-beta has yet to be described. Another feature of AD is extensive neuroinflammation, the process by which the brain responds to foreign pathogens or insults. It has been traditionally posited that microglia, immune cells of the central nervous system, are primarily responsible for promoting an inflammatory phenotype in AD. However, the role of mast cells, effector cells of the innate immune system, in promoting neuroinflammation in AD remains relatively unexplored. Our lab has previously demonstrated enzymes known as tyrosine kinases to be implicated in the regulation of both autophagy and neuroinflammation, identifying them as potential targets for therapeutic intervention for treating AD. Utilizing recently synthesized novel small molecule tyrosine kinase inhibitors, I have demonstrated that tyrosine kinase inhibition stimulates autophagic clearance of neurotoxic protein aggregates and mitigates microglial and mast cell-mediated neuroinflammation in animal models of AD to improve cognitive outcomes. I have also examined the outcomes of tyrosine kinase inhibition in human patients suffering from AD and correlated this with novel CSF biomarkers to better inform on signaling pathways affected by tyrosine kinase inhibition and whether these pathways may interact to contribute to disease pathology in AD.

Disclosures: **M. Stevenson:** None. **M. Hebron:** A. Employment/Salary (full or part-time):; Georgetown University Medical Center. **B. Kaluvu:** None. **R. Varghese:** A. Employment/Salary (full or part-time):; Georgetown University. **C. Wolf:** None. **C. Moussa:** 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.; Georgetown University Medical Center. F. Consulting Fees (e.g., advisory boards); KeifeRX LLC.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.28

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Proyectos de investigación en salud (PI19/01577)
SENC Travel Award
EU-LAC HEALTH 2020, 16/T010131

Title: Gene dosage determines behavioural phenotype in the 5xFAD mouse model of Alzheimer's disease: analysis of the contribution of brain insulin signalling and gut microbiota

Authors: *D. MEDINA-VERA[1], C. ROSELL-VALLE[2], E. ZAMBRANA-INFANTES[4], A. LÓPEZ-GAMBERO[1], J. NAVARRO[1], J. SUAREZ[4], P. RIVERA[2], F. PAVON[3], C. SANJUAN[5], F. RODRÍGUEZ DE FONSECA[2];
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Abstract: There are many hypotheses about the neuropathological origin of sporadic Alzheimer's disease (AD). The amyloid cascade hypothesis remains the most widely accepted by the scientific community, although the role of amyloid-β (Aβ) as the sole cause of neuropathological hallmarks of the non-inherited form of AD is questionable. Several lines of evidence show that integrated coordination of neuronal responses through the PI3K (phosphoinositide 3 kinase)/Akt pathway in the brain has a significant functional impact on key events that are negatively affected in AD. The 5xFAD mice are commonly used as AD animal models that co-overexpress human APP and PSEN1 transgenes with five AD-linked mutations. In the present study, we investigated whether D-Pinitol inositol, which acts as an insulin sensitizer, might affect central insulin resistance. Previous results showed that administration of D-Pinitol is capable of reducing the phosphorylation of Tau. Moreover, attention is paid to the effect of the genetic load, heterozygous (HTZ) versus homozygous (HZ) condition, on the behaviour, histology, metabolic physiology, and gut microbiota composition. To start addressing this issue, we studied the phenotype of HTZ and HZ mice of both sexes in two stages of the lifespan: 4-6 months (early onset of the disease) and 10-12 months of age (late onset of the disease). From 4-6 months of age, both HTZ and HZ 5xFAD mice exhibited hippocampal impairment caused by the accumulation of $A\beta_{40}$ and $A\beta_{42}$, increased neuroinflammatory markers, and an altered of PI3K-Akt pathway. However, only HZ mice showed cognitive impairment in the Y-maze test and the Morris water maze. In addition, dysregulation of insulin-linked metabolic pathways at the peripheral level was detected between HTZ and HZ mice. Taken

together, our results suggest that the Aβ aggregation may not be the only cause of the worsening of cognitive impairment, but other factors including the PI3K-Akt, insulin-linked metabolic pathways, and microbiota composition might be influencing the disease progression, allowing alternative disease-modifying interventions.

Disclosures: D. Medina-Vera: None. **C. Rosell-Valle:** None. **E. Zambrana-Infantes:** None. **A. López-Gambero:** None. **J. Navarro:** None. **J. Suarez:** None. **P. Rivera:** None. **F. Pavon:** None. **C. Sanjuan:** A. Employment/Salary (full or part-time):; Euronutra. **F. Rodríguez de Fonseca:** None.

Poster

701. APP/Abeta Cellular and Animal Models II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 701.29

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AG064067

Title: Visual cortical hyperactivity and functional connectivity alterations in a mouse model of Alzheimer's Disease

Authors: *O. J. L'ESPERANCE, G. W. DAVIDSON, J. MCGHEE, J. SUBRAMANIAN; Univ. of Kansas Dept. of Pharmacol. & Toxicology, Univ. of Kansas, Lawrence, KS

Abstract: Neuronal hyperactivity induces memory deficits in early-stage Alzheimer's Disease (AD) and amyloid mouse models, including impaired visual recognition memory. However, it is unknown if neuronal hyperactivity manifests in relation to patterns of amyloid levels in visual processing areas and whether these areas display structural changes in the balance between excitatory and inhibitory (E/I) synaptic inputs. Additionally, functional connectivity alterations between these hyperactive visual processing areas and the rest of the brain remain uncharacterized. We address these questions by labeling c-Fos, APP, and excitatory/inhibitory presynaptic vesicular transporters across the entire brain. We show that hyperactivity is localized to specific subregions of the visual cortex in a pre-plaque transgenic mouse model of AD (J20 line, 5-6 months old, both sexes) exhibiting visual memory deficits. Additionally, we show that functional connectivity is altered between these hyperactive visual cortical and other regions across the brain compared to that in non-pathological littermate controls. By relating c-Fos levels and the ratio of E/I presynaptic markers, we determine whether disrupted structural E/I ratio is associated with hyperactivity locally and in functionally connected regions. Together, our findings will shed light on how local disruption to structural E/I ratio influences global functional connectivity.

Disclosures: O.J. L'Esperance: None. **G.W. Davidson:** None. **J. McGhee:** None. **J. Subramanian:** None.

Poster

702. Abeta as a Therapeutic Target

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 702.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS Grant-in-Aid for Scientific Research C JP18K06653
JSPS Grant-in-Aid for Scientific Research B JP21H02622
JSPS Grant-in-Aid for Scientific Research A JP19H01015
AMED Brain/MINDS Beyond JP19dm0307030
AMED-PRIME JP22gm6410017

Title: Establishment of non-invasive Aβ photooxygenation using a novel photocatalyst

Authors: *Y. HORI[1], N. NAGASHIMA[2], Y. SOHMA[3], M. KANAI[2], T. TOMITA[1];
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Abstract: The aggregation and deposition of amyloid-β peptide (Aβ) in the brain are associated with the pathogenesis of Alzheimer disease (AD). Therefore, the inhibition of Aβ aggregation and clearance of deposited Aβ have been focused on as the therapeutic strategy for AD. We have established a photooxygenation technology using a catalyst that is activated by irradiation of light. When it bound to aggregated Aβ, the activated catalyst could generate singlet oxygen, leading to the oxygenation of the aggregated Aβ. The photooxygenation reduced the aggregation potency and promoted clearance of aggregated Aβ *in vitro* and *in vivo*. These data suggest the potential of photooxygenation as a therapeutic strategy against AD. However, the catalysts developed so far have low blood-brain barrier (BBB) permeability due to their high molecular weight and ionic structures. Here, we developed a new catalyst with high BBB permeability and tried non-invasive photooxygenation *in vivo*. We developed a novel photooxygenation catalyst with a substantially lower molecular weight than previous catalysts, based on the azobenzene-boron complex (Gon et al., 2018). The developed catalyst was activated by light irradiation at around 600 nm. Due to its small molecular weight, this catalyst also had BBB permeability, enabling its delivery into the brain by non-invasive administration. We showed that non-invasive light irradiation of the brain from outside of the skull of living AD model mice in which the catalyst was administered by intravenous injection led to the oxygenation of Aβ in the brain, indicating successful non-invasive photo-oxygenation *in vivo* without any surgery. In addition, we found a decrease in the amount of Aβ in the brain by this non-invasive photooxygenation. In summary, we have succeeded in non-invasive photooxygenation in the brain using a novel photocatalyst. In the future, we would like to further improve the catalyst and pursue the possibility of photooxygenation as a therapeutic technology for AD.

Disclosures: **Y. Hori:** None. **N. Nagashima:** None. **Y. Sohma:** None. **M. Kanai:** None. **T. Tomita:** None.

Poster

702. Abeta as a Therapeutic Target

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 702.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: PAPIIT-IN-206322
CONACYT Fellowship No. CVU 1146069

Title: Effects of amylovis in learning and memory and alpha-7nAChR expression in hippocampus of 3xTg-AD model

Authors: *P. RODRÍGUEZ ARELLANO[1], H. MARTINEZ-CORIA[2], E. ORTA-SALAZAR[1], S. Y. DÍAZ-CINTRA[1];
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Abstract: β-amyloid oligomers (oAβ) are more toxic than neuritic plaques because of its interactions with other molecules in Alzheimer's disease (AD). AD is a neurodegenerative disease and the most common type of dementia characterized by a cognitive impairment. It's two major histopathological features are neuritic plaques composed of β-amyloid peptide of 42-aminoacid ($A\beta_{1\text{-}42}$) and neurofibrillary tangles. In addition, some elements of the cholinergic system are also affected, for instance the binding between oβA and the α7 nicotinic acetylcholine receptor (α7nAChR), particularly in hippocampus. The α7nAChR plays a critical role in learning and memory and for the interaction with oβA is downregulated during this pathology. Amylovis (naphthalene derivative) binds to $A\beta_{1\text{-}42}$ and inhibits its oligomerization, aggregation and hinder its binding with other molecules (Rivera-Marrero et al., 2020), this brings the question if Amylovis could prevent the binding of the $A\beta_{1\text{-}42}$ with the receptor and subsequently rescues the expression of the α7nAChR and improves learning and memory. The aim of this study was to analyze the effects of Amylovis in learning and memory and in the expression of α7nAChR in the triple transgenic model (3xTg-AD), which overexpresses three human proteins ($PS1_{M146V}$, APP_{SWE} and Tau_{P301L}) involved in AD. A total of 40 (3xTg-AD n = 20, control n = 20) from 4-month-old female mice were used, divided into vehicle and Amylovis groups. Amylovis dissolved in starch at 0.5% were administrated orally for eight weeks at a daily dose of 1 mg/kg of body weight. Then, the spatial learning and memory were evaluated by using the Barnes maze task. After the cognitive task, we assessed expression of the α7nAChR protein by Western Blot in an SDS-Page of the hippocampus from five animals per group. Our findings are consistent with the hypothesis and provide the evidence that Amylovis exposure induced spatial learning and memory improvement in the 3xTg-AD and maybe is attributed to its ACh-mediated neuronal

hippocampal function. Following this idea, is in progress the study of α7nAChR expression for a better interpretation. We thank to A. Aguilar Vázquez, N. Hernández Ríos, A. Gonzalez and Dra. Deysi Gasca for their excellent technical support. The present work was supported by PAPIIT-IN-206322. CONACYT Fellowship R.A.P No. CVU 1146069. Rivera-Marrero, S., et al. (2020). A new naphthalene derivative with anti-amyloidogenic activity as potential therapeutic agent for Alzheimer's disease. *Bioorganic and Medicinal Chemistry, 28*(20). Doi:10.1016/j.bmc.2020.115700

Disclosures: P. Rodríguez Arellano: None. **H. Martinez-Coria:** None. **E. Orta-Salazar:** None. **S.Y. Díaz-Cintra:** None.

Poster

702. Abeta as a Therapeutic Target

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 702.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: K01AG057815
R61AT010408

Title: Human Nmnat1 promotes autophagic clearance of amyloid plaques in a Drosophila model of Alzheimer's Disease

Authors: Y. ZHU[1], A. LOBATO[1], G. ZHAI[1], ***M. PINTO**[2];
[2]Neurol., [1]Univ. of Miami, Miami, FL

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by irreversible cognitive decline with limited therapeutic approaches. We characterized a Drosophila model of amyloid pathology that expresses human amyloid-beta precursor protein (APP695) and b-site APP cleaving enzyme (BACE) in the nervous system. Our model recapitulates in vivo the age-dependent accumulation of BACE-derived C-terminal fragment (CTF) and amyloid plaques in the brain, one of the key pathological hallmarks of AD. Using this model, we assessed the effects on plaque formation of Nicotinamide mononucleotide adenylyl-transferase (Nmnat), an evolutionarily conserved nicotinamide adenine dinucleotide (NADC) synthase involved in cellular metabolism and neuroprotection. We compared the effects of overexpression of Drosophila Nmnat (dNmnat), human Nmnat1 (hNmnat1), human Nmnat2 (hNmnat2), and human Nmnat3 (hNmnat3), and observed that hNmnat1 has the highest efficacy in reducing amyloid aggregation and APP-CTF accumulation. We demonstrated that overexpression of hNmnat1 reduces amyloid plaques by promoting autophagic clearance. Our findings uncover a role of hNmnat1 in amyloid clearance and suggest an exciting neuroprotective potential of hNmnat1 in amyloid pathology.

Disclosures: Y. Zhu: None. **A. Lobato:** None. **G. Zhai:** None. **M. Pinto:** None.

Poster

702. Abeta as a Therapeutic Target

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 702.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Prion-like soluble misfolded oligomers induce neurodegeneration:in vitroneurodegenerative diseases models

Authors: *A. ALLOUCHE, J. COLIN, S. HIDALGO, J.-F. BISSON, N. VIOLLE; Etap-Lab, ETAP-Lab, Vandœuvre-lès-Nancy, France

Abstract: Developing disease-modifying therapies for neurodegenerative diseases (NDs) presents an immense challenge, with little success despite intense work over decades. Protein misfolding and aggregation is observed in many NDs including Alzheimer's and Parkinson's diseases. The pathophysiological mechanisms of these diseases are still not well understood. However, the most currently accepted hypothesis is that accumulation of oligomers of the key proteins is the primary cause of NDs and initiates a series of events leading to synaptic and neuronal degeneration. Attempts to establish therapeutic approaches have led to numerous clinical trial failures and, to date, no curative treatment is available for NDs despite the considerable number of research programs. One of the reasons why drug development continues to fail is the lack of translational models. Current models are unfortunately inadequate due to their artificial overexpression of mutated or truncated human proteins. Of note there is an urgent need for translational models that are recapitulating natural disease onset in these vastly (>95%) sporadic diseases.Here, we report the progress in our development of novel NDs models, employing small quantity of highly reproducible oligomeric preparations of human amyloid-beta (AβO), Tau (TauO) and alpha synuclein (αSO), which show a multitude of disease phenotypes, as found in patients. Highly stable, soluble and reproducible AβO, TauO and αSO were prepared from human monomers with our unique know-how without chemical modification or helper proteins. These preparations were characterized by various methods (SDS-page, electron microscopy and dot-plot tests). *In vitro*, they induced a significant dose-dependent neuronal cell death in rodent primary neurons (isolated from cortex, hippocampus, or midbrain), proven by various and complementary read-outs (MTT, live/dead and CellTiter-Glo® cell viability assays). Interestingly, neurotoxicity of Aβ, Tau and αSO was greater with oligomers than fibrillar, while monomers did not induce any neuronal damage. Oligomers-induced neurodegeneration was significantly attenuated by brain-derived neurotrophic factor (BDNF), providing a positive control for drug screening assays.This work strongly supports the hypothesis that soluble misfolded protein aggregates, called oligomers, are the toxic species responsible for disease induction and progression in NDs, and treatments counteracting their effects are thought to give rise to novel therapeutic intervention.

Disclosures: A. Allouche: None. **J. Colin:** None. **S. Hidalgo:** None. **J. Bisson:** None. **N. Violle:** None.

Poster

702. Abeta as a Therapeutic Target

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 702.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01DA038635-S1

Title: Sri 22136, a novel delta opioid receptor (dor) antagonist for the treatment of alzheimer's disease

Authors: *P. TANGUTURI[1], A. SUBRAMANIAM[2], V. PATHAK[2], P. VENUKADASULA[2], S. ZHANG[2], O. MOUKHA-CHAFIQ[2], C. AUGELLI-SZAFRAN[2], J. STREICHER[1]; [1]Univ. of Arizona, Tucson, AZ; [2]Southern Res. Institute, Birmingham, AL, USA, Birmingham, AL

Abstract: Alzheimer's disease (AD) is the most common form of dementia, which affects 47 million people worldwide. There are over five million AD patients over the age of 65 in the U.S. which is predicted to increase to 16 million by 2050. There are currently no approved disease-modifying therapies for AD and attempts to prevent or slow the progression of the formation of beta-amyloid plaques by targeting both the beta-secretase 1 (BACE1) and gamma-secretase enzymes have not yet achieved clinical success. Studies suggest that indirect modulation of the function of these enzymes via G-protein coupled receptors (GPCRs) may provide a novel strategy to reduce A-beta peptide production with potentially fewer side effects. Among GPCRs that influence amyloidogenesis, the delta opioid receptor (DOR), in particular, has been shown to play an important role in the trafficking and function of BACE1 and gamma-secretase and in the production of A-beta peptide. DOR activation increases BACE1 and gamma-secretase activity *in vitro* and in a mouse model of AD, and antagonism of DOR specifically blocks the amyloidogenic pathway and efficaciously prevents AD progression in mice. These effects were demonstrated using a known DOR antagonist, naltrindole. However, the potential of DOR antagonists as therapeutic agents for AD has yet to be explored.
The aim of this project is to create novel DOR antagonists via medicinal chemistry and identify the most promising lead compound based on binding, selectivity, and functional profile *in vitro*. Further, select a small set of the most promising compounds and evaluate the compound's ability to mitigate AD-like pathology *in vivo* using APP/PS double-transgenic mice. Lead DOR antagonist SRI-22136 with low nanomolar affinity/potency that have been shown to block BACE1 activity *in vitro* showed systemic stability and blood brain barrier penetration using the *in vivo* tail flick assay in CD-1 mice. SRI-22136, showed efficacy in Novel Object Recognition (NOR) behavioral studies at a dose of 1mg/kg twice daily for 90 days continuous treatment *in vivo* using the APP/PS AD model double-transgenic mice. Also, in our brain histological analysis the compound exhibited greater efficacy in reduction of the AD pathology markers such as Aβ and secondary inflammation and activated glia detected by GFAP (astrocytes) and CD11b (microglia) in APP/PS AD model double-transgenic mice. Further the compound exhibited

greater reduction in biochemical marker such as BACE-1 and Aβ using the cortex and hippocampus regions of the APP/PS AD model double-transgenic mice. These results suggest that SRI-22136 and similar DOR antagonists could be novel therapies for the treatment of AD.

Disclosures: **P. Tanguturi:** None. **A. Subramaniam:** None. **V. Pathak:** None. **P. Venukadasula:** None. **S. Zhang:** None. **O. Moukha-Chafiq:** None. **C. Augelli-Szafran:** None. **J. Streicher:** None.

Poster

702. Abeta as a Therapeutic Target

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 702.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JST Grant JPMJSP2153

Title: What cultivation factors affect the inhibitory activity for Aβ aggregation in the extract of Perilla?

Authors: *K. SHIMAMORI, T. NANBU, D. KAWAMATA, M. KURAGANO, T. IIMORI, S. YAMANAKA, K. UWAI, K. TOKURAKU;
Muroran Inst. of Technol., Muroran, Japan

Abstract: Alzheimer's disease (AD) is thought to be caused by the deposition of amyloid-β (Aβ), which begin to aggregate approximately 20 years before the expression of its symptoms. Previously, we developed a microliter-scale high throughput screening (MSHTS) system for inhibitors against Aβ aggregation using quantum-dot nanoprobes (Ishigaki *et al*., *PLoS One*, 2013). MSHTS system could evaluate crude plant extract samples, including various substances. Using this system, we evaluated 52 spices and revealed that spices belonging to the *Lamiaceae* showed significantly high activity. Then, we found that EtOH extracts of leaf of *Perilla frutescens* var. *crispa* '*Viridi-crispa*' exhibited extremely high activity. However, the activity was affected by the harvesting season and cultivation region even so same Perilla species. In this study, we investigate what cultivation factors affect the inhibitory activity for Aβ aggregation in Perilla extracts. We made the field on our institute campus and cultivated Perilla under various fertilization conditions (2019 - 2020). Using an automated MSHTS system (Sasaki *et al*., *Sci. Rep*., 2019), we evaluated the activity of over 500 extracts for 2 years. In 2019, we clarified that the standard (Std) sample, cultivated under minimal fertilizer of all the conditions, showed the highest inhibitory activity for Aβ aggregation just before flowering in early September. Interestingly, the activity of the wind-shielded sample, prevented from being exposed to the wind, was reduced to 1/5 of the Std sample just before flowering despite the standard soil conditions. We analyzed the relation between the activity and the amount of soil components for samples cultivated under approximately 30 different fertilization conditions. The scatter plots indicated a positive correlation between activity and the amount of nitrogen. Further, it was

revealed that the activity was highest at around 20% and dramatically decreased at higher water content. Next year (in 2020), to confirm whether nitrogen amounts affect the activity, we cultivated Perilla under 6 conditions with different nitrogen fertilization. MSHTS system demonstrated that the activity just before flowering increased at the middle range of nitrogen fertilization. In addition, we confirmed that the samples with appropriate nitrogen fertilization suppress Aβ-induced neuronal toxicity using the MTT assay with PC12 cells. In conclusion, we found flowering, wind, soil water content, and nitrogen affect inhibitory activity for Aβ aggregation. In particular, nitrogen fertilization might be effective in the mitigation of Aβ neurotoxicity.

Disclosures: **K. Shimamori:** None. **T. Nanbu:** None. **D. Kawamata:** None. **M. Kuragano:** None. **T. Iimori:** None. **S. Yamanaka:** None. **K. Uwai:** None. **K. Tokuraku:** None.

Poster

702. Abeta as a Therapeutic Target

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 702.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: KAKENHI 19H01015
KAKENHI 22H05036
AMED 20dm0107056h0005
JST JPMJMS2024

Title: Inhibition of NF-κB pathway in the astrocytes facilitates the proteolytic clearance of amyloid-β by kallikrein-related peptidase 7

Authors: *T. TOMITA, Y. SUDO, C. SUNG, K. KIKUCHI, S. TAKATORI, Y. HORI; Grad. Sch. Pharm. Sci., Univ. Tokyo, Tokyo, Japan

Abstract: Alzheimer disease (AD) is a progressive neurodegenerative disorder and the most frequent form of dementia. Aggregation and deposition of amyloid-β (Aβ) are implicated in the pathogenesis of AD. Thus, activation of the Aβ metabolic mechanism can be applied as a novel drug discovery tool for AD. We have identified Kallikrein-related peptidase 7 (KLK7) as an Aβ-degrading enzyme secreted by astrocytes (Kidana et al., EMBO Mol Med 2018). We also found memantine, an NMDA receptor antagonist, as a candidate compound to increase the expression level of KLK7. However, the molecular mechanism of how memantine regulates KLK7 expression in astrocytes remains unclear. To analyze the regulatory mechanism of KLK7 expression, we analyzed the promoter regions upstream of the KLK7 gene and found that the NF-κB binding site in the KLK7 promoter is critical in its transcriptional regulation by memantine. We then examined the effects of NF-κB pathway inhibitors, IKK-16 and JSH-23 on the KLK7 expression level. Both compounds increased the Klk7 mRNA expression and the Aβ degrading activity of the primary astrocytes. Finally, we injected IKK-16 into the hippocampus

of AD model NLGF mice. We found a marked decrease in soluble and insoluble Aβ without affecting the levels of APP and secretases. Furthermore, the effect of IKK-16 was canceled in the NLGF mice with Klk7 knockout background. These results suggest that the NF-κB pathway in the astrocytes is an important signaling mechanism in the regulation of the KLK7 expression level and the brain Aβ deposition.

Disclosures: **T. Tomita:** None. **Y. Sudo:** None. **C. Sung:** None. **K. Kikuchi:** None. **S. Takatori:** None. **Y. Hori:** None.

Poster

702. Abeta as a Therapeutic Target

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 702.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R15:1R15NS10160801A1

Title: Ire1 inhibition by STF-083010 decreases Aβ load at the Drosophila neuromuscular junction.

Authors: *F. BARMALEKI LIGHVAN[1], E. L. HENDRICKS[2], F. L. W. LIEBL[2];
[1]Southern Illinois Univ., [2]Southern Illinois Univ., Edwardsville, IL

Abstract: Alzheimer's disease (AD) is a neurological disease in which protein misfolding leads to pathology. The accumulation of abnormal extracellular aggregates formed by amyloid-β (Aβ) peptides interferes with normal synaptic function and leads to neurodegeneration in AD. Accumulation of Aβ fragments can disrupt endoplasmic reticulum (ER) function leading to ER stress. This may also activate the unfolded protein response (UPR) to maintain proteostasis. The ER stress-induced UPR mediators, protein kinase R-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor (ATF6), are activated during ER stress. To investigate the contribution of Aβ-induced ER stress, we pharmacologically inhibited the activity of PERK, IRE1, and ATF6 in a *Drosophila* AD model. *Drosophila* larvae expressing human amyloid precursor protein (APP) and BACE in neurons were raised on GSK2606414 (a PERK inhibitor), STF-083010 and MKC-3946 (IRE1 inhibitors), and the chemical chaperone Tauroursodeoxycholic acid (TUDCA) for their lifetime. Aβ load was decreased in AD model animals raised on 10 µM STF-083010 and 50 µM STF-083010 compared to nontreated animals expressing APP and BACE in neurons. To further investigate the effects of pharmacological inhibition of IRE1, we treated the AD model larvae with 10 µM STF-083010 for 24 h. 24 h exposure to 10 µM STF-083010, however, increased Aβ load compared to control AD model animals. We are currently assessing whether lifetime treatment with 10 µM STF-083010 can suppress behavioral and synaptic phenotypes of animals expressing APP and BACE in neurons. To determine whether IRE1 inhibition of UPR is responsible for the suppression of Aβ, we will examine the effects of UPR activation and additional IRE1 inhibitors on Aβ levels.

Disclosures: **F. Barmaleki Lighvan:** None. **E.L. Hendricks:** A. Employment/Salary (full or part-time):; Southern Illinois University. **F.L.W. Liebl:** A. Employment/Salary (full or part-time):; Southern Illinois University.

Poster

702. Abeta as a Therapeutic Target

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 702.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 AG030142

Title: Farnesyltransferase inhibitor LNK-754 attenuates axonal dystrophy and reduces amyloid pathology in mice

Authors: *L. K. CUDDY[1], A. O. ALIA[1], M. A. SALVO[1], S. CHANDRA[1], T. N. GRAMMATOPOULOS[2], C. J. JUSTMAN[3], P. T. LANSBURY JR[4], J. R. MAZZULLI[1], R. J. VASSAR[1];
[1]Neurol., Northwestern Univ., Chicago, IL; [2]BioEnergetics LLC, Boston, MA; [3]Lysosomal Therapeutics, Inc, Cambridge, IL; [4]Harvard Med. Sch., Cambridge, IL

Abstract: Amyloid plaque deposition and axonal degeneration are early events in AD pathogenesis. Aβ disrupts microtubules in presynaptic dystrophic neurites, resulting in the accumulation of impaired endolysosomal and autophagic organelles transporting β-site amyloid precursor protein cleaving enzyme (BACE1). Consequently, dystrophic neurites generate Aβ42 and significantly contribute to plaque deposition. Farnesyltransferase inhibitors (FTIs) have recently been investigated for repositioning toward the treatment of neurodegenerative disorders and block the action of farnesyltransferase (FTase) to catalyze farnesylation, a post-translational modification that regulates proteins involved in lysosome function and microtubule stability. In postmortem AD brains, FTase and its downstream signaling are upregulated. However, the impact of FTIs on amyloid pathology and dystrophic neurites is unknown. Here, we tested the effects of the FTIs LNK-754 and lonafarnib in the 5XFAD mouse model of amyloid pathology. In 2-month-old 5XFAD mice treated chronically for 3 months, LNK-754 reduced amyloid plaque burden, tau hyperphosphorylation, and attenuated the accumulation of BACE1, LAMP1 and LysoTracker-Green in dystrophic neurites. In 5-month-old 5XFAD mice treated acutely for 3 weeks, LNK-754 reduced dystrophic neurite size and lysosome accumulation in the absence of effects on Aβ deposits. Acute treatment with LNK-754 improved memory and learning deficits in hAPP/PS1 amyloid mice. In contrast to LNK-754, lonafarnib treatment was less effective at reducing plaques, tau hyperphosphorylation and dystrophic neurites, which could have resulted from reduced potency against FTase compared to LNK-754. We investigated the effects of FTIs on axonal trafficking of endolysosomal organelles and found that lonafarnib and LNK-754 enhanced retrograde axonal transport in primary neurons, indicating FTIs could support the maturation of axonal late endosomes into lysosomes. Furthermore, FTI treatment increased

levels of LAMP1 in mouse primary neurons and in the brains of 5XFAD mice, demonstrating that FTIs stimulated the biogenesis of endolysosomal organelles. We show new data to suggest that LNK-754 promoted the axonal trafficking and function of endolysosomal compartments, which we hypothesize decreased axonal dystrophy, reduced BACE1 accumulation and inhibited amyloid deposition in 5XFAD mice. Our results agree with previous work identifying FTase as a therapeutic target for treating proteinopathies and could have important therapeutic implications in treating AD.

Disclosures: L.K. Cuddy: None. **A.O. Alia:** None. **M.A. Salvo:** None. **S. Chandra:** None. **T.N. Grammatopoulos:** None. **C.J. Justman:** None. **P.T. Lansbury Jr:** None. **J.R. Mazzulli:** None. **R.J. Vassar:** None.

Poster

702. Abeta as a Therapeutic Target

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 702.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Anti-amyloidogenic effect of BACE1 expression lowering compound identified using high-throughput gene expression assay

Authors: *S. BAEK, S. HONG, D.-G. JO;
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Abstract: Accumulation of Aβ (amyloid-beta) in a brain is one of the pathological hallmarks of Alzheimer's disease (AD). Aβ is generated through sequential cleavage of amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase complex. BACE1 is one of the crucial targets for AD given that BACE1 expression is significantly upregulated in AD patients compared with non-AD. However, direct and complete inhibition of BACE1 activity can cause unpredictable or unintended effects because of numerous physiological substrates of BACE1. Therefore,a breakthrough without interfering BACE1 function is needed to overcome Alzheimer's disease. We screened xxxx small compounds, including drugs approved by the U.S. Food and Drug Administration to identify drugs that reduce promoter activity of BACE1. Here, we have found a new candidate drug which reduces promoter activity, mRNA, and protein levels of BACE1 in neuronal cells. We have confirmed that the drug decreases BACE1 gene expression, prevents accumulation of Aβ, and improves cognitive function in APP/PS1 transgenic mice. The ability of this compound reverses a wide range of deficits suggests that BACE1 expression-reducing agents may have therapeutic utility in the treatment of AD.

Disclosures: S. Baek: None. **S. Hong:** None. **D. Jo:** None.

Poster

703. Alpha-Synuclein-Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 703.01

Topic: C.03. Parkinson's Disease

Support: HBHL Grant
McGill IPN Award
CIHR FDN-154301

Title: Characterizing patterns of neural activity in midbrain organoids as a model for studying Parkinson's disease

Authors: *G. DEYAB[1], N.-V. MOHAMED[2], R. THOMAS[2], J. AO[2], X. E. DING[2], J. SIROIS[2], C. X.-Q. CHEN[2], L. BEITAL[2], T. M. DURCAN[2], E. A. FON[2];
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Abstract: Human derived midbrain organoids (hMOs) are a promising tool that can be used to study Parkinson's disease (PD) on a patient-specific level by capturing the genetic background of patients. Yet, much is unknown about how accurately hMOs recapitulate the human brain in health and disease. In human models of PD, the progression of the disease leads to changes in neural activity. In this study, we aim to determine whether hMOs can capture these changes in neural activity associated with PD. We have generated hMOs using induced pluripotent stem cells derived from PD patients and their CRISPR-corrected controls and recorded their network activity over nine months using a Micro-Electrode Array (MEA). Using custom Python scripts, we then compared these patterns of activity between mutant and control (CTL) hMOs to determine how changes in network activity are modelled in hMOs. In organoids derived from patients carrying a synuclein triplication mutation, we see a decrease in overall activity across the organoid compared to their isogenic CTLs. However, mutant hMOs showed an increase in the strength of single neuron and population wide bursts, as measured by the number bursts, the firing rate within a burst, and the duration of the burst. This suggests that although mutant hMO activity is decreased, the organization of neural activity is shifted towards strong bursting activity. These findings are complementary to neural activity described in mouse models of PD and may reflect compensatory mechanisms as a response to cell death. To test if this change in activity was due to a decrease in dopamine (DA) transmission, we treated hMOs with exogenous L-Dopa and recorded their activity before and after treatment. Here, we saw a decrease in both the number of single unit bursts and population bursts in mutant hMOs but not CTLs. Suggesting that the increase in bursting activity observed in mutant hMOs may be due to decreased DA transmission. In contrast hMOs harboring A53T mutations show little to no activity compared to their isogenic CTLs. A live-dead assay was performed on dissociated organoids through Fluorescence-Activated Cell Sorting (FACS) to determine the ratio of live to dead cells. At 50 days old the number of live cells was similar in A53T and CTL hMOs (>90% live cells). However, starting at 100 days old, the number of live cells in A53T hMOs dramatically decreased (~17% live cells) compared to CTL hMOs (~80% live cells). If shown to be reproducible in future experiments, the increase in cell death seen in A53T hMOs could explain

their lack of activity compared to CTLs. This study provides evidence towards the validation of using organoids as a model to study PD in a patient-specific manner.

Disclosures: **G. Deyab:** None. **N. Mohamed:** None. **R. Thomas:** None. **J. Ao:** None. **X.E. Ding:** None. **J. Sirois:** None. **C.X. Chen:** None. **L. Beital:** None. **T.M. Durcan:** None. **E.A. Fon:** None.

Poster

703. Alpha-Synuclein-Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 703.02

Topic: C.03. Parkinson's Disease

Support: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska Curie grant agreement No 814244.

Title: Development of an in vitro α-synuclein aggregation assay in primary cortical cultures for target discovery and validation

Authors: S. LARDELL, L. MOLL, ***C. NODIN**, L. STRID ORRHULT, J. PIHL; Cellectricon AB, Cellectricon AB, Mölndal, Sweden

Abstract: In Parkinson's disease (PD), the formation and propagation of α-synuclein (α-syn) insoluble amyloid structures is a process hypothesized to drive the pathology of disease. As part of this process, impaired protein clearance and protein aggregation within neurons occur. From a drug discovery perspective, preventing protein aggregation or promoting protein clearance provide interesting opportunities as pharmacological intervention points. However, there is currently a lack of biologically relevant in vitro systems modelling these mechanisms. Such models are much needed for e.g. development of small molecules, or for further increasing the understanding of pathological processes involved in neurodegenerative disease.
With this in mind, we initiated the development and validation of a high-capacity in vitro model based on primary embryonic mouse cortical cultures in a 384-well format, where endogenous α-syn aggregation was induced at 6 or 10 days in vitro (DIV) using recombinant human α-syn pre-formed fibrils. Endogenous α-syn aggregation and cell health were quantified at 14 or 17 DIV using immunocytochemistry and automated high content imaging and analysis.
Following the development of a robust protocol for induction and quantification of α-syn aggregation, the model was validated using lentiviral shRNAs for knock-down of a small set of genes (SNCA, LRRK2, GBA and TMEM175) known for their involvement in PD.
The outcome was a robust and sensitive high-capacity dual assay for assessment of α-syn aggregation, where it was possible to detect both negative and positive modulators of α-syn aggregation even in single point screening format. The knock-down of genes relevant for PD resulted in the expected effect on α-syn aggregation for all genes tested. We therefore conclude

that the developed model is relevant for characterization of genetic modulators of α-syn aggregation and can be used for target discovery and validation applications.

Disclosures: **S. Lardell:** A. Employment/Salary (full or part-time):; Cellectricon AB. **L. Moll:** A. Employment/Salary (full or part-time):; Cellectricon AB. **C. Nodin:** A. Employment/Salary (full or part-time):; Cellectricon AB. **L. Strid Orrhult:** A. Employment/Salary (full or part-time):; Cellectricon AB. **J. Pihl:** A. Employment/Salary (full or part-time):; Cellectricon AB.

Poster

703. Alpha-Synuclein-Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 703.03

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS R21 NS111333
NIH/NINDS R21 NS121393

Title: Synucleinopathy is associated with the presence of toxic A1 astrocytes and a coordinated activation of the classical complement cascade

Authors: *M. J. BENSKEY[1], C. J. KEMP[1], A. C. STOLL[1], J. R. PATTERSON[1], K. STEECE-COLLIER[1], M. HORE[1], K. C. LUK[2], C. E. SORTWELL[1];
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Abstract: Parkinson's Disease (PD) is a neurodegenerative disorder that culminates in the deposition of alpha synuclein (a-syn) containing protein aggregates and the degeneration of nigrostriatal dopamine neurons. Neuroinflammation, including activation of microglia and astrocytes, may play an active role in the degenerative process. Activated microglia can convert astrocytes to a subtype of toxic "A1- astrocyte", which coordinate neurodegeneration by releasing unknown neurotoxins. A1 astrocytes have only been identified in human PD tissue and animal models of PD after significant neurodegeneration has occurred. Thus, it is impossible to determine if A1 astrocytes appear in response to cell death or if they are present prior to cell death, where they may contribute to neurodegeneration. Here we aimed to test the hypothesis that A1 astrocytes are present in the substantia nigra pars compacta (SNc) prior to overt neurodegeneration in a model of synucleinopathy. Intra-striatal injection of recombinant a-syn pre-formed fibrils (PFFs) results in progressive aggregation of endogenous a-syn that peaks 2 months post injection, followed by significant nigral degeneration at 6 months post injection. During peak a-syn aggregation we observe peak microglial activation and astrogliosis. To determine if synucleinopathy triggers the conversion of astrocytes to the A1 phenotype prior to cell loss, we used ddPCR to quantify A1-associated transcripts in the SNc 2 months following unilateral, 2 site intra-striatal injections of mouse a-syn PFFs (total 16 μg, 2 x 2 μl, 4μg/μl) or PBS vehicle control (2 x 2ul) into male F344 rats. We observed a significant increase in many

A1-associated transcripts, including complement component 3 (C3), guanylate-binding protein 2, and Serping 1. Fluorescent *in situ* hybridization (FISH) combined with immunofluorescence (IF) was used to determine the cellular source of the A1 transcripts. Serping 1 colocalized to GFAP+ astrocytes. Surprisingly, C3 colocalized to IBA1+ microglia at 2 and 4 months post-PFF, but overwhelmingly colocalized to GFAP+ astrocytes at 6 months post-PFF. To identify the specific pathway of the complement system activated by synucleinopathy we performed ddPCR and FISH/IF in the SNc at 2 months post-PFF. We observed a significant increase in transcripts of the classical complement cascade, such as complement C1qa, which localized to IBA1+ microglia. These data suggest that reactive microglia and astrocytes coordinate the complement response to synucleinopathy at different phases of the degenerative process (i.e. peak aggregation vs. degenerative phases) both of which may potentially contribute to neurodegeneration.

Disclosures: M.J. Benskey: None. **C.J. Kemp:** None. **A.C. Stoll:** None. **J.R. Patterson:** None. **K. Steece-Collier:** None. **M. Hore:** None. **K.C. Luk:** None. **C.E. Sortwell:** None.

Poster

703. Alpha-Synuclein-Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 703.04

Topic: C.03. Parkinson's Disease

Title: Development of an in vitro alpha-synuclein aggregate model for use in drug discovery

Authors: *K. C. MCNEELY, M. K. SCHULTZ, C. A. DWYER;
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Abstract: Alpha-synuclein is a major component of Lewy bodies and is linked to familial forms of Parkinson's disease and Lewy Body dementia. The contribution of alpha-synuclein accumulation to neurodegeneration in sporadic Parkinson's disease is not clear. However, for targets with genetic association to both Lewy Body dementia and sporadic Parkinson's disease an in vitro alpha-synuclein aggregate assay in iPSC derived neural cells would provide valuable mechanism of action insights for respective drug discovery campaigns. A major challenge to adapting in vitro alpha synuclein aggregation assay for drug discovery is model inconsistency. The goal of our work is to overcome this challenge and develop a robust and semi-high throughput in vitro model of alpha-synuclein aggregation. We describe a parallel correlative measure workflow to evaluate alpha-synuclein pre-formed fibril quality. Using this workflow we compared different sources of alpha-synuclein pre-formed fibrils based on quality and their ability to seed aggregates in primary mouse neuron cultures. A reliable commercial source was selected. In an assay development frame-work we established an optimal preparation procedure and cellular treatment paradigm that led to the development of an alpha-synuclein aggregate model in primary mouse neurons. These learnings are being transitioned to develop a model in human iPSC-derived cells for drug screening.

Disclosures: **K.C. McNeely:** A. Employment/Salary (full or part-time):; GSK. **M.K. Schultz:** A. Employment/Salary (full or part-time):; GSK. **C.A. Dwyer:** A. Employment/Salary (full or part-time):; GSK.

Poster

703. Alpha-Synuclein-Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 703.05

Topic: C.03. Parkinson's Disease

Title: Insight Into Parkinson's Disease From a Yeast Model: How Three New Alpha-Synuclein Mutants May Cause Disease

Authors: *A. GRASSEL[1], T. NASSUNA[1], C. BORLAND[2], F. BERTOLOTTI[1], R. OSSELBORN[1], S. K. DEBBURMAN[1];
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Abstract: Parkinson's Disease (PD) is a fatal and incurable neurodegenerative disorder linked to the loss of dopaminergic neurons in the midbrain. A key pathological marker of PD is the presence of Lewy bodies, which are composed of misfolded α-synuclein protein. α-Synuclein is a highly post-translationally modified protein in both healthy and diseased states. Modifications on it include phosphorylation, nitration, SUMOylation, acetylation, and glycation. Known α-synuclein toxicity modifiers also include lipid dysregulation and interactions with other PD-associated genes. The toxicity of wildtype α-synuclein and six well-known mutant versions linked with familial PD (A30P, E46K, H50Q, G51D, A53T, A53E) is well-modeled in budding yeast systems. In contrast, the toxicity mechanisms of three newer PD-linked α-synuclein mutants (A18T, A29S, and A53V) is relatively understudied; particularly, the impact of post-translational modifications, lipid homeostasis, and other gene interactions on their toxicity is unknown. Using our lab's budding yeast model of PD, we investigated the toxicity potential of these three new mutants by assessing the impact of the mutations on yeast growth, α-synuclein localization, and α-synuclein expression in various yeast strains. We report that: 1) All three mutants are toxic to yeast, but to different degrees and, surprisingly, less than wild-type α-synuclein; 2) Yeast strains with altered triglycerides and diglycerides reduce α-synuclein toxicity; 3) Yeasts strains with enhanced acetylation or reduced glycation environments rescue α-synuclein toxicity; 4) Yeast strains with enhanced SUMOylation are protective against α-synuclein toxicity; 5) Yeasts strains deleted for specific PD-associated genes (SAC1, SWA2, VPS35) differentially enhance mutant α-synuclein toxicity; 6) And, finally, yeast strains with decreased nitrative stress levels rescue α-synuclein toxicity. This study expands the evaluation of genetic α-synuclein mutants linked with PD in yeast models and supports the relevance of covalent modifications, lipid homeostasis, and PD-associated genes on α-synuclein toxicity.

Disclosures: **A. Grassel:** None. **T. Nassuna:** None. **C. Borland:** None. **F. Bertolotti:** None. **R. Osselborn:** None. **S.K. Debburman:** None.

Poster

703. Alpha-Synuclein-Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 703.06

Topic: C.03. Parkinson’s Disease

Support: ERC starting grant 2016
Finnish Parkinson's Foundation
Doctoral School of Health Science, University of Helsinki
Foundation for Drug Research

Title: Effect of cerebral dopamine neurotrophic factor in novel alpha-synuclein aggregation models of Parkinson's disease

Authors: *A. SINGH, A. PANHELAINEN, M. H. VOUTILAINEN;
Fac. of Pharm., Univ. of Helsinki, Helsinki, Finland

Abstract: Drug research and development depend heavily on the study models used during the pre-clinical studies. Parkinson’s disease (PD) drug research lacks a reproducible pre-clinical model that would recapitulate both- the occurrence of robust DA neuron death and the formation of Lewy body (LB)-like inclusions- within a reasonable timeframe. The existing therapies for PD mainly have not been able to stop or slow down the degeneration of dopamine (DA) neurons and aim at mitigating the symptoms of the disease to improve the quality of life for the patients. Cerebral dopamine neurotrophic factor (CDNF) has previously shown neuroprotection and restoration of DA neurons, and improvement in the toxin-induced motor deficits in animal models of PD. CDNF recently reached its primary safety and tolerability endpoint in phase I/II clinical trial for PD. In this study, our first aim was to develop a model exhibiting both the alpha-synuclein aggregation pathology and loss of the nigral DA neurons over an optimal time course. For this, we combined alpha-synuclein pre-formed fibrils with another stressor in embryonic primary midbrain cultures and *in vivo* in mice. Secondly, we wanted to test the effects of CDNF in this combination model of PD for its effects on neuroprotection, restoration and alpha-synuclein aggregation. The pathology progression was analyzed by quantifying the DA neurons and the presence of intraneuronal pS129 alpha-synuclein-positive inclusions at different timepoints both *in vitro* and *in vivo*. This data was also supported by performing the motor behavioural tests, such as cylinder tests, amphetamine-induced rotations and rotarod, in mice with the stressors and the ones injected with CDNF. In primary dopamine neurons, there was a dose-dependent loss of DA neurons for the stressor combination-treated cultures, along with the occurrence of pS129 alpha-synuclein-positive inclusions. The mice injected with the stressor combination produced significantly more rotations than the mice injected with only pre-formed fibrils. There was no difference in the number of DA neurons between these groups. However, interestingly, they had reduced amounts of pS129 alpha-synuclein-positive inclusions. CDNF did not affect the motor behavior or the neuron count in these experimental systems. Our combination stressor model of alpha-synuclein aggregation produces a loss of dopamine neurons

in the experimental models, along with formation of pS129 alpha-synuclein-positive LB-like inclusions. Additionally, we conclude that the complexity of a multifactorial disease such as PD needs several different stressors in combination to mirror the various aspects of the disease.

Disclosures: **A. Singh:** None. **A. Panhelainen:** None. **M.H. Voutilainen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Herantis Pharma.

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703. Alpha-Synuclein-Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 703.07

Topic: C.03. Parkinson's Disease

Support: NINDS 5R01NS117968-02
NIGMS 5R35GM131814-04

Title: Alpha-synuclein fibril cavities are targetable motifs that modulate fibrillogenesis

Authors: *N. NATHAN KOCHEN[1], V. VASANDANI[1], D. SEANEY[1], A. K. PANDEY[1], E. E. LIAO[1], M. A. WALTERS[2], A. R. BRAUN[1], J. SACHS[1];
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Abstract: In the last decade, high-resolution structures of more than ten distinct polymorphs of alpha-synuclein (aSyn) fibrils have been published. We have recently demonstrated that aSyn fibril cavities are persistent structural motifs across aSyn fibril polymorphs whose defining residues modulate aggregation. We used computational docking to identify potential small molecule binders to these cavities and confirmed via Thioflavin T, ^{1}H-^{15}N HSQC and ^{19}F CPMG NMR that the top-scoring molecule in our docking studies, aprepitant, strongly promotes fibril growth while specifically interacting with aSyn fibrils and not monomer.
Future *in vitro* experiments will explore the effects of aprepitant on the monomeric, oligomeric and fibrillar fractions formed during aSyn aggregation. We will characterize these effects via biochemical analysis of aggregation products and proteinase-K digestion fingerprinting. Finally, to further explore aprepitant as a potential therapy for synucleinopathies, we will test its ability to rescue aSyn-induced pathology in neuronal cell models.

Disclosures: **N. Nathan Kochen:** None. **V. Vasandani:** None. **D. Seaney:** None. **A.K. Pandey:** None. **E.E. Liao:** None. **M.A. Walters:** None. **A.R. Braun:** None. **J. Sachs:** None.

Poster

703. Alpha-Synuclein-Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 703.08

Topic: C.03. Parkinson's Disease

Support: Okinawa Institute of Science and Technology
NRF-2019R1A5A2026045

Title: A Study on the Role of Glucocerebrosidase in Human Pluripotent Stem Cell-Derived Microglia and Midbrain Organoid Models

Authors: *C. R. DENMAN[1], H.-D. TRAN[1], R. HAN[1], M.-K. SHIN[1,2], B. KUHN[1], G. W. ARBUTHNOTT[1], J. JO[1,2];
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Abstract: Parkinson's disease (PD) is an incredibly debilitating illness frequently afflicting elderly people and severely impacting patient quality of life. Human brain organoids provide a novel method to bridge the gap between previous models of the disease and the human condition, allowing us to probe the underlying cell biology and test potential treatments in a clinically relevant model of PD. *GBA1*, the most common genetic risk factor for PD, encodes the enzyme glucocerebrosidase (GCase) and makes an unknown cell biological contribution to disease pathogenesis. It is possible that the disease process is modified by microglia in the brain, but organoids do not typically include this cell type. We have inserted the fluorescent reporter, EGFP in the TMEM119 locus (a known microglia-expressed gene) directly before the stop codon in human embryonic stem cells (hESCs) by CRISPR/Cas9 technology to enable us to visually track microglia. Using this hESC line, we performed another round of gene targeting to create a *GBA1* homozygous knock-out (KO) for PD modelling. The insertion of EGFP into the *TMEM119* locus was confirmed by sequencing and the hESC line exhibited a normal kayotype and expressed pluripotency markers. Furthermore, the absence of off-target insertions of the donor plasmid to the top 3 coding sites and top 5 non-coding sites were confirmed by sequencing. Sequencing was also used to confirm the KO cell line, as well as Western blot. Fluorescent activated cell sorting (FACS), immunohistochemistry, qRT-PCR and phagocytosis assays determine the authenticity and function of microglia in 2D culture of both the wildtype (H9 *TMEM119*-EGFP) and mutant (H9 *TMEM119*-EGFP::*GBA1* KO) cell lines. Functional properties of microglia with and without glucocerebrosidase can now be studied in monoculture and human midbrain-like organoids (hMLOs) to assess, for example, the accumulation of alpha-synuclein. We have successfully demonstrated by confocal microscopy that microglia infiltrate hMLOs. This protocol can be optimised by co-culturing haematopoeitic stem cells (HPCs) and midbrain progenitor cells (MPCs) in a defined ratio to recapitulate human brain development more closely. hMLOs infiltrated with microglia generated from the wildtype and mutant cell line can be used to explore the possibility that *GBA1* deficient microglia alone are sufficient to induce PD like pathology in neurons. This model has the potential to open new doors, allow us to explore the underlying mechanisms of this disease and to inform novel drug therapies.

Disclosures: C.R. Denman: None. **H. Tran:** None. **R. Han:** None. **M. Shin:** None. **B. Kuhn:** None. **G.W. Arbuthnott:** None. **J. Jo:** None.

Poster

703. Alpha-Synuclein-Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 703.09

Topic: C.03. Parkinson's Disease

Support: European Research Council Advanced Grant 694829 'neuroXscales'
ERC proof-of-concept project 875609 'HD-Neu-Screen'
Personalized Medicine project PMB-01-18 granted by ETH Zurich
Innosuisse Project 25933.2 PFLS-LS
Swiss National Science Foundation under contract 205320_188910 / 1
Swiss Data Science Center project grant C18-10

Title: Downregulating α-synuclein in iPSC-derived dopaminergic neurons mimics electrophysiological phenotype of the A53T mutation

Authors: *P. HORNAUER[1], G. PRACK[1], N. ANASTASI[2], S. RONCHI[1], T. KIM[1], C. DONNER[3], M. FISCELLA[1], K. BORGWARDT[1], V. TAYLOR[4], R. K. JAGASIA[2], D. ROQUEIRO[1], A. HIERLEMANN[1], M. SCHRÖTER[1];
[1]Dept. of Biosystems Sci. and Engin., ETH Zurich, Basel, Switzerland; [2]F. Hoffmann - La Roche Ltd. Pharma Res. and Early Development, Neurosci., Basel, Switzerland; [3]Swiss Data Sci. Ctr., Zurich, Switzerland; [4]Dept. of Biomedicine, Univ. of Basel, Basel, Switzerland

Abstract: Despite several decades of research, key pathophysiological mechanisms of Parkinson's disease (PD) remain poorly understood, and PD as of today is not curable. Since animal models cannot capture the full extent of the pathology, there is a desperate need for human-based model systems to study disease etiology and to develop new therapies. Patient-derived and genetically engineered human induced pluripotent stem cells (hiPSCs) represent exciting new tools to investigate fundamental aspects of the mechanisms and underlying pathways of neurological disorders in a clinically relevant setting. High-density microelectrode arrays (HD-MEAs) provide researchers the opportunity to probe the development of disease-specific electrophysiological phenotypes at scale. However, in contrast to genomic or proteomic analysis frameworks, there are currently no standardized procedures for functional characterization of human neurons. Novel analysis approaches are, therefore, urgently needed to fully capitalize on the rich data sets provided by HD-MEAs. To this end, we developed *DeePhys*, a modular analysis workflow that we used in a proof-of-concept study to probe the electrophysiological phenotype of PD cells. We apply *DeePhys* to hiPSC-derived dopaminergic (DA) neuron-astrocyte co-cultures harboring a well-known genetic mutation associated with early-onset PD (*SNCA*^{A53T}) and an isogenic control line. We demonstrate how *DeePhys* can facilitate the assessment of cellular and network-level electrophysiological features to build functional phenotypes and to evaluate potential treatment interventions. We find that electrophysiological features across all scales proved to be specific for the A53T phenotype, enabled to identify the genotype and the age of individual cultures with high accuracy, and

revealed a mutant-like phenotype after downregulation of α-synuclein (α-syn). Quantification of α-syn levels revealed location-specific differences between the two cell lines, with a distinct a-syn reduction in A53T DA neurites, which indicated that α-syn is essential for the regulation of sustained synaptic activity in DA neurons. This finding may be linked to previous results regarding the role of α-syn in the maintenance of the neuronal synaptic vesicle pool. Our results show that *DeePhys* provides an easy-to-use, scalable, quantitative analysis platform for functional phenotype screening and for addressing important biomedical questions in the development of potential treatments.

Disclosures: P. Hornauer: None. **G. Prack:** None. **N. Anastasi:** None. **S. Ronchi:** None. **T. Kim:** None. **C. Donner:** None. **M. Fiscella:** A. Employment/Salary (full or part-time):; MaxWell Biosystems AG, Zürich, Switzerland. **K. Borgwardt:** None. **V. Taylor:** None. **R.K. Jagasia:** None. **D. Roqueiro:** None. **A. Hierlemann:** None. **M. Schröter:** None.

Poster

703. Alpha-Synuclein-Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 703.10

Topic: C.03. Parkinson's Disease

Title: Validation of an in vitro alpha-synuclein aggregation assay in primary cortical cultures for high throughput RNA interference screening

Authors: *S. LARDELL[1], Å. JÄGERVALL[1], A. BACK[1], J. SJÖHOLM[1], M. SVEDMAN[1], T. BELLANDE[2,3], R. MELKI[2], J. TÄGER[4], P. HEUTINK[4], C. VOLBRACHT[5], G. K. TOFARIS[6], J. PIHL[1];
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Abstract: In Parkinson's disease (PD), the formation and propagation of alpha-synuclein (alpha-syn) insoluble amyloid structures is a process hypothesized to drive the pathology of disease. As part of this process, impaired protein clearance and protein aggregation within neurons occur. From a drug discovery perspective, preventing protein aggregation or promoting protein clearance provide interesting opportunities as pharmacological intervention points. However, there is currently a lack of understanding with regards to the pathways and proteins responsible for progression of alpha-syn aggregation in particular in idiopathic PD, and in vitro genetic screens is one way to increase the knowledge about this.
Therefore, Cellectricon developed a high-capacity *in vitro* model based on primary embryonic mouse cortical cultures in the 384-well format, where lentiviral shRNA was added at 3 days *in vitro* (DIV) to induce gene silencing, and endogenous alpha-syn aggregation was induced at 10 DIV using recombinant human alpha-syn pre-formed fibrils. Endogenous alpha-syn aggregation

and cell health were then quantified at 17 DIV using immunocytochemistry and automated high content imaging and analysis.
In order to validate the assay, Cellectricon together with the IMPRiND consortium (a EU funded consortium that aims to map and target critical steps in the propagation of misfolded tau and alpha-synuclein) carried out an *in vitro* genetic screen targeting 300 individual genes with the aim of finding new targets and pathways involved in alpha-syn aggregation. For this work the assay was adapted to accommodate IMPRiNDs reagents i.e. the pre-formed fibrils and lentiviral shRNA library.
The outcome was a robust and sensitive alpha-syn aggregation assay for high throughput RNA interference screening. The throughput was more than sufficient for managing the library of 900 oligos targeting 300 genes with the required number of technical replicates and biological test occasions. Upon completion of the screen, the quality control metrics, e.g. signal to noise ratio, the variability in total cell count, no of neurons & SSMD all confirmed that the screen was a technical success. We can therefore conclude that the developed assay is well-suited for high throughput RNA interference for the discovery of new genes involved in alpha-syn aggregation.

Disclosures: **S. Lardell:** A. Employment/Salary (full or part-time):; Cellectricon AB. **Å. Jägervall:** A. Employment/Salary (full or part-time):; Cellectricon AB. **A. Back:** A. Employment/Salary (full or part-time):; Cellectricon AB. **J. Sjöholm:** A. Employment/Salary (full or part-time):; Cellectricon AB. **M. Svedman:** A. Employment/Salary (full or part-time):; Cellectricon AB. **T. Bellande:** A. Employment/Salary (full or part-time):; CEA, Institut François Jacob (MIRcen), CNRS, Laboratory of Neurodegenerative Diseases. **R. Melki:** A. Employment/Salary (full or part-time):; CEA, Institut François Jacob (MIRcen). **J. Täger:** A. Employment/Salary (full or part-time):; Center for Neurodegenerative Diseases (DZNE). **P. Heutink:** A. Employment/Salary (full or part-time):; Center for Neurodegenerative Diseases (DZNE). **C. Volbracht:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **G.K. Tofaris:** A. Employment/Salary (full or part-time):; University of Oxford. **J. Pihl:** A. Employment/Salary (full or part-time):; Cellectricon AB.

Poster

703. Alpha-Synuclein-Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 703.11

Topic: C.03. Parkinson’s Disease

Support: NIH RO1 AG058820
NIH R56 AG074473

Title: Effects of antiseizure drugs on epileptic activity and synaptic and cognitive dysfunction in transgenic mice expressing A53T human α-synuclein

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Abstract: Background: Abnormal α-synuclein (αS) plays an important role in the pathology of Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). New evidence shows network hyperexcitability can accelerate synaptic and cognitive deficits in PDD and DLB. While 90% of epileptiform activity is detected during sleep in Alzheimer's disease (AD), epileptiform activity during sleep in PDD or DLB is poorly understood. There are currently no known treatments to delay PDD or DLB progression. Although antiseizure drugs (ASDs) have been used to improve memory deficits in AD, this treatment approach has not been investigated in α-synucleinopathies.
Methods: To explore the effect of ASDs in attenuating αS-dependent seizure activity, we used transgenic mice expressing the A53T mutant human α-synuclein (TgA53T) as a model of motor and cognitive decline in PDD and DLB. We have begun screening FDA-approved ASDs using cortical electroencephalography with electromyography to examine epileptic events 24 hours before and after intraperitoneal injection. The two ASDs exhibiting the strongest efficacy in reducing epileptic activity across sleep-wake states will be tested for effects on cognitive function and synaptic plasticity following chronic administration. We are also quantifying pathological high frequency network oscillations (HFOs), biomarkers of epileptogenesis.
Results: 3-4-month-old TgA53T mice experienced epileptiform events but had normal long-term potentiation (LTP) and memory, indicating that epileptic activity onset precedes αS-induced synaptic and cognitive deficits. Starting at 6 months of age, TgA53T hippocampal slices show the absence of LTP, with reduced c-fos and calbindin and increased neuropeptide Y indicating alterations in hippocampal inhibitory circuitry. In behavioral testing, TgA53T mice exhibit impairment in fear conditioning, Y-maze spatial recognition, and Barnes maze spatial learning and memory with age. Preliminary studies indicate lacosamide and brivaracetam as the most effective of ASDs tested in reducing epileptic myoclonus and interictal epileptiform events. We also found more HFOs in TgA53T mice and TgA53T mice with tau ablation.
Conclusion: Suppression of epileptic activity by ASDs would support ASDs as a novel treatment for reducing or preventing cognitive dysfunction in DLB and PDD. Furthermore, ASD-induced reversal of synaptic and cognitive deficits would provide evidence that epileptic activity plays a causal role in αS-dependent pathology.

Disclosures: R. Vaknalli: None. **K. Hwang:** None. **K. Addo-Osafo:** None. **M. Vicente:** None. **S.T. Peters:** None. **A. Phillips:** None. **J.M. Choquette:** None. **A. Bragin:** None. **M.K. Lee:** None. **K.A. Vossel:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.01

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS NS099738
University of Florida Moonshot Program
University of Florida Summer Neuroscience Internship Program
NIA T32 AG061892

Title: Mhcii regulates transmission of α-synuclein seeded pathology in mice

Authors: *Q. VO[1], E. GONZALEZ DE LA CRUZ[1], K. MOON[1], K. N. MCFARLAND[2], M. WEINRICH[1], T. L. WILLIAMS[3], B. I. GIASSON[4], P. CHAKRABARTY[3];
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Abstract: MHCII molecules, expressed by professional antigen presenting cells (APC) such as T cells and B cells, is hypothesized to play a key role in the response of cellular immunity to α-synuclein (α-syn). However, the role of cellular immunity in neuroanatomic transmission of α-syn prion seeds is undetermined. To illuminate whether cellular immunity influences the transmission of α-syn seeds from periphery into the CNS, we injected preformed α-syn fibrils (PFF) in the hindlimb of Line M83 transgenic mouse model of synucleinopathy lacking MhcII. We show that complete deficiency of MhcII accelerates the appearance of seeded α-syn pathology and shortens the lifespan of the PFF-seeded M83 mice. To characterize whether B cell and T cell inherent MhcII function underlies this accelerated response to PFF seeding, we next injected α-syn PFFs in Rag1-/- mice that completely lack these mature lymphocytes. There was no alteration in lifespan or burden of endstage α-syn pathology in the PFF-seeded Rag1 deficient M83+/- mice. Together, these results suggested that MhcII function on immune cells other than these classical APCs are potentially involved in the propagation of α-syn in this model of experimental synucleinopathy. We focused on microglia next, finding that while microglial burden was significantly upregulated in PFF-seeded MhcII deficient mice relative to controls, the microglial activation marker Cd68 was reduced in these mice suggesting that these microglia were not responsive. Additional analysis of the CNS showed early appearance of neurotoxic astrocyte A1 signature and induction of the Ifnγ-inducible anti-viral response mediated by MhcI in the MhcII deficient PFF-seeded mice. Overall, our data suggests that loss of MhcII function leads to dysfunctional response in non-classical APCs such as brain resident microglia and astrocytes and that this response could potentially play a role in determining PFF induced pathology. Collectively, our results identify the critical role of MhcII function in synucleinopathies induced by α-syn prion seeds.

Disclosures: Q. Vo: None. **E. Gonzalez De La Cruz:** None. **K. Moon:** None. **K.N. McFarland:** None. **M. Weinrich:** None. **T.L. Williams:** None. **B.I. Giasson:** None. **P. Chakrabarty:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.02

Topic: C.03. Parkinson's Disease

Support: P3E-UDG-2021
CONACYT 1028543

Title: Temporality in the expression of alpha synuclein and dopaminergic neuronal death after intracerebral lipopolysaccharide injection

Authors: *A. K. LOMELI LEPE, S. J. LÓPEZ PÉREZ, J. L. CASTAÑEDA CABRAL, M. E. UREÑA GUERRERO;
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Abstract: Alpha-synuclein (α-syn) is a marker for synucleinopathies, with early activation states, whose consequences are visible long after, so understanding the initial cellular and molecular events in these conditions is relevant. In this sense, the aim of this work was to determine the temporality in the initial expression of monomeric and oligomeric forms of α-syn after a stimulus with lipopolysaccharide (LPS) in the substantia nigra (SN) and striatum (STR). In addition, the expression of thyroxine hydroxylase (TH) was analyzed to explore the viability of dopaminergic cells in response to post-stimulus events in these regions. Male Wistar rats (200-250 g) were used and injected with LPS (2.5 µg) (LPS group) or vehicle (SHAM group) via intra-nigral. The results were compared with animals without any procedure (Naive group). The expression of the monomeric/oligomeric α-syn and TH proteins was measured by western-blot at 3-, 5-, and 7-days post-injection (DPI) of LPS or vehicle. We find that the LPS induced an increase in monomeric α-syn expression at 7 DPI in SN ($p=0.0119$ vs SHAM) and at 3 and 5 DPI in STR ($p=0.0474$ vs Naïve); in case of the oligomeric forms, we observed a high expression of 60kDa α-syn at 5 DPI in SN and STR ($p=0.0077$ and $p=0.029$, respectively, vs Naïve). Furthermore, the expression of TH was observed decreased at 5 DPI in SN ($p=0.0020$ vs SHAM) and at 3 DPI in STR ($p=0.0298$ vs Naïve) in both ipsilateral areas. These results indicates that the initial expression of monomeric and oligomeric α-syn forms stimulated by LPS is a sudden event, and once this happens, expression tends to increase slowly, which is consistent with the gradual development of the synucleinopathies. On the other hand, the decrease in TH expression suggests that there is a death of dopaminergic neurons, which is probably related to the initial increase of α-syn.

Disclosures: A.K. Lomeli Lepe: None. **S.J. López Pérez:** None. **J.L. Castañeda Cabral:** None. **M.E. Ureña Guerrero:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.03

Topic: C.03. Parkinson's Disease

Support: Humboldt Post-doctoral Fellowship

Title: Immune-mediated trafficking of aSyn in a brain-first model of Parkinson's Disease

Authors: *R. MCFLEDER, A. MAKHOTKINA, A. PETERANDERL, J. VOLKMANN, C. IP;
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Abstract: INTRODUCTION Parkinson's disease (PD) is classically known for its characteristic motor symptoms of bradykinesia, rigidity, and tremor. However, this disease is riddled with an assortment of non-motor manifestations, such as constipation, one of the initial symptoms that patients experience. Investigations in the intestines of PD patients, have revealed the presence of α-Synuclein accumulations similar to the detrimental aggregates found in the Substantia Nigra (SN) of patients' brains. Where these aggregates originate and how they propagate throughout the body, however, remains unclear. Recent focus on the immune system has revealed a role for immune cells in the neurodegeneration in PD. As these cells are capable of traveling throughout the body, they may be the key to αSyn propagation and PD progression. Uncovering the role of the immune system in αSyn propagation is crucial for the development of early interventions aimed at halting the progression of PD. **OBJECTIVE** To test if expression of αSyn in the brain results in intestinal αSyn accumulation and inflammation in a mouse model of PD. **METHODS** We utilized a mouse model of PD, where an Adeno-associated Virus serotype 1/2 (AAV1/2), expressing a human mutated form of αSyn (haSyn) associated with familial PD, is injected into the SN of WT mice. The AAV1/2 leads to neuronal expression of the haSyn and PD-like motor dysfunction in mice. As a control, an equal amount of empty AAV (EV) was used. At different time points following injection, the brains and intestines were isolated and evaluated by either immunohistochemistry, flow cytometry, or single cell sequencing. **RESULTS** Localized expression of haSyn in the brain, resulted in increased expression and accumulation of both endogenous αSyn and haSyn in the intestines of mice. This αSyn accumulation started as early as 1 week after viral injection and continued for up to 10 weeks. Interestingly these accumulations were not present in the intestinal ganglia but rather in the immune-cell rich lamina propria of the ileum. These αSyn-containing cells were associated with both an increased infiltration and increased activation of CD4+ and CD8+ T cells in both the intestines and the brains of the haSyn mice. **CONCLUSIONS** αSyn can traffic from the brain to the gut and result in activation of intestinal T cells. This data provides new insight into the origination of PD and can therefore help guide studies focused on prevention and early treatment of PD.

Disclosures: R. McFleder: None. **A. Makhotkina:** None. **A. Peteranderl:** None. **J. Volkmann:** None. **C. Ip:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.04

Topic: C.03. Parkinson's Disease

Support: NRF-2021R1F1A1059784

Title: Nuclear α-synuclein-derived cytotoxic effect via the alteration of ribosomal RNA processing in primary mouse embryonic fibroblast.

Authors: *D. HO[1,3], H. KIM[2], D. NAM[2], J. HEO[3], I. SON[2];
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Abstract: α-Synuclein (αSyn) is a major component of Lewy body, which is known as a whole marker of Parkinson's disease (PD). And the oligomerization of αSyn is a putative cause of pathologic progression. However, the pathway of synucleinopathy-mediated neurodegeneration is still elusive. Most of unfolding αSyn is accumulated in cytoplasm, but some of αSyn is found in nucleus of neuron. The excessive nuclear localization of αSyn might disrupt the nucleolar structure. The nucleolar stress is related to the apoptosis via the abnormal ribose nucleic acid (RNA) processing. To test the effect of nuclear α-syn, we generated αSyn conjugated with nuclear export signal (NES) or nuclear localization signal (NES) and compared them along with wild type αSyn in primary mouse embryonic fibroblast (MEF) using the DNA transfection. And the over-expression of NLS αSyn increased cytotoxicity and hydrogen peroxide levels in the cytosol of MEF. And the levels of apoptotic marker, such as p53, pro-caspase 3, and cleaved poly-ADP ribose polymerase (PARP), were induced by the NLS αSyn in MEF. Interestingly, the increase of 40S ribosomal protein 15 (RPS15) was showed in MEF with expression of NLS αSyn along with the increase of cleaved nucleolin (NCL). And the MEF with expression of NLS αSyn showed higher 28S rRNA levels and lower 18S RNA levels than vector-transfected MEF. Intriguingly, the expression of NLS αSyn in MEF enhanced the accumulation of NCL in cytosol, thereby diminishing the nuclear NCL levels. We also observed that the downregulation of NCL using shRNA promoted the decrease in 18S RNA and increase in 28S rRNA in MEF. These results propose that the nuclear location of αSyn contribute to the alteration of rRNA processing in cells. Eventually, Conclusively, the progression of Parkinson's disease via the dopaminergic neuronal degeneration would be associated to abnormal rRNA processing-mediated apoptosis by the αSyn accumulation.

Disclosures: **D. Ho:** A. Employment/Salary (full or part-time):; Wonkwang Univ. Sanbon Medical Center. **H. Kim:** A. Employment/Salary (full or part-time):; Wonkwang Univ. Sanbon Medical Center. **D. Nam:** A. Employment/Salary (full or part-time):; Wonkwang Univ. Sanbon Medical Center. **J. Heo:** A. Employment/Salary (full or part-time):; Curahora Inc. **I. Son:** A. Employment/Salary (full or part-time):; Wonkwang Univ. Sanbon Medical Center.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.05

Topic: C.03. Parkinson's Disease

Title: Analysis of seeding behaviours in α-synuclein aggregation related to Parkinson's disease using biophysical analysis combined with cell-based assessment in mouse cortical cultures

Authors: M. GHAEIDAMINI[1], M. SJÖGREN[1], F. HAVERMEISTER[1], L. STRID ORRHULT[2], Å. JÄGERVALL[2], A. BACK[2], ***J. PIHL**[2], E. ESBJÖRNER[1];
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Abstract: Amyloid formation and accumulation of phosphorylated α-synuclein (α-syn) into cytosolic Lewy body inclusions is a key pathological hallmark of Parkinson's disease and other so-called Lewy body related disorders. The exact molecular mechanisms underlying α-syn-induced neurotoxicity are, however, still unclear, especially in relation to the propagation of α-syn aggregation between neurons.
We have studied the seeding and cross-seeding of WT and mutant forms of recombinant human α-syn using a range of complementary biophysical techniques and cellular analyses to better understand the kinetics and templating mechanisms underlying amyloid propagation in idiopathic as well as genetically inherited PD. Using thioflavin-T kinetic assays, atomic force microscopy, and secondary structure determination methods, we have explored the formation mechanisms of α-syn amyloid fibril seeds, as well as characterised their size, structure, and morphology. Through this, we have discovered that WT and several pathological mutant α-syn variants cross seed effectively, whereas other mutants are incompatible, both with respect to fibril elongation and secondary nucleation.
Furthermore, through use of an imaging-based screening platform with mouse embryonic cortex cultures, we have found that both WT and different mutant α-syn seeds induce endogenous phosphorylated α-syn inclusions, hence have the capacity to propagate aggregation. Importantly, we observed as strong negative correlation between seeding capacity and α-syn fibril length, extending previous observations that short fibrils (< 100 nm) are the most toxic species (1). Furthermore, we show that the pathological inheritable A53T mutation formed fibril seeds that had significantly higher propagation capacity in the cell model compared to WT. Interestingly, the biophysical analyses showed that A53T fibril seeds had a high propensity to spontaneously elongate in in vitro samples, whereas WT fibril seeds (under corresponding conditions) partly dissociated. This exploratory study highlights the power of combining biophysical analysis of amyloid formation in vitro with cell-based assays to understand structure-function relations in α-syn pathology; here specifically pin-pointing that fragmentation of fibril seeds as well as their intrinsic thermodynamic stability may be decisive for their ability to propagate amyloid formation in neurons.
1. Zhang, Xiaolu, et al. "Correlation between cellular uptake and cytotoxicity of fragmented α-synuclein amyloid fibrils suggests intracellular basis for toxicity." ACS Chemical Neuroscience 11.3 (2020): 233-241.

Disclosures: **M. Ghaeidamini:** A. Employment/Salary (full or part-time):; Chalmers University of Technology. **M. Sjögren:** None. **F. Havermeister:** A. Employment/Salary (full or part-time):; Chalmers University of Technology. **L. Strid Orrhult:** A. Employment/Salary (full or part-time):; Cellectricon AB. **Å. Jägervall:** A. Employment/Salary (full or part-time):; Cellectricon AB. **A. Back:** A. Employment/Salary (full or part-time):; Cellectricon AB. **J. Pihl:**

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Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.06

Topic: C.03. Parkinson's Disease

Support: JSC "Center for the International Programs" - Bolashaq

Title: Karyopherin abnormalities in alpha-synuclein mediated neurodegenerative disease

Authors: *D. SHARIPOV[1], E. BERECZKI[3], T. HORTOBAGYI[2], C. TROAKES[1], D. AARSLAND[2], F. HIRTH[1];
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Abstract: Alpha-synuclein (ASYN) is an intrinsically disordered protein prone to liquid-liquid phase separation (LLPS) from soluble monomers and oligomers to irreversible aggregates found in synucleinopathies like Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB), and Parkinson's Disease Dementia (PDD). LLPS is associated with nuclear transport receptors called karyopherins that can act as disaggregases against misfolding proteins. Karyopherin abnormalities have been implicated in synucleinopathies, but their role in disease formation remains enigmatic. We used proteomics data to screen for karyopherin alterations in brain areas BA9, BA24 and B40 of PDD and DLB cases vs Controls. Quantitative western blotting (qWB), immunohistochemistry and immunofluorescence were used to characterise levels and localisation of karyopherin and ASYN in human post-mortem brain tissue of Controls, PD, DLB and PDD. qWB of karyopherin and startle-induced locomotion were assessed in newly generated *Drosophila* models of synucleinopathy that accumulate either wildtype or A30P mutant ASYN. Proteomics analysis identified karyopherin alterations in PDD and DLB, with the most prominent for karyopherin alpha 3 (KPNA3). This was validated by qWB, and KPNA3 was shown to be mislocalised with ASYN in the nucleus of PD, DLB, and PDD cases. *Drosophila* experiments revealed that accumulating ASYN caused downregulation of fly KPNA3 and progressive motor impairment that was exacerbated by A30P mutant ASYN. These findings establish altered levels and localisation of karyopherin and ASYN in PD, PDD and DLB, and demonstrate that accumulating ASYN causes KPNA3 alterations and progressive motor dysfunction in *Drosophila*, suggesting a direct role of karyopherin abnormalities in the onset and progression of neurodegenerative synucleinopathies.

Disclosures: D. Sharipov: None. **E. Bereczki:** None. **T. Hortobagyi:** None. **C. Troakes:** None. **D. Aarsland:** None. **F. Hirth:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.07

Topic: C.03. Parkinson’s Disease

Support: NINDS grant NS101134

Title: PP2A Methylesterase, PME-1, exacerbates alpha-synuclein mediated toxicity in mice

Authors: *S. MADDILA[1], J. LIU[1], J. ZHANG[1], E. JUNN[1], R. NICHOLS[2], M. MOURADIAN[1];
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Abstract: alpha-Synuclein (p-Syn) that accumulates in Lewy bodies and Lewy neurites in Parkinson’s disease (PD) and Dementia with Lewy Bodies (DLB) is typically hyperphosphorylated at Serine 129. This post-translational modification accelerates α-Syn aggregation and fibrillization in vitro and, therefore, identifying factor(s) that drive this process can provide insight into the molecular pathogenesis of synucleinopathies and may lead to the identification of new disease modifying therapeutics. Considering that multiple kinases phosphorylate α-Syn, rendering the use of a specific kinase inhibitor ineffective, we have focused on identifying the phosphatase for phospho-S129-α-Syn. Using a series of *in vitro* and cellular experiments, we found that B55alpha subunit-containing protein phosphatase 2A (PP2A) isoforms dephosphorylate p-S129-α-Syn. The assembly of this B55alpha subunit-containing PP2A isoforms into functional phosphatases is regulated by methylation of the catalytic C subunit. Notably, the PP2A demethylating enzyme, methylesterase 1 (PME-1), is upregulated in PD and DLB brains leading to reduced PP2A activity. We hypothesized that increased PME-1 expression and activity may contribute to the accumulation of hyper-phosphorylated α-Syn leading to misfolding and toxicity. To test this hypothesis, we subjected mice that over-express PME-1 in forebrain neurons to intrastriatal α-Syn preformed fibril (PFF) injection. At three and six months post-PFF injection, PME1 over-expressing mice exhibited worse performance on the rotarod and nesting behavior compared with PFF injected control mice. Immunohistochemical stains revealed a profile consistent with the behavioral outcome. These findings suggest that PME-1 overexpression exacerbates α-Syn seeding and propagation and the associated neurodegeneration. Consequently, our observations also point to PME-1 as a promising therapeutic target to be inhibited in order to keep PP2A functionally active, de-phosphorylate phospho-S129-α-Syn, reduce its tendency to misfold, and prevent or slow down disease progression in synucleinopathies.

Disclosures: S. Maddila: None. **J. Liu:** None. **J. Zhang:** None. **E. Junn:** None. **R. Nichols:** None. **M. Mouradian:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.08

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS DP1 NS116783
NIH/NIA R01 AG064051
NIH/NIBIB R01 EB030884
NIH/NIMH RF1 MH114227
NIH/NINDS R01 NS091461
NIH S10 OD025176

Title: Optogenetic neuromodulation modifies α-synuclein spreading dynamics and is predicted by changes in whole-brain function

Authors: E. DADGAR-KIANI[1], G. BIERI[2], R. MELKI[5], A. D. GITLER[3], ***J. LEE**[4]; [1]Bioengineering, Stanford Univ., Stanford, CA; [2]Stanford Univ., Menlo Park, CA; [3]Dept. of Genet., [4]Stanford Univ., Stanford Univ., Stanford, CA; [5]Inst. François Jacob, Fontenay-aux-Roses, France

Abstract: The seeding and spreading of misfolded proteins can lead to widespread pathology and has been implicated in many neurodegenerative diseases. However, many treatments for these diseases only compensate for circuit function changes caused by neurodegeneration, such as deep brain stimulation in Parkinson's Disease. Here we report on an optogenetic stimulation paradigm guided by brain clearing and quantification that allows for the tracking and modulation of whole brain α-synuclein pathology. In a mouse pre-formed fibril (PFF) model where injection of α-synuclein PFFs into the striatum results in widespread pathology, repeated daily optogenetic stimulation led to consistent changes in brain-wide pathology after two weeks. Aggregation decreased at both the site of stimulation and various ipsilateral regions of interest, while the contralateral cortex saw a consistent increase in pathology. Meanwhile, the treatment did not affect the total whole brain aggregate count. Aligning the modified spreading patterns with brain activity during stimulation, as measured by optogenetic fMRI, confirmed that the polarity and spatial localization of these changes in pathology could be predicted by whole brain functional changes. Altogether, these results demonstrate the ability to both modulate and readout whole brain pathology using a longitudinal neurostimulation paradigm, which can guide future treatments for neurodegenerative disease.

Disclosures: E. Dadgar-Kiani: None. **G. Bieri:** None. **R. Melki:** None. **A.D. Gitler:** None. **J. Lee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); LVIS. F. Consulting Fees (e.g., advisory boards); LVIS.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.09

Topic: C.03. Parkinson's Disease

Support: SERB, Govt of India (CRG/2018/004960)

Title: Carbamylation induced amyloid fibrillization in KTKEGV repeat motif of α-synuclein and the protein itself.

Authors: *S. SHAH, J. GADHAVI, S. GUPTA;
IIT Gandhinagar, Gandhinagar, India

Abstract: Alpha-synuclein (α-syn) is an intrinsically disordered protein that is one of the major components of Lewy bodies and Lewy neurites, pathological hallmarks of Parkison's Disease (PD). α-syn has been observed to be heavily post-translationally modified. Also, there are differences between the proteoforms isolated from the PD patients and normal controls. Hence, post-translational modifications are likely to play an essential role in modulating the aggregation kinetics of α-syn. Recently, literature has postulated that charge neutralization could play a huge role in forming different amyloid fibrillar cores as identified from cryo-EM structures of Tau and α-Synuclein fibrils. One such charge neutralizing PTMs is carbamylation, a non-enzymatic age-dependent charge neutralizing PTM that replaces the positive charge of the lysine side-chain with an ureido functionality. In this work, we have studied the effect of carbamylation on various KTKEGV repeats present in α-syn protein by various biophysical assays such as ThT assay, fluorescence microscopy, and SEM. We observed that carbamylation has a site-specific effect on the aggregation kinetics of different KTKEGV repeats. While none of the seven repeat regions aggregates on its own, we identified four regions that rapidly formed amyloid fibrils when carbamylated. Similarly, while 43-50 peptide WT sequence didn't aggregate even after carbamylation, disease-relevant mutated versions formed amyloid readily. We also extended the study to full-length α-syn protein. At low concentrations, carbamylated α-syn aggregation kinetics indicated the formation of aggregates with many-fold higher amyloidogenic content than WT α-syn. Finally, we demonstrated that these aggregates of carbamylated α-syn can readily seed aggregation in WT monomeric α-syn preparations. This points to the strong amyloidogenic nature of carbamylated α-syn. Conclusion: Our studies indicate that carbamylation and other similar chemically similar PTMs can significantly alter the physicochemical characteristics as well as aggregation propensity. Some of these proteoforms could very well be the elusive toxic seed responsible for initiating the amyloid cascade.

Disclosures: S. Shah: None. **J. Gadhavi:** None. **S. Gupta:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.10

Topic: C.03. Parkinson's Disease

Support: Branfman Family Foundation
Indiana Clinical and Translational Sciences Institute
Bilsland Dissertation Fellowship

Title: Phosphoproteomic changes as an early-stage predictive indicator of cortical synaptic dysfunction in synucleinopathies

Authors: S. DUTTA[1], J. A. HENSEL[1], R. M. FERREIRA[1], J. FRANCO[1], U. K. ARYAL[1], C. R. FERREIRA[1], L. A. VOLPICELLI-DALEY[2], ***J.-C. ROCHET**[1];
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Abstract: Cortical dysfunction plays a critical role in non-motor symptoms associated with PD and other synucleinopathies. Recent studies have reported functional changes in cortical circuitry in pre-clinical models of PD, but with limited mechanistic insight. Therefore, in search of causative or predictive factors, we hypothesized that aSyn aggregation leads to alterations of the cellular proteome and lipidome. To address this hypothesis, we utilized an *in vivo* model of aSyn aggregation involving the injection of aSyn preformed fibrils (PFFs) in rat striatum to study the downstream effects of aggregation. In this model, we showed that PFF injection leads to the presence of aSyn aggregates that stain positive for the phosphorylated form of serine residue 129 (pSer129) in the sensorimotor cortex, SNpc, and other anatomically connected brain regions. Proteomic analysis of brain homogenates indicate that intrastriatally injected PFFs do not induce significant changes in the global proteome of the sensorimotor cortex compared to injected aSyn monomer 3 months post-injection. Similarly, no changes were observed in 13 lipid classes, including lipids that play a central role in synaptic composition and cellular signaling. However, analysis of the phosphoproteome of the sensorimotor cortex revealed significant differences between the PFF and monomer groups 3 months post-injection. Gene ontology analysis of the phosphoproteomic changes suggested that aSyn PFF administration led to perturbations in synaptic transmission. Moreover, we identified phosphosites that were previously not reported and distinct from sites reported for acute synaptic excitation. Collectively, these findings deepen our understanding of the molecular underpinnings of synucleinopathy disorders, laying the groundwork for developing well-tailored intervention strategies in the brains of patients.

Disclosures: S. Dutta: None. **J.A. Hensel:** None. **R.M. Ferreira:** None. **J. Franco:** None. **U.K. Aryal:** None. **C.R. Ferreira:** None. **L.A. Volpicelli-Daley:** None. **J. Rochet:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.11

Topic: C.03. Parkinson's Disease

Support: Lewy Body Society (LBS-007)
Alzheimer's Research UK Northern Network centre grant

Title: Genomic DNA damage and nuclear alpha-synuclein in Dementia with Lewy bodies cases.

Authors: *D. KOSS[1], D. ERSKINE[1], A. PORTER[2], P. PALOMSKI[2], O. TODD[1], H. MENON[1], F. LEBEAU[3], J. ATTEMS[1], T. OUTEIRO[1];
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Abstract: Dementia with Lewy bodies (DLB) is the second most common form of dementia and presents with cognitive fluctuations, hallucinations and REM sleep disruptions. Pathologically DLB is defined by the neuronal accumulation of cytoplasmic alpha-synuclein (aSyn) aggregates known as Lewy bodies (LBs). Despite the hallmark status of LBs, their association with cellular damage remains unclear as does the initial molecular trigger for aSyn aggregation. Predominately pre-synaptic, nuclear aSyn ($aSyn^{Nuc}$) has been observed *in-vitro* and is associated with altered DNA integrity. Nevertheless, the presence and role of $aSyn^{Nuc}$ in the human brain remains controversial and its relevance to DLB pathology uncharacterised. Here, aSyn and DNA damage within nuclei of post-mortem human brains is demonstrated via immunohistochemistry, immunoblot and mass-spectrometry. In both control and DLB cases, $aSyn^{Nuc}$ was apparent in neuronal and non-neuronal populations. Critically, however, in cases of DLB an increase in pathological $aSyn^{Nuc}$ phosphorylation (pS129; $p<0.05$) and oligomerisation was observed. Nuclear pathology occurred alongside elevations of genomic DNA (gDNA) damage in the form of double strand breaks (yH2.AX; $p<0.05$), yet not of single strand breaks (XRCC1, $p>0.05$). Given the potential of DNA and histones to facilitate aSyn aggregation in recombinant systems, LBs were examined for evidence of ectopic cytoplasmic gDNA. Indeed, immunohistochemical analysis of the nuclear material within LBs, demonstrates the presence of the double strand break marker yH2.AX, in the absence of constitutive nuclear proteins (p53BP-1). Assessment of temporal cortex LBs, demonstrated ~ 90% of LBs to be positive for yH2.AX. Such an immunoreactive profile of LBs is consistent with inclusion of cytoplasmic chromatin fragments known to occur in response to excessive DNA damage and suggests that ectopic gDNA and histones may trigger cytoplasmic aSyn aggregation *in-situ*. This study highlights an under-investigated aspect of DLB pathology and points to novel mechanism(s) for aSyn aggregation and cellular dysfunction which may be clinically exploited via the repurposing of existing DDR targeted therapeutics and/or the development of novel drugs.

Disclosures: D. Koss: None. **D. Erskine:** None. **A. Porter:** None. **P. Palomski:** None. **O. Todd:** None. **H. Menon:** None. **F. LeBeau:** None. **J. Attems:** None. **T. Outeiro:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.12

Topic: C.03. Parkinson's Disease

Support: MOST 110-2320-B-182-028-
CMRPD1K0512
EMRPD1K0481

Title: Intra-substantia nigra alpha-synuclein induced Parkinson's disease dementia

Authors: *Y.-C. KUO, J.-C. CHEN, Y.-T. HUANG;
Grad. Inst. of Biomed. Sci., Chung-Gung Univ., Tauyuan, Taiwan

Abstract: Parkinson's disease is the most common neurodegenerative disease after Alzheimer that affects movement. Because of the characteristic feature of PD is the loss of dopamine neurons in the substantia nigra (SN), hence impairs the motor function. The accumulation of Lewy Bodies (LBs), of which the protein alpha-synuclein (α-syn), seems to be the hallmark that cause PD. The LBs accumulation and spreading to other brain regions may also cause Parkinson's disease dementia (PDD). The motor dysfunction combined with dementia seriously affect the patient's quality of life, but the cause of PDD remains unclear. In this study, our purpose is to explore the neuropathological changes in PDD. We injected AAV9-α-Syn in SN to mimic the motor and cognitive defect in PDD, in addition to investigate the microglia immune response to α-Syn. Our preliminary results showed that AAV-α-Syn-treated mice developed motor dysfunction after 6 months via Rota-rod test and gait analysis. AAV-α-Syn injection also induced anxiety and depression-like behaviors than vehicle control after 6 months by open field, elevated plus-maze and sucrose preference tests. Moreover, AAV-α-Syn injected mice has recognition and working memory problems after 12 months. Consequently, we analyzed the biochemical alteration aiming to identify the potential target(s) in the immune system that might correlate with α-Syn aggregation. We found that AAV-α-Syn persistently overexpressed human-α-Syn and accumulated in the SN and hippocampus. We also found the α-Syn/p-Ser129, the pathological α-Syn marker, abundantly expressed in the SN. We next analyzed complement system and NMDA receptor mRNA in hippocampus and found that expression of C3 and NR2A has a trend of decrease compared to vehicle control. In *in vitro* system, we treated α-Syn PFF in BV2 microglia cell line, and measured the mRNA changes of cytokine and complement system. There are significantly increase in levels of IL-6 (887.9 ± 98.02, n=6), TNF-α (10.69 ± 1.077, n=6), IL1-β (748.7 ± 181.1, n=6) 6 hr post-PFF, but there is no difference in levels of C3 (1.323 ± 0.2153, n=6) and C1qa (1.014 ± 0.2537, n=6) 6 hr post-PFF. Our current data suggest that pathological α-Syn accumulation apparently disturbs the immune system and may affect the neural function. In addition, pathological α-Syn may also spread to other brain regions that leads to affective and cognitive problems.

Disclosures: Y. Kuo: None. **J. Chen:** None. **Y. Huang:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.13

Topic: C.03. Parkinson's Disease

Support: NIH NINDS Grant R01 NS102257
NIH NINDS Grant R56 NS117465
NIH NINDS Grant T32 NS095775
Merck & Co.

Title: Heterozygosity of GBA1 L444P mutation enhances hippocampal pathology and lipid accumulation

Authors: *D. L. RUSSELL[1], C. L. MAHONEY-CRANE[1], M. VISWANATHAN[1], R. A. C. CURTISS[1], J. FREIRE[1], S. BOBBA[1], M. KANDEBO[2], L. YAO[2], B.-L. WAN[2], N. G. HATCHER[2], S. M. SMITH[2], J. N. MARCUS[2], L. A. VOLPICELLI-DALEY[1];
[1]Ctr. for Neurodegeneration and Exptl. Therapeut., Univ. of Alabama at Birmingham, Birmingham, AL; [2]Neurosci. Discovery, Merck & Co., Inc., West Point, PA

Abstract: Heterozygosity for the neuropathic mutation GBA1 L444P ($GBA1^{+/L444P}$) increases the risk of cognitive impairments in Parkinson's Disease (PD) by 5.6-fold. We used $GBA1^{+/L444P}$ mice to determine the effects of this severe GBA1 mutation on lipid metabolism, behavior, α-synuclein (α-syn) inclusion formation, and loss of dopamine neurons in the substantia nigra pas compacta (SNpc). $GBA1^{+/L444P}$ mice demonstrated impaired contextual fear conditioning, a behavior test of hippocampal function. In the brains of $GBA1^{+/L444P}$ mice, compared to $GBA1^{+/+}$ mice, levels of glucosylsphingosine (GlcSph), but not glucosylceramide (GlcCer), were elevated. α-Syn inclusions were increased in the hippocampus of $GBA1^{+/L444P}$ mice compared to $GBA1^{+/+}$ mice, but not in the cortex, or SNpc. Pathologic α-syn caused a loss of dopamine neurons in the SNpc in both $GBA1^{+/L444P}$ mice and $GBA1^{+/+}$ mice, but there were no differences between GBA1 L444P expression groups. Overall, these data suggest the critical importance to evaluate the contribution of glucosylsphingosine and hippocampal pathology in PD-GBA1.

Disclosures: D.L. Russell: None. **C.L. Mahoney-Crane:** None. **M. Viswanathan:** None. **R.A.C. Curtiss:** None. **J. Freire:** None. **S. Bobba:** None. **M. Kandebo:** A. Employment/Salary (full or part-time):; Merck & Co. **L. Yao:** A. Employment/Salary (full or part-time):; Merck & Co. **B. Wan:** A. Employment/Salary (full or part-time):; Merck & Co. **N.G. Hatcher:** A. Employment/Salary (full or part-time):; Merck & Co. **S.M. Smith:** A. Employment/Salary (full or part-time):; Merck & Co. **J.N. Marcus:** A. Employment/Salary (full or part-time):; Merck & Co. **L.A. Volpicelli-Daley:** 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.; Merck & Co..

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.14

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS102227
OHSU Knight Cancer Institute PhD Scholar Award

Title: Alpha-synuclein in nucleolar DNA double-strand break repair: the cross-talk between Parkinson's Disease and melanoma

Authors: *M. ARNOLD[1], S. WITT[2], P. CASSIDY[1], V. UNNI[1];
[1]Oregon Hlth. and Sci. Univ., Portland, OR; [2]Louisiana State Univ. Hlth., Shreveport, LA

Abstract: Parkinson's Disease (PD) is the second most common neurodegenerative disease associated with a complex combination of genetic and environmental risk factors, which manifests into devastating movement and coordination deficits. Interestingly, strong evidence suggests unexpected links between neurodegeneration and cancer, since epidemiological studies have found that PD patients are at an increased risk of developing melanoma. Furthermore, this relationship is bidirectional; individuals diagnosed with melanoma are at an increased risk of developing PD. Although these clinical associations are well-established, the cellular and molecular pathways linking these diseases are poorly understood. Recent research has uncovered a previously unrecognized role for the PD neurodegeneration-associated protein alpha-synuclein (αSyn) in melanomagenesis, highlighting the role of αSyn in regions outside of the central nervous system. Several studies have shown that melanoma cells overexpress αSyn and that this is important for promoting cell proliferation and growth; however, the underlying role of αSyn within melanogenesis is unknown. We have previously demonstrated that αSyn is important in DNA double-strand break (DSB) repair, and our new studies show an important role for αSyn within the nucleolus. Therefore, we hypothesize that melanoma upregulates αSyn expression to improve DSB repair function within the nucleolus. Using the human melanoma cell line, SK-Mel28, our data suggest that αSyn and γH2AX are preferentially enriched within the nucleolus and the colocalization between these two proteins is significantly greater in the nucleolus compared to the nucleoplasm. Furthermore, knocking out αSyn significantly increases DSBs within the nucleolus, and these levels are attenuated when αSyn is transgenically reintroduced into the knockout background. Within the nucleolus, αSyn significantly colocalizes with nucleophosmin and treacle, two proteins important for DSB repair of ribosomal DNA (rDNA). Lastly, inducing rDNA DSBs using the endonuclease, I-PpoI, significantly increases not only nuclear γH2AX, but also αSyn and its colocalization to proteins important for nucleolar DSB repair. Knocking out αSyn significantly increases the amount of DBSs after I-PpoI induction. These results suggest that upregulation of αSyn may play a critical and underappreciated role in melanogenesis, by allowing melanoma cells to more faithfully repair DSBs within the nucleolus, thereby supporting increased cell survival and growth.

Disclosures: **M. Arnold:** None. **S. Witt:** None. **P. Cassidy:** None. **V. Unni:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.15

Topic: C.03. Parkinson’s Disease

Support: DOD/PRP/IIRA W81XWH2010781
NIH/NINDS R01 NS118669).

Title: Alpha-synuclein Aggregates in Red Blood Cell (RBC)-derived Extracellular Vesicles (EVs) as Potential Prodromal Biomarker of Environmentally Linked Parkinsonism

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Abstract: Chronic environmental exposure to neurotoxic pesticides and herbicides such as Agent Orange (AO) has been associated with a variety of harmful health effects in humans, including neurological conditions such as Parkinson’s disease (PD) and other related neurological conditions. Military personnel, who are often exposed to a wide range of environmentally persistent neurotoxic pesticides and herbicides including as Agent Orange (AO) in the unique circumstances of their service and deployments, are at higher risk of developing PD than are civilians. The prodromal clinical diagnosis and treatment of PD have remained challenging despite several advances in the understanding of its pathogenesis. Since the definitive diagnosis of PD is only achieved at autopsy, the development and validation of sensitive and qualifiable peripheral biomarkers are urgently needed to accurately monitor and inform the effects of environmental neurotoxic chemical exposures on PD pathogenesis. Since red blood cell (RBC)-derived extracellular vesicles (EVs) is a major source of extracellular α-synuclein (αSyn) in blood, we examined whether human RBC-derived EVs containing αSyn aggregates can serve as a valid biomarker for PD using an αSyn real-time quaking-induced conversion (RT-QuIC) seeding assay (SAA). Healthy human RBCs procured from Blood Bank were exposed to polychlorinated AO (30-100 µM) for 1-7 days. Following the neurotoxicant exposure EVs were isolated from the AO-treated and control RBCs by sequential ultracentrifugation and were subjected to nanoparticle tracking analysis to quantify their concentration and size distribution. EVs were then subjected to an aggregated αSyn RT-QuIC assay, which uses thioflavin-T (ThT), a dye that has a strong affinity to αSyn fibrils. In this microplate-based seeding assay (SAA), αSyn aggregates in isolated EVs serve as the seeds for a recombinant human monomeric αSyn substrate. These results reveal significant dose- and time-dependent increases in EVs in AO treated samples. More importantly, increased αSyn fibrilization as measure by SAA in AO-treated EVs, suggesting the presence of potentially pathogenic αSyn aggregates. Collectively, these results provide evidence that the ultrasensitive SAA based detection of misfolded αSyn in RBC-derived EVs may serve as a promising prodromal biomarker for environmentally linked PD in civilian and military personnel.

Disclosures: **C. Janarthanam:** None. **H. Jin:** None. **V. Anantharam:** None. **A. Kanthasamy:** None. **A. Kanthasamy:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.16

Topic: C.03. Parkinson's Disease

Support: Alzheimer's Association NIRG-15-363678
American Federation for Aging Research New Investigator in Alzheimer's Research Grant
NIH 1R01NS102181
NIH 1R01NS113960
NIH 1R01NS121077
NIH 1R01NS095988
NIH 1R01AG052505

Title: Release of pathogenic α-synuclein species from neurons via SNARE-dependent lysosomal exocytosis

Authors: *Y. XIE[1], N. N. NASERI[3], J. FELS[1], P. KHAREL[1], Y. NA[1], D. LANE[2], J. BURRÉ[1], M. SHARMA[1];
[1]Appel Inst. for Alzheimer's Res. and Feil Family Brain & Mind Res. Inst., [2]Feil Family Brain & Mind Res. Inst., Weill Cornell Med., New York, NY; [3]Dept. of Chem., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Considerable evidence supports the release of pathogenic aggregates of the neuronal protein α-Synuclein (αSyn) into the extracellular space. While this release is proposed to instigate the neuron-to-neuron transmission and spread of αSyn pathology in synucleinopathies including Parkinson's disease, the molecular-cellular mechanism(s) remain unclear. We show that pathogenic species of αSyn accumulate within neuronal lysosomes in mouse brains and primary neurons. We then find that neurons release these pathogenic αSyn species via SNARE-dependent lysosomal exocytosis; proposing a central mechanism for exocytosis of aggregated and degradation-resistant proteins from neurons.

Disclosures: **Y. Xie:** None. **N.N. Naseri:** None. **J. Fels:** None. **P. Kharel:** None. **Y. Na:** None. **D. Lane:** None. **J. Burré:** None. **M. Sharma:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.17

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS DP1 NS116783
NIH/NIA R01 AG064051
NIH/NIBIB R01 EB030884
NIH/NIMH RF1 MH114227
NIH/NINDS R01 NS091461
NIH S10 OD025176

Title: Whole-brain modeling of α-synuclein spreading, aggregation, and decay dynamics as informed by mesoscale connections and gene expression

Authors: *E. DADGAR-KIANI[1], G. BIERI[2], R. MELKI[5], A. D. GITLER[3], J. LEE[4]; [1]Stanford Univ., Stanford Univ., Stanford, CA; [2]Stanford Univ., Menlo Park, CA; [3]Dept. of Genet., [4]Stanford Univ., Stanford, CA; [5]Inst. François Jacob, Fontenay-aux-Roses, France

Abstract: An emerging view of neurodegenerative diseases is that seeding of misfolded proteins in discreet brain regions leads to widespread pathology. The mechanisms by which misfolded protein seeds form in distinct brain regions and cause differential whole-brain pathology remain elusive. We used whole-brain tissue clearing and high-resolution imaging to longitudinally map pathology in an α-synuclein pre-formed fibril injection model of Parkinson's disease. We used machine-learning based quantitative three-dimensional analysis of these images and identified distinct phases of spreading and decline. We then fit a network model with parameters that represent α-synuclein pathology spreading, aggregation, and decay. Remarkably, our model can predict α-synuclein spreading patterns from several distinct brain regions and can even pinpoint their origins. These models empower mechanistic understanding and accurate prediction of disease progression, paving the way for the development and testing of therapeutic interventions.

Disclosures: E. Dadgar-Kiani: None. **G. Bieri:** None. **R. Melki:** None. **A.D. Gitler:** None. **J. Lee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); LVIS. F. Consulting Fees (e.g., advisory boards); LVIS.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.18

Topic: C.03. Parkinson's Disease

Support: Cluster of Excellence "Multiscale Bioimaging: from Molecular Machines to Networks of Excitable Cells" (MBExC), University of Göttingen, Göttingen, Germany

Title: Alpha-synuclein (auto)antibodies - their relevance as a biomarker and role in (patho)physiology of parkinson's disease

Authors: P. GARG, JR, F. MAASS, F. HOBBIE, JR, F. WÜRTZ, JR, S. KÜGLER, ***M. BAEHR**;
Univ. Med. Goettingen, Goettingen, Germany

Abstract: ***Objectives:*** The presence of α-synuclein (α-syn) autoantibodies (AAb) in the serum of all individuals has been widely reported. Their use as a biomarker for Parkinson's disease (PD) has been long debated with little insight into their physiological role. In this study, using samples from two independent cohorts, we validated the relevance of α-syn AAbs as a biomarker for PD and examined their (patho)physiological effects.***Methods:*** We acquired 295 serum samples comprising age- and gender-matched healthy subjects, two PD cohorts, and patients with other neurological disorders. α-syn AAb levels were investigated by performing ELISA and immunoblots. To study the physiological role of α-syn AAbs, we used synuclein overexpressing rat primary neuron-astrocyte cocultures and astrocyte-enriched cultures that were exposed to α-syn AAbs containing serum or commercially available α-syn antibodies. The effects on cell survival and network activity were studied using immunofluorescence, immunoblots, and calcium imaging. ***Results:*** The serum levels of α-syn AAb were significantly reduced in patients with PD as well as patients with other neurological disorders versus healthy subjects. Furthermore, α-syn AAb levels displayed high inter-and intra-cohort variability with no correlation to clinical parameters like age, gender, disease duration, or severity. Our findings question the implication of α-syn AAb levels as a biomarker for PD. At the physiological level, α-syn AAbs mediated a dose-dependent loss of α-syn overexpressing neurons. A similar loss of neurons was observed upon exposure to commercially available α-syn antibodies. The removal of α-syn AAbs from the serum rescued neurotoxicity. α-syn (auto)antibodies did not affect astrocyte survival, thereby indicating a rather direct effect of α-syn AAbs on neurons. To this end, we found that blocking NMDA receptors with its competitive antagonist AP5 rescued the loss of neurons upon treatment with α-syn AAbs containing serum. Our data suggest that α-syn AAbs-mediated neurotoxicity is dependent on the neuronal spontaneous activity.***Conclusions:*** High inter-and intra-cohort variability and lack of correlation to clinical parameters make it difficult to determine the true predictive values of α-syn AAbs, thereby limiting their use as a biomarker for PD. Furthermore, the α-syn (auto)antibodies cause loss of α-syn overexpressing neurons but not astrocytes. We hypothesize that this neurotoxicity is potentially dependent on neuronal activity and might serve as a route to early neuronal cell death in PD where the blood-brain barrier is compromised and peripheral α-syn AAbs could invade the brain.

Disclosures: P. Garg: None. **F. Maass:** None. **F. Hobbie:** None. **F. Würtz:** None. **S. Kügler:** None. **M. Baehr:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.19

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation
NIH/NINDS R03NS108229
Branfman Family Foundation
Indiana Clinical and Translational Sciences Institute (CTSI)

Title: Impact of post-translational modifications on membrane-induced alpha-synuclein aggregation in synucleinopathy disorders

Authors: *M. GUZMAN SOSA[1], O. ALI[1], S. DONZELLI[2], S. DUTTA[1], T. JOHNSON[1], A. SADEK[2], H. A. LASHUEL[2], J.-C. ROCHET[1];
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Abstract: Alpha-synuclein (aSYN) is a presynaptic protein that forms aggregates in the brains of individuals with Parkinson's disease (PD) and other synucleinopathy disorders. aSYN is a natively unfolded protein in solution but can adopt an alpha-helical structure upon binding to phospholipid membranes, and this interaction is thought to play a role in vesicle trafficking and the release of neurotransmitters. Data from our group and others suggest that the aggregation of membrane-bound aSYN plays a central role in the protein's neurotoxicity in PD via a mechanism involving vesicle disruption. Furthermore, increasing evidence suggests that the mechanism of membrane-induced aggregation is distinct from the more extensively studied process of aSYN aggregation in the absence of membranes. Although various post-translational modifications (PTMs) of aSYN identified in cell culture, animal models, or human brain have been shown to modulate aSYN aggregation in the absence of lipids, little is known about the effects of PTMs on membrane-induced aSYN self-assembly. We hypothesize that certain PTMs promote the protein's aggregation at the surface of phospholipid membranes, resulting in enhanced aSYN neurotoxicity, based on evidence that some PTMs alter the conformation of membrane-bound aSYN and/or perturb aSYN-membrane interactions. To address this hypothesis, aSYN variants with N- and C-terminal truncations previously identified in the human brain were characterized in terms of their relative propensities to undergo membrane-induced self-assembly and elicit vesicle disruption. We found that aSYN variants with C-terminal truncations underwent more extensive oligomerization and accelerated fibrillization (yielding fibrils with altered morphologies visualized by EM) compared to WT aSYN when incubated with phospholipid vesicles at a low pH mimicking the acidic conditions of endocytic compartments. Moreover, the rate of aSYN-mediated vesicle disruption at pH 7 (relevant to cytosolic conditions) increased with the extent of the C-terminal truncation. In general, N-terminal aSYN truncation mutants formed oligomers or fibrils more rapidly than WT aSYN in the presence of vesicles at low pH but had a reduced ability to elicit membrane permeabilization at pH 7. Current efforts are focused on characterizing our panel of aSYN truncation variants in terms of aggregation propensity and toxicity in neuronal cell culture models. The results of these studies will provide new insights into the role of aSYN PTMs and membrane-induced aggregation in the pathology

of synucleinopathy disorders, setting the stage for developing therapies targeting aSYN in the brains of patients

Disclosures: **M. Guzman Sosa:** None. **O. Ali:** None. **S. Donzelli:** None. **S. Dutta:** None. **T. Johnson:** None. **A. Sadek:** None. **H.A. Lashuel:** None. **J. Rochet:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.20

Topic: C.03. Parkinson's Disease

Title: Cell therapy of Astrocytes treat α-synuclein pathology through cell transplant in Parkinson's disease

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Abstract: Intra-neuronal inclusions of misfolded α-synuclein (α-syn) and prion-like spread of the pathologic α-syn contribute to progressive neuronal death in Parkinson's disease (PD). Despite the pathologic significance, no efficient therapeutic intervention targeting α-synucleinopathy has been developed. In this study, we provide evidence that astrocytes, especially those cultured from the ventral midbrain (VM), show therapeutic potential to alleviate α-syn pathology in multiple in vitro and in vivo α-synucleinopathic models. Regulation of neuronal α-syn proteostasis underlies the therapeutic function of astrocytes. Specifically, VM-derived astrocytes inhibited neuronal α-syn aggregation and transmission in a paracrine manner by correcting not only intra-neuronal oxidative and mitochondrial stresses, but also extracellular inflammatory environments, in which α-syn proteins are prone to pathologic misfolding. The astrocyte-derived paracrine factors also promoted disassembly of extracellular α-syn aggregates. In addition to the aggregated form of α-syn, VM-astrocytes reduced total α-syn protein loads both by actively scavenging extracellular α-syn fibrils and by a paracrine stimulation of neuronal autophagic clearance of α-syn. Transplantation of VM-astrocytes into the midbrain of PD model mice alleviated α-syn pathology and protected the midbrain dopamine neurons from neurodegeneration. Additionally, we manipulated functional human NSC-derived ventral midbrain astrocytes (hVM-Ast) using organoid based protocol and confirmed the similar functions of mouse VM-Ast. Finally, we showed that co-grafting of VM-astrocytes could be exploited in stem cell-based therapy for PD, in which host-to-graft transmission of α-syn pathology remains a critical concern for long-term cell therapeutic effects.

Disclosures: **J. Song:** None. **Y. Yang:** None. **Y. Choi:** None. **S. Kim:** None. **M. Seok:** None. **N. Wulansari:** None. **W. Darsono:** None. **O. Kwon:** None. **M. Chang:** None. **T. Kam:** None. **S. Park:** None. **S. Lee:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.21

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation for Parkinson's Research Grant MJFF-004005

Title: Transglutaminase 2 transamidation activity is essential for α-synuclein mediated toxicity in mice

Authors: *J. LIU, J. ZHANG, M. SONG, S. MADDILA, Y.-S. KIM, E. JUNN, M. MOURADIAN;
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Abstract: Misfolded alpha-synuclein (α-Syn) accumulates in Lewy-bodies and Lewy neurites in Parkinson's disease (PD) and Dementia with Lewy Bodies, and the formation of toxic aggregates of α-Syn in the brain is closely linked with the pathogenesis of α-synucleinopathies. The *transglutaminase* 2 (TG2) gene encodes a multifunctional enzyme, displaying a wide range of activities, including cross-linking between glutamine and lysine residues in substrate proteins. We previously demonstrated that TG2 catalyzes the cross-linking of α-Syn *in vitro* and in cultured cells to form insoluble, high molecular-weight aggregates. We also demonstrated that TG2 exacerbates α-syn aggregation and toxicity using α-Syn transgenic mice that over-express TG2 ($TG2^{Tg}/Syn^{Tg}$), and found the converse using α-Syn transgenic mice that have a deletion of the TG2 gene ($TG2^{-/-}/Syn^{Tg}$). Here, we investigated whether the cross-linking activity of TG2 specifically contributes to α-Syn toxicity *in vivo*. To this end, we generated and characterized mice transgenic for a point mutant of TG2, W241A, which has no transamidation activity but retains full GTP binding. In contrast to human α-Syn and wild-type TG2 ($TG2^{Tg}/Syn^{Tg}$) double transgenic mice, $W241A^{Tg}/Syn^{Tg}$ double transgenic mice exhibited no apparent increase in the amount of high-molecular weight insoluble species of α-Syn in brain lysates or in phosphorylated α-Syn aggregates in sections of brain tissue when compared with single α-Syn (Syn^{Tg}) transgenic mice. Similarly, the neuroinflammatory response to α-Syn detected by GFAP and Iba1 staining, and neuronal integrity detected by MAP2 and c-FOS staining in $W241A^{Tg}/Syn^{Tg}$ mice were equivalent to those in Syn^{Tg} mice. Consistent with this neuropathological profile, the motor and spatial learning performance of $W241A^{Tg}/Syn^{Tg}$ mice on behavioral tasks was better relative to $TG2^{Tg}/Syn^{Tg}$ mice and no different than Syn^{Tg} mice. These findings indicate that the transamidation activity of TG2 is specifically involved in α-Syn aggregation and its downstream neuropathologic consequences, thus, supporting the

development of specific TG2 inhibitors as a disease modifying therapeutic strategy in α-synucleinopathies.

Disclosures: J. Liu: None. **J. Zhang:** None. **M. Song:** None. **S. Maddila:** None. **Y. Kim:** None. **E. Junn:** None. **M. Mouradian:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.22

Topic: C.03. Parkinson's Disease

Support: NIH R01 NS110085

Title: Honokiol, a natural, brain permeable small molecule reveals mechanistic insight into SNCA gene regulation

Authors: S. J. FAGEN, J. D. BURGESS, M. J. LIM, D. AMERNA, S. L. BOSCHEN, M. DELENCLOS, *P. J. MCLEAN;
Neurosci., Mayo Clin., Jacksonville, FL

Abstract: Alpha-synucleinopathies are a group of neurological disorders defined by the presence of intracellular inclusions of aggregated α-synuclein (αsyn). Duplications or triplications of the *SNCA* locus result in increased αsyn and supports a gene dosage effect contributing to disease pathogenesis. Although copy number variants have only been associated with rare familial forms of Parkinson's disease (PD), previous studies have shown that genetic variability in the promoter and 3' region of *SNCA* can contribute to increased risk of sporadic disease. As such, decreasing *SNCA* expression is a recognized target for PD modifying therapeutics. Here**,** we report a natural, brain permeable, small molecule that downregulates *SNCA* at the level of transcription as a new genetic modifier of *SNCA* expression. Multiple cell types were treated with 10μM honokiol for 72hrs and subjected to western blot and RT-PCR analysis to detect changes in *SNCA* expression. In H4 cells overexpressing αsyn, honokiol reduced αsyn protein and *SNCA* mRNA levels by 62% and 52% respectively. A similar decrease in endogenous αsyn and *SNCA* was observed in primary cortical neurons and iPSC-derived neurons harboring the *SNCA* triplication. Degradation assays performed on H4 cells overexpressing αsyn show no significant differences between the rate of protein or RNA degradation, suggesting regulation at the level of transcription. RNA sequencing of primary cortical neurons treated with honokiol revealed several differentially expressed genes (DEGs) of interest. Studies to validate a direct relationship between the DEGs and *SNCA* expression are ongoing. We believe that genes modified by honokiol warrant attention in the context of PD to identify novel disease mechanisms with important therapeutic implications.

Disclosures: S.J. Fagen: None. **J.D. Burgess:** None. **M.J. Lim:** None. **D. Amerna:** None. **S.L. Boschen:** None. **M. Delenclos:** None. **P.J. McLean:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.23

Topic: C.03. Parkinson's Disease

Support: Sigrid Juselius Foundation

Title: Effects of brain-derived neurotrophic factor on pre-formed fibril-induced alpha-synuclein aggregation

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Abstract: Parkinson's disease is the second most common progressive neurodegenerative disease characterized by loss of dopamine neurons in the substantia nigra and Lewy bodies - intraneuronal inclusions- as neuropathological hallmarks. The aim of this study is to investigate if brain-derived neurotrophic factor (BDNF) can reduce pre-formed fibril (PFF) induced Lewy body-like alpha-synuclein aggregation in mouse primary dopaminergic neurons. Dopaminergic neurons isolated from the ventral midbrain floor of 13.5 mouse embryos were plated in 96-well plates and maintained in a culture medium without neurotrophic factors until the day *in vitro* (DIV)8. Glial cell line-derived neurotrophic factor (GDNF) was used as a positive control since it reduces the aggregation of alpha-synuclein in cultured dopaminergic neurons and the mouse brain. BDNF was added on a DIV8 1 hour after the PFF-treatment, or on DIV12. The cultures were fixed on DIV15 and stained with tyrosine hydroxylase (TH) and phosphoSer129-alpha-synuclein (pS129-alpha-syn) antibodies. Quantification of TH+ neurons and pS129-alpha-syn+ and TH+ neurons was performed with unbiased image analysis using CellProfiler™ software. Neither GDNF nor BDNF added at the late stages of culturing did not significantly affect the survival of TH+ neurons. Like GDNF, BDNF added either on DIV8 or DIV12 decreased pS129-alpha-syn positive aggregates in dopaminergic neurons. The effect of BDNF was slightly more pronounced when added earlier on DIV8 instead of on DIV12. Research on neurotrophic factors' protective effects on multiple neuropathologies can help the development of new therapies against Parkinson's disease.

Disclosures: V. Kulmala: None. **M. Airavaara:** None. **T.P. Rantamaki:** None. **I. Hlushchuk:** None. **S. Er:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.24

Topic: C.03. Parkinson's Disease

Support: Intramural support by NHLBI/NIH

Title: Correlated mutation analysis suggests tau and alpha-synuclein have coevolved

Authors: *J. M. GRUSCHUS;
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Abstract: Alpha-synuclein lies at the center of Parkinson's disease etiology, and polymorphisms in the gene for the microtubule-associated protein tau are risk factors for getting the disease. Tau and α-synuclein interact *in vitro*, and α-synuclein can also compete with tau binding to microtubules. To test whether these interactions might be part of their natural biological functions, a correlated mutation analysis was performed between tau and α-synuclein, looking for evidence of coevolution. Analyses were performed between tau and β- and γ-synuclein, as well. For comparison, analyses were performed between tau and the neuronal tubulin proteins, which are known interaction partners with tau. Potential correlated mutations were detected between tau and α-synuclein, one involving an α-synuclein residue known to interact with tau *in vitro*, Asn122, and others involving the Parkinson's disease-associated mutation A53T. No significant correlated mutations were seen between tau and β- and γ-synuclein. While the correlated mutations between tau and α-synuclein suggest the two proteins might have coevolved, additional study will be needed to confirm that their interaction is part of their normal biological function in cells.

Disclosures: J.M. Gruschus: None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.25

Topic: C.03. Parkinson's Disease

Support: JSPS KAKENHI Grant JP19K07834
JSPS KAKENHI Grant JP20K16505
JSPS KAKENHI Grant JP20K16506

Title: Neuronal activity modulates extracellular secretion of α-synuclein via an autophagy-based unconventional machinery

Authors: *Y. NAKAMURA, T. SAWAI, K. KAKIUCHI, S. ARAWAKA;
Osaka Med. and Pharmaceut. Univ., Takatsuki, Japan

Abstract: Extracellular α-synuclein (α-syn) secretion play a key role in developing cell-to-cell transmission of α-syn pathology in progressive neurodegeneration of α-synucleinopathies. Previous studies have demonstrated that α-syn is secreted under physiological conditions in neuronal cell lines and primary neurons. However, the molecular mechanisms that regulate extracellular α-syn secretion remain unclear. We investigated how increasing neuronal activity regulates α-syn secretion in mouse primary cortical neurons and SH-SY5Y cells stably expressing α-syn (n=3~6 per group). Increasing neuronal activity by glutamate or KCl and elevating intracellular calcium levels by calcium ionophore A23187 enhanced α-syn secretion in primary neurons. Secretion of α-syn induced by glutamate and A23187 were suppressed by intracellular calcium chelator, BAPTA-AM. Additionally, rapamycin-mediated mTOR inhibition increased α-syn and autophagy cargo receptor protein p62 secretions, whereas these increases were suppressed in Beclin 1-heterozygously deficient mouse primary neurons. siRNA-mediated knockdown of Atg5 inhibited glutamate-induced α-syn and p62 secretions in SH-SY5Y cells stably expressing α-syn. Increasing neuronal activity by glutamate or KCl and A23187 also increased LC3-II to β-actin ratio and decreased intracellular p62 levels in primary neurons. BAPTA-AM inhibited increasing LC3-II to β-actin ratio induced by glutamate. Blocking amphisome formation by tetanus toxin significantly reduced glutamate-induced α-syn and p62 secretions in primary neurons. Treatment with ATP-binding cassette (ABC) transporter inhibitors, probenecid and glyburide, decreased α-syn secretion induced by glutamate and A23187. Additionally, treatment with probenecid decreased α-syn secretion in both exosome-enriched extracellular vesicles (EVs) and non-EVs fractions in primary neurons. Taken together, neuronal activity facilitates extracellular α-syn secretion via an autophagy-based unconventinal machinery in intracellular calcium concentration- and amphisome formation-dependent manners, and this machinery involves ABC transporter in autophagy-related structures containing EVs. Our data have shown the close link between secretory autophagy and neuronal activities in physiological release of α-syn and secretory autophagy may affect cell-to-cell transmission of α-syn.

Disclosures: **Y. Nakamura:** None. **T. Sawai:** None. **K. Kakiuchi:** None. **S. Arawaka:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.26

Topic: C.03. Parkinson’s Disease

Support: NIH Grant K08NS109287

Title: The role of alpha-synuclein in the ascending arousal system in attention and arousal of mice.

Authors: *G. GRYC, G. DE CHOISY, R. THANGAVEL, M. A. WEBER, O. HALHOULI, K. DENIZ, A. BERTOLLI, P. BOSCH, J. ZHANG, G. M. ALDRIDGE;
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Abstract: Dementia with Lewy Bodies (DLB) and Parkinson's Disease dementia (PDD) are devastating disorders that represent the second most common cause of dementia around the world. DLB is defined by dementia with an executive pattern of cognitive impairments plus the presence of more than one core features: visual hallucinations, parkinsonism, cognitive fluctuations, or REM behavior sleep disorder. Of these, cognitive fluctuations, which are defined as changes in arousal, attention and excessive sleep, dramatically impair quality of life, but remain difficult to study and poorly understood. Our long-term goal is to determine the etiology of these symptoms to develop effective therapies. DLB is characterized by deposition of aggregated alpha-synuclein (a-syn) visualized as Lewy Bodies/Lewy neurites in the brain. This pathology is thought to cause both changes in neuronal activity and progressive neuronal degeneration of specific vulnerable cell populations. Evidence from mice studies suggest that overexpression and aggregation of a-syn can model some symptoms observed in patients. In this study, we are investigating whether a-syn alters aspects of mouse behavior that relate to fluctuations in attention/cognition, arousal, and sleep. First, we injected a-syn pre-formed fibrils, which cause aggregation and spread of native a-syn, in the prefrontal cortex (PFC) of adult mice. 20 months following injection, there was significant aggregation of a-syn in the prefrontal cortex, striatum, and amygdala. However, our results show sparse/absent aggregation in the brainstem. Behaviorally, these mice showed enhanced exploration of objects and decreased thigmotaxis, providing some evidence for changes in spontaneous behavior. As PFC injections did not induce significant a-syn spread to brainstem neurons, we next injected pre-formed fibrils in the central hub of the ascending arousal system, the locus coeruleus. This nucleus is comprised of noradrenergic neurons which connect to widespread brain regions for arousal maintenance that also degenerate in DLB patients. Our current research will evaluate attention, arousal and sleep using objective, repeated monitoring to investigate aspects of cognitive fluctuations. As cognitive fluctuations are reversable by definition, there is great potential to understanding underlying mechanisms at play. Ultimately, this research could lead to treatments that stabilize function and improve quality of life in DLB patients.

Disclosures: G. Gryc: None. **G. De Choisy:** None. **R. Thangavel:** None. **M.A. Weber:** None. **O. Halhouli:** None. **K. Deniz:** None. **A. Bertolli:** None. **P. Bosch:** None. **J. Zhang:** None. **G.M. Aldridge:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.27

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: A preformed fibril (PFF) rat model of synucleinopathy as a tool to investigate neuroinflammation and synaptic dysfunction in Parkinson's Disease.

Authors: *J. TELLO VELASQUEZ[1], A. FREEBURN[2], D. DISHA[2], C. MCGURK[3], J. B. KOPRICH[4], J. M. BROTCHIE[4], A. PUSUNG[4], M. P. HILL[5], M. BIANCHI[2];
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Abstract: Although the pathogenesis of Parkinson's Disease (PD) is extremely complex, several studies suggest that neuroinflammation is critically involved in the process of neuronal degeneration by producing deleterious pro-inflammatory cytokines. Furthermore, excessive neuroinflammation potentially contributes to impairments in synaptic plasticity, a crucial feature in the onset and the progression of motor and non-motor symptoms of PD. The preformed fibril (PFF) synucleinopathy model in rodents has been shown to be able to recapitulate the molecular and nigrostriatal pathology associated with PD, as well as the progressive decline in dopaminergic function. However, its use as a tool to examine neuroinflammation and synaptic dysfunction in PD has not been deeply explored.One major event regulating the secretion of pro-inflammatory cytokines, particularly IL-1β, is activation of the inflammasome. Both monomeric and fibrillar αSyn can induce gene expression of pro-IL-1β promoting its synthesis, but just fibrillar αSyn can activate the inflammasome. NRLP3activation subsequently may aggravate neuroinflammation, exacerbate degeneration of dopaminergic neurons and promote PD progression.We analysed the progression of synaptic pathology and activation of the NLRP3 inflammasome by using a PFF model in female rats and evaluated endpoints at three-time points following aSyn-PFF orαSyn-monomer (control) injected into the striatum (Day 30, n=8/8; Day 60, n=8/8; and Day 120, n=8/8). Using Multiplex Infrared Western Blotting (IFWB), relative levels of synaptic markers: synaptophysin, PSD-95 and Spinophilin were analysed in the striatum. Components of the NLRP3 Inflammasome activation were also analysed. Preliminary results suggest a decrease in the expression of PSD-95 compared to controls at day 30 and a similar trend for synaptophysin. Interestingly, these trends are not observed at later time points, suggesting a possible synaptic dysfunction at early stages. On Day 30 and Day 120, we show an increase in TNFα and IL-5, respectively in the striatum of animals receiving PFF treatment vs. Control. No significant changes were observed in the levels of IL-1β, however, an increase in striatal NLRP3activation was observed 30 and 120 days after PFF administration. Ongoing experiments are evaluating the components of NLRP3 assembly, as well as the production of pro-IL-1β, IL-1β, and NF-Kβ p65. These results begin to form the basis of a preclinical platform using the PFF rat model to identify novel biomarkers of synaptic integrity and neuroinflammation in PD.

Disclosures: J. Tello Velasquez: None. **A. Freeburn:** None. **D. Disha:** None. **C. McGurk:** None. **J.B. Koprich:** None. **J.M. Brotchie:** None. **A. Pusung:** None. **M.P. Hill:** None. **M. Bianchi:** None.

Poster

704. Parkinson's Disease: Alpha Synuclein Mechanism and Transmission

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 704.28

Topic: C.03. Parkinson's Disease

Support: K08NS109287

Title: Investigation of alpha synuclein overexpression localized to mouse prefrontal cortex and subsequent assessment of cognitive flexibility and neuronal function

Authors: *R. DEAN, P. J. BOSCH, Y. KIM, G. M. ALDRIDGE;
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Abstract: Lewy Body dementias (LBD), including Parkinson's disease dementia (PDD), are neurodegenerative disorders characterized by intracellular aggregates of the protein alpha synuclein (alpha-Syn). Cognitive deficits in LBD include impaired executive functions, such as reduced cognitive flexibility. Previous research indicates that alpha-Syn overexpression can recapitulate some aspects of LBD; however, data on prefrontal cortical perturbations of alpha-Syn is limited. Thus, we overexpressed human alpha-Syn in the M2 region of the prefrontal cortex of Thy1-GCaMP6s transgenic mice using intracranial injections of adeno-associated virus. The injection was followed by implantation of a cranial window and headplate to allow for 2-photon calcium imaging of the prefrontal cortex in a head-fixed behaving mouse. Our data suggests that alpha-Syn overexpression leads to an abnormal proportion of active cells in response to the initiation of movement compared with controls. In order to assess cognitive flexibility, we developed a head-fixed behavioral task (STOP task), in which a mouse explored a custom 3D printed plate containing different tactile rewarded zones to obtain sucrose delivered via lick spout. During training for this task, we found that control mice progressively initiated more trials and received more rewards per session ($p=0.002$, 2-way ANOVA), whereas the overexpression mice did not demonstrate the same improvement ($p=0.99$). We then tested mice by dynamically switching rewarded sites within a session and recorded the number of trials initiated, rewards obtained, and zone switches. We found no significant difference in trial initiation between control and overexpression mice; however, control mice obtained significantly higher correct trial percentage ($F(1,10)=10.68$, $p=0.0085$) and thus received significantly more rewards per session ($F(1,10)=7.406$, $p=0.0215$), suggesting that alpha-Syn overexpression mice have impaired cognitive flexibility. The substantia nigra, ventral tegmental area (VTA), and dopamine terminals in the striatum were immunostained for tyrosine hydroxylase to check for dopamine system integrity. To further assess the role of dopamine in this task, we used targeted injections of the neurotoxin 6-OHDA into the VTA, followed by testing on our STOP task. Our results have implications for the role that alpha-Syn in the prefrontal cortex plays in cognitive function alterations in LBD.

Disclosures: R. Dean: None. **P.J. Bosch:** None. **Y. Kim:** None. **G.M. Aldridge:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Augusta University Start-Up Fund

Title: Investigating the potential synergistic role of a-synuclein and tau in cognitive declinein Alzheimer's and Parkinson's Diseases

Authors: *J. E. VINCENT[1], D. E. MOR[2];
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Abstract: Alzheimer's disease (AD), followed by Parkinson's disease (PD), are the most common age associated neurodegenerative disorders, both with no cure or disease-modifying treatments. AD is primarily defined by pathologies of amyloid-β and tau proteins, while PD is defined by α-synuclein (α-syn) protein deposits. However, these pathologies often coexist in AD and PD and may potentially act synergistically to promote neuron degeneration. Cholinergic neurons in the basal forebrain degenerate in both AD and PD, and the loss of these cells is thought to contribute to cognitive decline. Yet, it remains unknown what causes protein aggregation and how this leads to neuronal death and cognitive dysfunction. To investigate cognitive impairment, we are using the C. elegans model system, which has a rapid life cycle that facilitates aging studies, a complex nervous system that gives rise to cognitive functions, and is easily genetically manipulated. Transgenic strains expressing pan-neuronal human α-syn, tau, or a α-syn;tau double transgenics are being tested in learning and memory assays. Compared to non-transgenic controls, α-syn alone only showed mild learning and memory deficits. Similarly, tau alone caused mild or no effects on learning and memory. However, when combined, α-syn and tau eliminate learning and memory function, consistent with synergistic toxicity leading to cognitive deficits. To visualize protein aggregation, we are using the Congo Red derivative, X-34 dye, in live C. elegans. We confirmed the validity of the dye by testing it with a strain expressing human α-syn aggregates in muscle tissue. Next, to determine the mechanisms by which α-syn and tau induce cognitive decline, we are isolating cholinergic neurons from the disease strains and are performing RNA-sequencing. Thus far, we have been able to successfully isolate cholinergic neurons from a non-diseased strain and perform RNA-seq. Analyzing RNA-seq data from isolated neurons will help identify genes upregulated or downregulated in the diseased models. By identifying genes and pathways that are specifically affected by α-syn, tau, or their combination, novel treatment strategies to increase cholinergic cell survival and preserve cognitive ability can potentially be designed to adequately treat AD and PD.

Disclosures: J.E. Vincent: None. **D.E. Mor:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH-R01AG061188

Title: Caspase mediated tau cleavage linked to synaptotoxicity in Alzheimer's disease

Authors: *C. K. OPLAND, M. BRYAN, X. TIAN, T. J. COHEN;
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Abstract: Alzheimer's disease (AD) is a debilitating neurodegenerative disease resulting in memory loss due to the accumulation of extracellular amyloid beta plaques and intracellular neurofibrillary tau tangles in the brain. Normally, tau is a microtubule associated protein that binds and stabilizes axonal microtubules. In an AD neuron, tau forms straight or paired helical filaments which result in tangles correlated with neuronal degeneration. Tau undergoes many different post-translational modifications (PTMs); however, their impact on toxicity is not known. Tau cleavage by caspases, is one modification believed to generate a more toxic species of tau that precedes other pathological PTMs and drives neuronal toxicity in AD. The current model of tau cleavage suggests that active caspases cleave tau at the aspartic acid^{421} site in the carboxy terminal region. The larger 1-421 fragment, recognized in pre-tangles, is believed to then change its conformation generating a disease-associated species. However, little is known about the regulation of tau cleavage and its role in AD, as there are few reliable model systems with which to study this process. Here, we developed a proteasome impairment model that activates caspase-3 resulting in robust tau cleavage. In the absence of caspase-3, tau cleavage is no longer produced suggesting caspase-3 is the main mediator driving cleavage. To address where tau cleavage occurs in the neuron, we observed both cleaved tau and caspase-3 enriched at the post-synaptic density (PSD) where it may cause toxicity by damaging the synapse. Expression of cleaved tau in neurons gives us the ability to further characterize the downstream effects cleavage is causing in a neuron. By measuring synaptic activity, we observe alterations in neuronal activity and synchronization compared to controls suggesting cleaved tau results in synaptic dysfunction. Our study suggests that the accumulation of cleaved tau in neurons is an early neurotoxic species of tau in AD and other tauopathies.

Disclosures: C.K. Opland: None. **M. Bryan:** None. **X. Tian:** None. **T.J. Cohen:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JHU USRCA Abstein Research Grant

Title: Brain-specific transmembrane transport receptor 2 mediates the functional rescue of tauopathies through neuron-localized internalization of tau aggregates

Authors: *S. KOTHA[1,2], H. LIU[1], V. DAWSON[1], T. DAWSON[1], X. MAO[1];
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Abstract: Alzheimer's disease (AD) is a tauopathy, a neurodegenerative disease characterized by an abnormal aggregation of misfolded tau, a structural, microtubule-associated protein native to neurons. Hyperphosphorylation of tau protein in AD causes the fiber-like aggregation of p-tau (phosphorylated tau, the neuropathological hallmark of tauopathies in AD. Thus, recent understanding of the disease mechanism leads us to focus on developing new drugs towards slowing the progression of AD by prevention of abnormal accumulation of p-tau and clearance of aggregated tau fibrils in neurons. Through a high-throughput screening and binding assay, we have identified Brain-specific transmembrane transport receptor 2 (BTTR2) as a membrane receptor with high binding efficiency to tau aggregates. Through *in vitro* and *in vivo* immunohistochemical antibody labelling of native tau and BTTR2 expression and observation of cell-to-cell transmission of phosphorylated tau in AAV9-CBA-eGFP-2a-P301Ltau injected BTTR2-knockout and wild-type C57BL/6J mouse models, we show that BTTR2 is associated with decreased p-tau aggregation and pathology propagation and verify the role of BTTR2 in mediating the internalization of tau aggregates. Our study localizes BTTR2 expression specifically to the neuron cell type, rather than microglia or astrocytes, verifying the mechanism of BTTR2 function is through neuronal internalization or endocytosis. Furthermore, BTTR2 is shown to have the greatest expression in the hippocampus, the site of memory, supporting the role of BTTR2-mediated p-tau endocytosis in the function of memory, consistent with the functional memory loss seen in AD. Altogether, our data strongly supports that BTTR2 has a critical role in regulating tauopathy through a neuron-localized internalization of p-tau fibrils with a neuroprotective effect against pathological tau propagation. Considering the negative association between BTTR2 expression and p-tau fibrils we demonstrate here, the upregulation of BTTR2 in neurons is becoming a promising way to rescue hyperphosphorylation of tau and further abnormal aggregation in AD.

Disclosures: S. Kotha: None. **H. Liu:** None. **V. Dawson:** None. **T. Dawson:** None. **X. Mao:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF(18R1A2B2003955)

Title: Characterization of negative regulatory mode of dual specificity kinase DYRK1A through PPM1B-mediated dephosphorylation and its implication to abberant tau aggregation and neurotoxic pathogenesis of Down syndrome

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Abstract: Down syndrome (DS) is mainly caused by an extra copy of chromosome 21 (trisomy 21), and patients display a variety of developmental symptoms, including characteristic facial features, physical growth delay, intellectual disability, and neurodegeneration (i.e., Alzheimer's disease; AD). One of the pathological hallmarks of AD is insoluble deposits of neurofibrillary tangles (NFTs) that consist of hyperphosphorylated tau. The human *DYRK1A* gene is mapped to chromosome 21, and the protein is associated with the formation of inclusion bodies in AD. For example, DYRK1A directly phosphorylates multiple serine and threonine residues of tau, including Thr212. However, the mechanism underpinning DYRK1A involvement in Trisomy 21-related pathological tau aggregation remains unknown. Here, we explored a novel regulatory mechanism of DYRK1A and subsequent tau pathology through a phosphatase. Using LC-MS/MS technology we analyzed multiple DYRK1A-binding proteins, including PPM1B, a member of the PP2C family of Ser/Thr protein phosphatases, in HEK293 cells. We found that PPM1B dephosphorylates DYRK1A at Ser258, contributing to the inhibition of DYRK1A activity. Moreover, PPM1B-mediated dephosphorylation of DYRK1A reduced tau phosphorylation at Thr212, leading to inhibition of toxic tau oligomerization and aggregation. In conclusion, our study demonstrates that DYRK1A autophosphorylates Ser258, the dephosphorylation target of PPM1B, and PPM1B negatively regulates DYRK1A activity. This finding also suggests that PPM1B reduces the toxic formation of phospho-tau protein via DYRK1A modulation, possibly providing a novel cellular protective mechanism to regulate toxic tau-mediated neuropathology in AD of DS.

Disclosures: G. Park: None. **Y. Lee:** None. **E. Im:** None. **J. Park:** None. **K.C. Chung:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Scully Initiative
Taube Family Foundation
Jean Perkins Foundation
Horngren Family

Title: Modulation of the p75 neurotrophin receptor promotes spine resilience in mouse hippocampal neurons seeded with tau oligomers

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Abstract: Synaptic degeneration is core pathological event in Alzheimer's Disease (AD), frontotemporal dementia and other tauopathies. Increasing evidence from mouse models and postmortem AD studies suggests that pathological forms of tau, including tau oligomers, may mediate synaptic dysfunction and subsequent synapse loss. Preservation of dendritic spines is associated with cognitive resilience in the setting of AD and accompanying accumulations of amyloid and tau; therefore, methods for preventing spine loss induced by amyloid or tau could have significant therapeutic potential. The p75 neurotrophin receptor ($p75^{NTR}$) regulates an intracellular degenerative signaling network that shares considerable overlap with degenerative signaling networks activated in AD which affect accumulation of pathological forms of tau and dendritic spine status. In previous studies, downregulation of degenerative signaling using the LM11A-31, a small molecule modulator of $p75^{NTR}$, was found to prevent degeneration of dendritic spines induced by amyloid oligomers and in PS19 tauopathy model mice. To further investigate mechanisms of these effects we examined accumulation of pathologic tau and dendritic spine loss induced directly by oligomeric tau. Primary hippocampal neuron cultures from WT mice were matured for 21 days and were then exposed for 24 hrs to either recombinant tau oligomers or a tau-enriched hippocampal extract fraction derived from PS19 tauopathy mice, in the presence or absence of LM11A-31. Immunostaining with AT8 p-tau antibody showed that addition of pathological tau resulted in increased levels of AT8 signal and this increase was prevented in the presence of LM11A-31. Morphological analyses demonstrated an approximately 45% loss in dendritic spine density induced by recombinant tau oligomers and tauopathy brain fractions; and this reduction was largely prevented in the presence of LM11A-31. Western blot analysis demonstrated increased PKC phosphorylation (activation) and reduced cofilin phosphorylation triggered by the addition of pathological tau, consistent with established effects of PKC/ROCK/cofilin regulation of dendritic spine status. Thus, pharmacologic modulation of $p75^{NTR}$ may provide resilience to degenerative effects of pathological forms of tau, including dendritic spine loss. Further studies will establish the extent to which downregulation of aberrant PKC/ROCK/cofilin signaling by modulation of $p75^{NTR}$ is a primary mechanism leading to resilience of synaptic spines.

Disclosures: Y. Ay: None. **S. Kaur:** None. **T. Yang:** None. **K.C. Tran:** None. **H. Liu:** None. **S.M. Massa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Massa is an inventor on patents relating to p75NTR modulators which are assigned to UNC, UCSF and the VA. Dr. Massa is eligible for royalties distributed by the assigned universities. **F.M. Longo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Longo is listed as an inventor on patents relating to p75NTR modulators and has financial interest in PharmatrophiX, a company developing these modulators, including LM11A-31.

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705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG056976
NIH Grant AG058081
University of Minnesota College of Pharmacy

Title: Small GTPase H-Ras modulates endogenous tau aggregation induced by exogenous pathogenic tau in the mouse brain

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Abstract: Alzheimer's disease (AD) is an incurable form of age-related dementia that is currently the 7th leading cause of death in the United States. It is characterized by the presence of extracellular amyloid-beta plaques and intracellular neurofibrillary tangles, though the precise mechanisms behind AD pathogenesis are not fully understood. Neurofibrillary tangles are formed through self-aggregation of hyperphosphorylated tau proteins within neurons and disrupt neural transport systems. Studies have shown that the aggregation of endogenous hyperphosphorylated tau may possess prion-like properties inducible by external pathogenic tau. While the exact biological mechanisms underlying the onset of neurofibrillary tangle formation remains elusive, emerging evidence suggests that small GTPases, including H-Ras that is extensively studied in cancer and regulates synaptic function, affect tau propagation and aggregation. The proper cellular trafficking and localization of H-Ras depends on farnesylation, a crucial lipid modification process of proteins. Increased protein farnesylation is associated with mild cognitive impairment and AD in humans. Treatment with a farnesyltransferase inhibitor reduces tau/tangles in transgenic mice with tauopathy. Previous studies also showed beneficial effects of genetic inhibition of protein farnesylation or deletion of Hras on cognitive function and amyloid pathology in AD mice. This study aims to determine the impact of H-Ras on endogenous tau aggregation induced by exogenous pathogenic Tau. Aged Hras-deficient (Hras-/-) and wild-type (WT) mice (18-22 months) were intracerebrally injected in the hippocampal and overlying cortical regions with pathogenic tau isolated from brains of rTg4510 mice, a human tau transgenic mouse model. Brains of injected mice were then sectioned and immunostained with both phosphorylated and total tau-specific antibodies to assess the degree of induced tau pathology at 3 days, 38 days, and 3 months post-injection. Preliminary results showed that p-tau staining was observed at the injection site 3 days post injection, which was not detectable at 38 days post injection, indicating the presence and clearance/absence of the injected material at early and later time points, respectively, following the injection. At 3 months post injection, while p-tau staining was clearly detected in the hippocampus and cortex of WT mice, indicating the development of endogenous tau aggregation, there was little p-tau staining in Hras-/- mice.

These findings suggest that reduction or inhibition of H-Ras may hinder endogenous tau aggregation and block the pathogenic process of AD.

Disclosures: J. Thieschafer: None. **W. Qu:** None. **L. Li:** None.

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705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BrightFocus Foundation A2021038S

Title: Identification of novel modifiers of tau aggregation and pathology using a proximity proteomics approach

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Abstract: Background: Alzheimer's disease (AD) and related neurodegenerative diseases are characterized by the accumulation of abnormal protein aggregates. A defining hallmark of AD is the formation of neurofibrillary tangles (NFTs) by aggregation of the microtubule-associated protein tau into pathological oligomers and fibrils. Although NFTs are believed to play a pivotal role in the disease process, we have a poor understanding of how their formation, toxicity, and spread across brain regions is regulated. Recent data suggest that the seeding behavior of tau is governed by patterns of posttranslational modifications and varying filament structures. Understanding how tau-associated proteins regulate the oligomerization, pathological accumulation, and seeding of tau in affected neurons and glia is of critical importance for therapy development.
Method: To profile the interactome of tau aggregates, we have established proximity-dependent biotin-identification (BioID) as a novel method to identify the composition and proximal molecular environment of insoluble protein aggregates in the context of living brain cells and tissue. Using an *in vitro* and *ex vivo* model approach coupled with mass spectrometry, we are generating datasets containing top identified proteins, stratified based on significance and molecular pathway. Once we validate their co-localization with NFTs in the context of human AD pathology, functional characterization of putative modifiers will be performed to assess their impact on tau-aggregate and toxicity.

Result: To determine the physiological and aggregate specific interacting partners of tau, we are comparing wild type tau (TauWT) with mutant tau (Tau3xMUT) carrying three tauopathy-associated mutations (A152T/P301L/S320F) that form hyper-phosphorylated and thioflavin S-positive aggregates even in the absence of seeding. The proteomic analysis from our pilot study revealed that significantly changed proteins included candidates involved in RNA processing, as well as protein ubiquitination and proteasome degradation.
Conclusion: This study provides novel insights into cellular pathways and molecular mechanisms of neurodegeneration, by identifying in the context of living neurons and brain tissue different functional classes of tau-associated proteins with relevance for AD pathophysiology. These are expected to include proteins that may mediate the toxic effect of NFTs, facilitate the formation or degradation of pathological tau aggregates, and catalyze posttranslational modifications of tau oligomers and associated proteins.

Disclosures: J.H. Lee: None. **D. Morderer:** None. **B. Khalil:** None. **M.C. Wren:** None. **C. Tsai:** None. **C.L. Croft:** None. **Y. Carlomagno:** None. **M. DeTure:** None. **M. Salemi:** None. **B. Phinney:** None. **D.W. Dickson:** None. **C.N. Cook:** None. **T.E. Golde:** None. **L. Petrucelli:** None. **W.O. Rossoll:** None.

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705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R56AG057469
R01 NS094597
P30 AG062429
R01 AG073979
K99 AG070390

Title: Differential dysregulation of tau-promoting exosome proteomes generated by neurons expressing mutant tau or mutant presenilin 1

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Abstract: The accumulation and propagation of hyperphosphorylated tau (p-tau) is a neuropathological hallmark of Alzheimer's disease (AD), frontotemporal dementia, and other related tauopathies. Extracellular vesicles, specifically exosomes are thought to mediate p-tau

propagation in the diseased brains. Exosomes derived from human-induced pluripotent stem cell (hiPSC) neurons expressing P301L and V337M tau mutations of FTDP-17 (mTau) are capable of inducing tau deposits *in vivo*. Similarly, tau deposition has been observed in the brains of mice injected with exosomes derived from hiPSC-derived neurons expressing the AD familial A246E mutant form of presenilin 1 (mPS1). To gain insights into the exosome cargo that potentially mediate p-tau propagation pathology, proteomic profiling and bioinformatic analyses were conducted. Exosomes were isolated from the cell culture media of control hiPSC neurons and hiPSC neurons expressing either mTau or mPS1 followed by nano-LC-MS/MS tandem mass spectrometry. As compared to exosomes derived from control hiPSC neurons, several of the mTau exosome-specific proteins are known to participate in AD mechanisms involving lysosomes, inflammation, secretases, and phosphatases including ANP32A, an endogenous inhibitor of the PP2A phosphatase which regulates the phosphorylation state of p-tau. mTau exosomes lacked a substantial portion of proteins present in control exosomes involved in pathways of localization, vesicle transport, and protein binding functions. mPS1 exosomes contained proteins related to extracellular matrix (ECM) functions, deletion of proteins involved in RNA, and protein translation systems. Notably, mPS1 exosomes lacked many phosphatase components known to participate in the de-phosphorylation of p-tau that were present in control exosomes. While both types of exosomes have been shown to promote tau pathogenesis in mouse brain, we determined that differential cargo expression exists between exosomes derived from iPSC neurons expressing mtau or mPS1. Together, these data suggest that the presence of mTau or mPS1 results in the recruitment of distinct proteins to exosomes however further review is required to determine how mutant tau or mutant PS1 facilitate exosome-mediated propagation of p-tau pathology in the brain.

Disclosures: C.N. Winston: None. **S. Podvin:** None. **S.H. Yuan:** None. **T. Ikezu:** None. **R.A. Rissman:** None. **V. Hook:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Hypoxia promotes coincident neuroinflammation and pathological tau spreading in AAV-Tau^{P301L} stereotaxic injection model.

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Abstract: Alzheimer's disease (AD) is a progressive neurologic disorder, the most common cause of dementia, memory loss is one of the key symptoms and will increased with age. Around 5.8 million age 65 and older live with AD in the United States, 80% of them are above 75 years and older. During the aging process, hypoxia is a major factor in the development of age-related neurological diseases, however the underlying mechanisms remain unknown.AD is characterized by tau hyperphosphorylation and intraneuronal neurofibrillary tau tangles in the brain. Previous studies indicate induced chronic hypoxia in transgenic p301l mice expressing human tau is associated with increased hyperphosphorylated tau. We aimed to specifically investigate the spread of pathological tau by measuring the correlation between hypoxia and tau propagation in C57BL/6J wild type mice injected with AAV CBA.eGFP.2a.hu P301L tau. In our study, we found that the injection of AAV CBA.eGFP.2a.hu P301L tau caused greater spread of tau pathology. However, our data shows that this effect was much more prevalent in aged mice (2yo) in comparison to adult mice (8wo), indicating hypoxia has a different mechanistic effect on the cell-to-cell transmission of tau in the aged model.Past research has shown that neuroinflammation has a key role in the pathogenesis of AD, of which hypoxia is an imminent inducer, indicating a possible mechanistic interaction between the observed hypoxia-induced tau propagation and neuroinflammatory response, microglial activation was observed in WT, AAV CBA.eGFP.2a.hu P301L tau injected, hypoxia, and hypoxia+ AAV CBA.eGFP.2a.hu P301L tau injected mice. Our study demonstrates greater microglial activation in the aged mice with hypoxia-induced tau propagation than adult mice with less observed tau pathology.Altogether our data strongly support that hypoxia plays an important role in tau propagation, which may be related to a microglia-induced neuroinflammatory response. This highlights the neuroinflammatory response as a target of investigation in the spread of pathological tau.

Disclosures: S. Su: None. **H. Liu:** None. **M. Ying:** None. **V.L. Dawson:** None. **T.M. Dawson:** None. **X. Mao:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH GRANT 2R44AG053150-05

Title: Preclinical profiling of pharmacokinetic and pharmacodynamic readouts of a small molecule inhibitor of tau self-association in a mouse model of tauopathy

Authors: *D. R. PATEL[1], C. SUSSMAN[1], M. GRECO[1], E. CHEESMAN[1,2], P. LOPEZ[1], E. J. DAVIDOWITZ[1,2], J. G. MOE[1,2];
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Abstract: Tau aggregation is being targeted for therapeutic intervention because it strongly correlates with and facilitates disease progression in Alzheimer's disease and related tauopathies. We have used a small molecule approach to target tau self-association to inhibit the initiation and progression of tau aggregation. This approach translated in vivo in htau and JNPL3 mouse models of tauopathy, and in a therapeutic study of aged JNPL3 mice with pre-existing tau aggregates. The selected compound inhibited the accumulation of self-associated tau, insoluble tau aggregates, and rescued impaired motor function. Here, we show the initial results of a study evaluating acute measures of efficacy that will ultimately be used to establish a PK/PD model of our lead small molecule (OLX-07010) to inform dosing in the clinic. First, exposure of the compound in the serum and brain was performed using single oral doses ranging from 40 to 200 mg/kg in aged JNPL3 mice to evaluate two vehicles and to select doses for pharmacokinetic (PK) studies and dose selection for the acute efficacy study in aged JNPL3 mice. The vehicle providing better solubility for the compound enabled an approximate two-fold improvement in exposure of the selected compound at Cmax in the brain and serum. Based on the results of the PK studies, the vehicle and treatment doses of OLX-07010 were selected for pharmacodynamic (PD) evaluation. Briefly, homozygous female JNPL3 mice were first aged to 9 months and then treated for 1 month using oral gavage with vehicle or OLX-07010 at 20 or 40 mg/kg dose. The sample size of the treatment groups included n=20 mice/group. For PD evaluation, the primary endpoint includes biochemical reduction of self-associated tau with statistical significance. While the secondary endpoints include dose-dependent rescue of motor behavior deficits, and reduction of Sarkosyl-insoluble, and phosphorylated tau. Motor behavior phenotype will be evaluated using Open-field and Rotarod tests. Overall, the most informative markers of efficacy will be used to develop a PK/PD model for supporting the dose selection of OLX-07010 in future clinical studies.

Disclosures: **D.R. Patel:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **C. Sussman:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **M. Greco:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **E. Cheesman:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **P. Lopez:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **E.J. Davidowitz:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **J.G. Moe:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc..

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIAAA R01 AA028931
NIAAA R00 AA024215
NIH T32-GM067795

Title: Human dorsal raphe tau pathology and related depressive-like behaviors in adult C57BL/6J mice

Authors: *S. R. PIERSON[1], K. L. FIOCK[2], K. M. KHAN[1], M. M. HEFTI[2], C. M. MARCINKIEWCZ[1];
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Abstract: Alzheimer's disease (AD) pathology is thought to begin in the entorhinal cortex and hippocampus, but there is growing evidence that pathology first begins in subcortical structures. The majority of studies investigating tau pathology focus on cortical structures, although subcortical structures, such as the locus coeruleus and dorsal raphe nucleus (DRN) are affected by tau pathology early in AD. Specifically, monoaminergic nuclei like the DRN undergo significant cell loss and tau burden. The DRN is known to be involved in depression, anxiety, and memory processes, which are manifested in behavioral, psychological, and cognitive symptoms of AD. We hypothesize that tau pathology in monoaminergic structures may underlie mood or affective changes and possibly early-onset of cognitive deficits in AD. To assess whether DRN pathology might be an indicator of AD-related pathology in cognitively normal individuals, we immunostained for the serotonergic marker TPH2 and hyperphosphorylated tau marker AT8 in post-mortem samples of 7 cognitively normal individuals, and 10 AD-diagnosed individuals. We found DRN tau pathology in 4/7 otherwise normal individuals, and 9/10 AD-diagnosed individuals. We additionally tested this hypothesis in a pre-clinical model by infusing an AAV containing the P301L mutation of human tau or GFP into the DRN of C57BL/6J male mice. The P301L tau mutant is associated with frontotemporal dementia in humans and has successfully been used by other groups to induce human-like tau pathology. Following AAV-tau infusion, animals (n=20) underwent assays to assess anxiety- and depressive-like phenotypes, as well as memory: elevated plus maze (EPM), open field test (OFT), social interaction (SI), sucrose preference test (SPT), Barnes maze (BM), and contextual fear conditioning (CFC). We found that tau pathology in the DRN is sufficient to produce depressive-like behavior in mice, indexed by decreased social interaction and sucrose preference. The results from these experiments demonstrate the influence of early tau pathology in subcortical regions on the etiology AD disease. These ongoing and future experiments provide a pathway for us to study tau pathology in some of the earliest affected brain regions in AD, allowing us to better understand how early stages of AD influence monoaminergic function and behavior. By gaining a deeper understanding of the role of 5-HT dysfunction in the etiology of the disease, we can identify and develop earlier interventions. In future experiments, we will investigate the roles of

sex differences, neuroinflammation, and alcohol use in monoaminergic pathology and possible resulting deficits.

Disclosures: S.R. Pierson: None. **K.L. Fiock:** None. **K.M. Khan:** None. **M.M. Hefti:** None. **C.M. Marcinkiewcz:** None.

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705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG064066
Alzheimer's Association

Title: The Role of Tau Pathology on Hippocampal Function

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Abstract: It is unclear as to why tau accumulates first in the LC (Locus Coerelus) in young adults despite the evidence of tau pathology originating rather in entorhinal cortex (EC). It is established that LC subserves a pivotal function in attention and memory, being one of the regions responsible for arousal and sleep regulation. PPP knockin mice, APPNL-G-F, which have physiological levels of APP in the brain were probed to pin down alterations, if any, of electrophysiological properties of neurons in HPC (Hippocampus) region, as a result of tau accumulation in LC. In addition, region-specific memory tests were administered to identify their cognitive status. Our preliminary data from single unit recording indicate that accumulation of tau facilitates impairments in spatial memory rendered by altered remapping that seems to be consistent with the changes in the environment as seen in the SLR (spontaneous location recognition) and NOR (novel object recognition) tasks. Altered firing properties is reflective of the limited accuracy in decoding spatial behavior mapping in neurons. Furthermore, the LFP (local field potential) measurements in the area CA1 in HPC region shows impairments in sleep recordings in comparison to control, tying it back possibly to the mechanistic deterrence in circadian rhythm brought about by the accumulation of tau in LC. Tau pathology in LC leads to neuronal and network dysfunction leading to spatial memory deficits. These novel findings in turn may substantiate EEG as a useful biomarker for early diagnostics of tauopathy in its vulnerability towards a specific brain region in the Alzheimer's condition and to identify changes not known thus far.

Disclosures: R. Raghuraman: None. **M. Herman:** None. **S.A. Hussaini:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.13

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Female sex hormones are necessary for the expression of neuroprotective factors following irisin treatment in female htau mice

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Abstract: Hyperphosphorylated/misfolded tau protein is the main component of the intracellular filamentous inclusions that are involved in a subset of neurodegenerative diseases known as tauopathies, including Alzheimer's disease (AD), progressive supranuclear palsy, corticobasal syndrome, and chronic traumatic encephalopathy. To date, no disease modifying therapies exist for these disabling and dementia-causing conditions. Increasing evidence suggests that physical exercise may reduce risk for neurodegenerative disease but the mechanisms by which exercise exerts these beneficial effects remain unclear. Irisin, a novel exercise-induced hormone, has recently gained attention as a mediator of exercise's beneficial effects on the brain as well as for its potential to protect against neurodegenerative diseases. Recent data published by our lab show that systemic enhancement of irisin (via injections of recombinant human irisin) in transgenic tauopathy model "htau" mice reduces early brain pathology in female but not male animals. Thus, the goal of our current study was to identify the mechanisms underlying this sex-divergent irisin treatment effect in htau mice. We hypothesized that circulating estrogens mediated irisin's neuroprotective effect and performed a study where female htau and C57 control mice underwent bilateral ovariectomy (OVX) or sham surgical procedure followed by weekly injections of recombinant irisin (i.p.) or vehicle (control) for 4 weeks. Brain tissue was then processed for changes in key proteins associated with inflammation and pathology. Our results demonstrate that endogenous female sex hormones mediate irisin's efficacy in reducing early accumulation of hyperphosphorylated tau in the hippocampus of female htau mice. Ongoing analyses are further evaluating whether estrogenic status impacts irisin's ability to reduce neuroinflammation (TNFα) and whether early indicators of blood brain barrier compromise shown in female htau might be repaired via exogenous irisin treatment in sham and OVX female htau mice. These preliminary findings emphasize an important need to identify sex-specific disease mechanisms that can be more precisely targeted for neurodegenerative disease prevention.

Disclosures: S.J. Terrill: None. **K.A. Bretland:** None. **V.N. Palmer:** None. **L. Lin:** None. **G. Leone:** None. **S.M. Fleming:** None. **C.M. Dengler-Crish:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R01AG077692
NIA T32AG000255
NINDS R37NS115439

Title: Development of a novel mouse model and whole brain mapping pipeline to quantify tau spread and seizure interactions.

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Abstract: Development of a novel mouse model and whole brain mapping pipeline to quantify tau spread and seizure interactions.
Aaron J Barbour, Bo Xing, Virginia MY Lee, Delia M Talos, Frances E Jensen
The accumulation and spread of beta amyloid and tau pathology underlie the neuropathological progression of Alzheimer's disease (AD) with tau spread correlating closely with cognitive decline. Epileptiform activity occurs in up to 64% of AD patients with recent data demonstrating enhanced AD pathology in these patients and mouse models. Data from AD patients as well as *in vivo* and *in vitro* models suggest that neuronal activity may underlie the spread of tau. Given that epilepsy induces neuronal network hyperactivity and targets pathways involved in tau pathology, we hypothesized that seizures enhance the propagation of tau. To study our hypothesis, we induced tau spread via hippocampal injection of human AD brain derived tau and induced seizures with pentylenetetrazol (PTZ) kindling in our novel mouse model, T40PL-GFP x FosTRAP (Targeted Recombination in Activated Populations; T40-TRAP) mice. These mice contain human pathogenic P301L *MAPT* tagged with GFP and tamoxifen inducible, Fos driven tdTomato expression. We administered 4-hydroxytamoxifen on the final day of PTZ kindling to permanently label all seizure-activated neurons with tdTomato. Elucidating all brain regions and subregions affected by tau spread, seizures, and how seizures may hasten or exacerbate the spread of tau is vital to understanding neurocognitive outcomes and the mechanisms underlying the neuropathology of AD and epilepsy. To this end, we utilized CUBIC brain clearing and imaged intact T40-TRAP hemispheres both ipsi- and contralateral to AD-tau injection site by light sheet fluorescence microscopy (LSFM). We utilized Arivis cell detection and machine learning algorithm to detect tdTomato+ (seizure-activated, TRAP'd cells) and GFP+ (tau inclusion) cells, respectively. LSFM images were registered to the Allen Brain Atlas by linear transformation with QuickNII (Puchades et al. 2019) followed by nonlinear transformations with the Big Warp plugin for Image J. Cell detection results were then applied to the warped atlas and matched to brain region by color code and ordered within the Allen Brain Atlas hierarchy with a custom R script. Overall, we demonstrate the utility of our novel mouse model and brain mapping pipeline for the examination of all brain regions involved in and affected by the seizure engram, the spread of tau, and their interactions.

Disclosures: **A.J. Barbour:** None. **B. Xing:** None. **V.M.Y. Lee:** None. **D.M. Talos:** None. **F.E. Jensen:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH K99AG068602
JPB foundation
Harrison Gardner Jr. Innovation Award

Title: Flexible electronics enable new insight into neuronal network dysfunction that progresses with aging in Alzheimer's disease model mice

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Abstract: A major challenge in studying aging processes in mammalian brains is that they occur over months or years and across brain regions, yet they involve changes in individual neurons with millisecond activity. Recent advances in the design of implantable mesh electronics allow the study of the same individual neurons and circuits over multiple months. These properties enable the study of functional changes in brain processes that occur over long periods of time, such as the onset of dementia associated with Alzheimer's disease pathology. We designed and implanted flexible, neuron-like mesh electronics into the brains of mice that progressively accumulate Alzheimer's disease tau pathology with age. Specifically, two mesh electronics probes were implanted into one hemisphere of youngThyTau22 (n=5) or WT (n=2) mice. One probe was targeted to the hippocampus (HPC), and the other to the medial entorhinal cortex (mEC). Recordings were made once per week over 6 months while mice run along a linear track in virtual reality. Mice run along one track over multiple trials for 10 minutes, then the screen is turned off and recordings continue for 5 minutes to probe the influence of context on electrophysiology. Analysis of electrophysiology data show aging and tau-pathology correlated with decreases in local field potential (LFP) coherence at multiple frequencies. In ThyTau22 mice, theta and gamma frequency LFP show increased coherence between recording sites at early ages compared to WT. As ThyTau22 mice age they show a decrease coherence both within and across brain regions, leading to near-complete decoherence between the HPC and mEC. In contrast, WT mice show stable or increasing LFP coherence over time. Approximately 300-500 individual neurons were identified in each mouse through super-paramagnetic clustering (WaveClus 3), and nearly all recorded neurons were present across the entire 6 month study.

Analysis of spike timing shows neurons in WT mice HPC and mEC have consistent firing rates across sessions and contexts. In stark contrast, ThyTau22 mice show substantial increase in neuronal firing rates in the mEC while running on the virtual track, and these firing rates become depressed when the context is switched. Firing rates of neurons decrease over 6 months in both HPC and mEC of ThyTau22 mice. Pairwise correlations of spike firing times show connectivity between neurons both within and across brain regions, and future analyses will probe their change over time. Together, these data show aging in mice with tau-pathology leads to a substantial decrease in neuronal network integrity at the level of individual neurons and their populations, both within and between the HPC and mEC.

Disclosures: T.J. Zwang: None. **N.L. Pettit:** None. **M. Lysandrou:** None. **C.D. Harvey:** None. **C.M. Lieber:** None. **B.T. Hyman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dewpoint, Novartis. F. Consulting Fees (e.g., advisory boards); AbbVie, Avrobio, Axon, Biogen, BMS Cell Signaling, Genentech, Ionis, Novartis, Seer, Takeda, US Dept of Justice, Vigil, Voyager, Dewpoint.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.16

Topic: C.02. Alzheimer’s Disease and Other Dementias

Support: 1 F31 AG074649-01
NIA-RF1

Title: Sleep Disruption in the Progression and Treatment of Alzheimer's disease

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Abstract: Sleep is an essential physiological behavior that supports brain health and cognitive function. Alzheimer’s disease (AD) patients experience accelerated sleep loss which correlates with onset and progression. Tau is an axonal microtubule stabilizing protein that forms aggregates in AD and contributes to cognitive decline, synapse loss and neuronal death. In AD, tau mislocalization and aggregation at synapses may further impair sleep and restorative sleep-dependent homeostatic plasticity. However, the synaptic biochemical consequences of acute versus chronic sleep deprivation have not been explored in the context of tau pathology. I hypothesize that sleep disruption occurs early in AD progression and subsequently drives further tau mislocalization and aggregation, and cognitive decline. Preliminary data using P301S (PS19) transgenic mice shows that differences in sleep behavior arise as early as 3 months in females and 6 months in males. Accumulation of tau becomes apparent between 6-9months. These results highlight sex differences in the onset of sleep disruption and support sleep disruption as

an early-stage symptom. Preliminary data also shows an increase in expression of synaptic proteins after chronic sleep deprivation in the hippocampus but not the cortex of female PS19 mice. These differences are not present after acute sleep deprivation. Endocannabinoids provide an intriguing avenue for therapeutic intervention because of their role in promoting sleep and anti-inflammatory signaling. Preliminary work shows that sleep disruption in PS19 mice can be acutely reversed by increasing the endocannabinoid anandamide. Therefore, the objectives of this work are to investigate the differences between acute and chronic sleep deprivation on synaptic proteins, and to identify the therapeutic window targeting endocannabinoid signaling during sleep in advance of tau pathology and cognitive decline. These studies will provide a deeper understanding of the behavioral and molecular changes that occur during abnormal sleep in AD and highlight endocannabinoids as a suitable signaling pathway for enhancing the restorative benefits of sleep.

Disclosures: S. Martin: None. **K. Joyce:** None. **J.S. Lord:** None. **G.H. Diering:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Departmental fund: Translational Neuroscience
NIH/NIA R01AG067762

Title: EFhd2 transforms monomeric and filamentous tau into tangle-like structures in vitro

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Abstract: Aggregated tau is the primary pathological culprit in several neurodegenerative disorders, collectively named tauopathies. The best known tauopathy is Alzheimer's Disease (AD). Abnormally modified tau undergoes pathogenic conformational transformations into transmissible toxic oligomers that coalesce into filaments and, ultimately, into intracellular innocuous ultrastructures known as neurofibrillary tangles (NFTs) in AD brain. The evolving premise deems sequestering tau oligomers to filaments and tangles a protective response against cell demise. Nonetheless, the molecular events that regulate the pathological transitions of tau into oligomers and then into NFTs have yet to be unraveled. We discovered EFhd2 as a protein associated with pathological tau in postmortem brains of various tauopathies and a tauopathy mouse model. We demonstrated that EFhd2 transforms the dynamic tau liquid droplets into less

dynamic solid-like structures. Herein, we test the hypothesis that EFhd2 induces tau aggregation in vitro in the presence and absence of arachidonic acid (ARA)—a tau aggregation inducer. Equimolar concentrations of recombinant human EFhd2 (hEFhd2) and full-length tau (hTau40) were incubated for 16 h with and without ARA. Data were collected from three independent experiments. Visualized by electron microscope, hEFhd2 induced the formation of tangle-like structures that are starkly different from ARA-induced tau filaments. Immunogold labeling confirms the colocalization of hEFhd2 and hTau40 in these aggregates. Seeding competency and cellular propagation of EFhd2-induced tangle-like structures were tested using HEK 293 tau biosensor cells that stably express the microtubule binding repeat domain of P301S tau fused with fluorescent proteins. Treating the cells with pre-aggregated tau species (i.e., ARA-induced tau aggregates) causes the seeding of fluorescently tagged tau monomers into aggregates. In this experiment, cells were treated with 150 nM tau aggregates, or monomers as a negative control, using Lipofectamine2000. After 48 h, cells were counterstained with DAPI and imaged with a Lionheart FX automated microscope. The quantitative analysis of seeded aggregates (GFP/CFP fluorescence normalized to DAPI), using Gen5 software, showed that treatment with hEFhd2-hTau40 (with and without ARA) elicited significantly reduced seeded aggregation compared to hTau40-ARA. Our data suggest that EFhd2 promotes the formation of less transmissible tau tangle-like structures. Future in vivo studies will determine the role of EFhd2 on tau-mediated neurodegeneration.

Disclosures: **A.S. Soliman:** None. **A. Umstead:** None. **R.L. Mueller:** None. **J. Lamp:** None. **N.M. Kanaan:** None. **I.E. Vega:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA R01AG060718
NIH/NIA R01AG069433
NIH/NIA R01AG072883

Title: Calcineurin inhibition promotes CNS clearance of toxic tau oligomers

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Abstract: Calcineurin (CN), an important Calmodulin-dependent phosphatase regulator of synaptic function, is dysfunctionally increased in the CNS of Alzheimer's Disease (AD) patients as well as in transgenic AD animal models. We previously showed that CN mediates the detrimental effect of amyloid beta on synapses and memory function. Notably, we further

reported that humans chronically treated with the CN inhibitor FK506 were protected from developing AD, suggesting a key role of CN in onset and progression of AD. To further investigate this novel possibility, here we determined the impact of CN inhibition with FK506 on tau pathology, tau toxic oligomers and autophagy. Using immunofluorescence microscopy, Western blotting and IP we studied the presence and phosphorylation status (as appropriate) of tau, CN, GSK3b and several elements of the autophagy pathway (including Beclin, LC3/2, Atg16 and LAMP1) in the CNS of mice after ICV injection of preformed human tau oligomers (TauO) followed, 18 hrs later, by FK506. Similar measurements were also done in 3xTgAD mice sub-chronically treated with FK506. We found that the presence and phosphorylation of TauO was significantly reduced in mice injected with TauO icv and further treated with FK506. Presence of endogenous tau was also significantly reduced in 3xTgAD mice treated with FK506. In both cases, we found that key elements of the autophagy pathway were decreased by TauO and returned to basal levels by FK506. Our results indicate that TauO disrupt proper autophagy function, which is reversed by CN inhibition with FK506 thus promoting clearance of toxic tau. Collectively these results suggest, for the first time, a method to clear toxic TauO via inhibition of CN. Since FK506 is FDA-approved for the use in humans, this new approach future development of CN inhibition as an effective treatment for AD appears to be warranted.

Disclosures: **A. Fracassi:** None. **B. Tumurbaatar:** None. **W. Zhang:** None. **R. Kayed:** None. **G. Taglialatela:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.19

Topic: C.02. Alzheimer’s Disease and Other Dementias

Support: NIH Grant R21AG061674-01
Garrison Family Foundation

Title: The role of mitochondrial fission protein Drp1 in mitophagy process in transgenic mouse model (Tau-P301L).

Authors: ***M. MANCZAK**, X. YIN, D. BURUGU, J. LAWRENCE, V. NEUGEBAUER; Garrison Inst. of Aging, Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Mounting evidence suggests that Aβ and Phosphorylated Tau induced mitochondrial dysfunction and synaptic damage are largely involved in AD progression and pathogenesis. Failure in the removal of dysfunctional mitochondria induces cellular stress and is linked to human diseases including Alzheimer's disease (AD). In the current study we explore the effect of Drp1 on the mitophagy process. DRP1 (Dynamin related protein 1) is a member of the dynamin superfamily of GTPases that mediates mitochondrial fission. We studied the protective effects of reduced Drp1 on mitophagy in Tau- transgenic mice by crossing Tau (P301L) with knockdown

Drp1 (+/-) mice to create double mutant (TauXDrp1+/−) mice. We studied also the adverse effects of overexpressed Drp1 on mitophagy in the Tau (P301L) mice by overexpressing Drp1 using the adeno-associated viral approach (AAV9- CMV-m-DNM1L). Using real-time PCR, immunoblotting, and immunostaining analyses, we measured genes related to the mitochondrial dynamics, mitochondrial biogenesis, mitophagy and mitophagy receptors and adaptors. Our findings suggest that a partial reduction of Drp1 rescues PINK1 deficiency, which regulates mitophagy independent of Parkin. After overexpression of DRP1in Tau mice, we observed downregulation of Pink1 and upregulation of Parkin. Mitophagy is probably most likely mediated by distinct mechanisms, predominantly by a Parkin-dependent pathway. Regulatory mechanisms by which Drp1 switches between physiological and pathological roles still need to be identified, and further investigations are required to clarify interaction between the fission machinery and the mitophagy machinery. Acknowledgment: We thank Dr. Hiromi Sesaki from Johns Hopkins University School of Medicine, who generously provided breeding pairs of knockdown Drp1 (+/-) mice.

Disclosures: M. Manczak: None. **X. Yin:** None. **D. Burugu:** None. **J. Lawrence:** None. **V. Neugebauer:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.20

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AARF-17-533378

Title: Long term exposure to Levetiracetam decreases pathology in a mouse model of tauopathy.

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Abstract: Abnormal tau hyperphosphorylation and its accumulation into neurofibrillary tangles are linked to neurodegeneration and decreased learning and memory in Alzheimer's disease and similar tauopathies. Tg4510 mice are characterized by tau deposition in the brain together with cognitive and non-cognitive impairments that resemble those seen in patients. Levetiracetam is an FDA approved anticonvulsant drug known to decrease seizures and kindling in several animal models of epilepsy and showed improvements in models of amyloidosis. The aim of this study was to test the effects of a Levetiracetam diet on tau pathology and cognition in a mouse model of tauopathy, the Tg4510 mice. Three-month old Tg4510 transgenic and non-transgenic littermate mice were equally randomly assigned to treated (food containing 240mg/kg Levetiracetam) or placebo (control diet) groups (n=10, 5F & 5M). Food intake and body weight

were recorded weekly. After 2.5 months of diet the following behavioral tests were performed: open field, Y-maze, marble burying, RAWM with reversal, rotarod, novel object recognition and fear conditioning. After 3 months of diet the brain was dissected, blood sample was collected, and muscle mass, white fat, and brown fat were weighed. Treatment with Levetiracetam did not improve memory in Tg4510 in all the tests assayed but induced a decrease in Tau phosphorylation at ser396 in the hippocampus. Interestingly, Levetiracetam diet had significantly more impact in non-transgenic mice than Tg4510 mice. Indeed, we observed a decrease in body weight, food intake, increased time spent on rotarod and a decrease of anxiety like behavior in non-transgenic mice but not in Tg4510 mice treated with Levetiracetam when compared to control diet. This seemed to indicate that some of the Levetiracetam biological response was dysregulated in Tg4510 mice. We found that SV2A, a molecule of Levetiracetam pathway, was decreased in the hippocampus of Tg4510 mice under chow diet when compared to controls and that 3 months of Levetiracetam diet restored SV2A levels in Tg4510 mice, while having no effect in non-transgenic. In summary, we observed that 3 months of diet with FDA approved Levetiracetam drug did not improve memory in a mouse model of Alzheimer's disease but decreased tau pathology in the hippocampus. This was accompanied by restoration of SV2A levels in Tg4510 mice under Levetiracetam. In addition, we found some Levetiracetam effects in the control mice but not in the Tg4510 mice, indicating a possible disruption in Levetiracetam mechanism. Further study of this pathway could bring new insight on Levetiracetam action and understanding of Alzheimer's disease pathology.

Disclosures: A. Joly Amado: None. **M. Novoa:** None. **L. Alvarez:** None. **H. Peck:** None. **J. Willman:** None. **M. Willman:** None. **K.R. Nash:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.21

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG054223
NIH Grant AG063175
NIH Grant AG077610

Title: Identifying novel binding partners of BIN1's SH3 domain in Alzheimer's disease

Authors: *D. BLAZIER, E. LEWANDOWSKI, S. WANG, X. ZHANG, S. HILL, J. MCMILLAN, L. BLAIR, Y. CHEN, G. THINAKARAN;
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Abstract: Genome-wide association studies identified Bridging Integrator 1 *(BIN1)* as the second most significant susceptibility locus for late-onset Alzheimer's disease (AD) development. While BIN1 has been implicated in tau pathology, the exact mechanism by which

BIN1 facilitates AD onset remains unclear and warrants further investigations. Through the identification of novel BIN1 binding partners by structural techniques, including x-ray crystallography and surface plasmon resonance (SPR), we aim to characterize BIN1's role in AD development in the brain and identify novel targets for molecular docking and the discovery of specific small molecule inhibitors/activators. Under homeostatic conditions, BIN1 functions in multiple cellular pathways, including synaptic transmission, endocytosis, cytoskeletal remodeling, and generating membrane curvature, and is alternatively spliced to form tissue/cell-type-specific and ubiquitous isoforms. A common denominator unites all BIN1 isoforms - the C-terminal Src homology 3 (SH3) domain, a highly conserved functional module that facilitates protein-protein interactions, typically through hydrophobic interactions of side chains. BIN1's SH3 domain has been shown to bind a class II proline-rich motif on tau through hydrophobic and electrostatic interactions, implicating it in tau pathology. We used SPR to ascertain the affinity of BIN1's SH3 domain to full-length 0N4R wild-type tau, and the results showed the equilibrium dissociation constant (K_D) of 1.186 μM. We are using complementary experimental approaches to expand the repertoire of neuronal and non-neuronal proteins interacting with the BIN1 SH3 domain at an affinity similar to or better than tau. Developing a comprehensive interaction map of BIN1's SH3 domain may contribute to advancing the development of therapeutics against AD.

Disclosures: **D. Blazier:** None. **E. Lewandowski:** None. **S. Wang:** None. **X. Zhang:** None. **S. Hill:** None. **J. McMillan:** None. **L. Blair:** None. **Y. Chen:** None. **G. Thinakaran:** None.

Poster

705. Tau and Tauopathies: Animal Models

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 705.22

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BrightFocus Foundation A2021043S
NIH Grant R00NS101065
NIH Grant R35GM142490
Whitehall Foundation

Title: Altered neuronal cooperativity in Alzheimer's disease

Authors: *K. X. LI[1], V. SANCHEZ FRANCO[1], Y. XIE[1], A. N. HUTSON[1], Y. ZHANG[1], S. D. DANIELS[1], M. TABUCHI[1], A. KNAUSS[2];
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Abstract: While neuronal cooperativity has been implicated in the etiology of Alzheimer's disease (AD), its mechanistic causality is poorly understood. Not only has early cooperativity of cortical inhibitory interneurons been identified in mammalian models of AD, but the synergistic

interaction between sleep loss and AD pathogenesis to alter neuronal cooperativity has also been demonstrated. Previous research using a Drosophila model of AD has shown altered intrinsic membrane properties due to decreased conductance of voltage-gated potassium channels. Here, we found that in addition to voltage-gated potassium currents, voltage-gated sodium currents have also been altered in our Drosophila model of AD. Specifically, we found that sodium channel inactivation status was significantly prolonged in neurons expressing Tau. Further, we found that this prolonged sodium channel inactivation was synergistically enhanced by chronic sleep deprivation, suggesting a positive feedback loop between sleep and AD pathogenesis in shaping neuronal cooperativity. Strikingly, we also observed that the introduction of both Levetiracetam (LEV) and Brivaracetam (BRV) within the fly's food negated the AD-induced prolongation of the sodium channel inactivation status. Together, our results indicate that changes in sodium channel inactivation status could be a novel predictor to improve deficits in neuronal cooperativity induced by sleep and AD pathology, which has the potential to reduce attrition in the late phases of neuroprotective medication development. Currently, we seek to understand the relationship between sleep deprivation at different ages and AD pathology. Moreover, we are working on comparing these results with human iPS-derived neuronal networks for better insight on the mechanisms described above.

Disclosures: K.X. Li: None. **V. Sanchez Franco:** None. **Y. Xie:** None. **A.N. Hutson:** None. **Y. Zhang:** None. **S.D. Daniels:** None. **M. Tabuchi:** None.

Poster

706. Neurodegenerative Disease Models and Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 706.01

Topic: C.06. Neuromuscular Diseases

Support: Bavarian Research Consortium "Interaction of Human Brain Cells" (ForInter)
German Research Foundation, 270949263/GRK2162, WI 3567/2-1, 125440785/SFB877 project B11 and Z2
the Interdisciplinary Center for Clinical Research of the University Hospital Erlangen, Germany (E30)
the Marohn Foundation (Pyroglutamic-acid-alpha-synuclein)

Title: SNCA gene duplication induces a redistribution of distinct alpha synuclein species from the nucleus to neurites, linked to neuritic alterations in neurons derived from patients of Parkinson's disease

Authors: *W. XIANG[1], K. PIEGER[2], L. SEEBAUER[1], Y. SCHNEIDER[1], R. BRAZDIS[3], I. PROTS[3], B. WINNER[3], J. BRANDSTÄTTER[2], J. WINKLER[1];
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Abstract: Parkinson's disease (PD) is the most neurodegenerative movement disorder, which is neuropathologically characterized by the loss of midbrain dopaminergic neurons (mDANs) and accumulation of aggregated alpha-synuclein (aSyn). Since point mutations and multiplications of aSyn gene (*SNCA*) are sufficient to cause familial forms of PD, aSyn and its abnormal aggregation are believed to play a crucial role in the pathogenesis of PD. There is mounting evidence that neuritic degeneration and dysfunction temporally precede the loss of neuronal cell bodies. Using mDANs differentiated from human-induced pluripotent cells (hiPSCs) derived from PD patients carrying a heterozygous *SNCA* gene duplication ($SNCA^{Dupl}$), we previously investigated the effect of an increased *SNCA* gene dosage on triggering neuritic impairments. We observed in $SNCA^{Dupl}$ carrying mDANs PD-related phenotypes, including elevated levels of aSyn and its aggregation, accompanied by enhanced oxidative stress. Importantly, aggregated aSyn in $SNCA^{Dupl}$ mDANs directly interacted with microtubule elements. Consequently, $SNCA^{Dupl}$ neurons exhibited alterations in microtubule organization and impaired axonal transport activity. Since aSyn is primarily known for its localization in the nucleus and presynaptic terminals and not evenly distributed throughout the neuron, we hypothesized that aggregated aSyn is enriched in the neurites of $SNCA^{Dupl}$ neurons, whereby promoting its interference with neuritic homeostasis. To verify this hypothesis, we investigated aSyn distribution patterns during the differentiation of hiPSC-derived neurons by employing an antibody targeting the C-terminus of aSyn (aSyn-C). A spatial and temporal analysis demonstrated that aSyn-C has a high immunoaffinity towards aSyn in the nucleus of proliferating cells and preferentially binds to aggregated aSyn. Moreover, we observed a redistribution of aSyn-C immunosignals from the nucleus towards neurites during neuronal differentiation. Interestingly, we detected an increased shift of aSyn-C positive species from the nucleus to neurites, specifically in differentiated mDANs carrying $SNCA^{Dupl}$. Collectively, our data suggest an anterograde translocation of distinct aSyn aggregated species in developing neurites of $SNCA^{Dupl}$ mDNAs, compromising neuritic functions and finally leading to neuronal loss.

Disclosures: W. Xiang: None. **K. Pieger:** None. **L. Seebauer:** None. **Y. Schneider:** None. **R. Brazdis:** None. **I. Prots:** None. **B. Winner:** None. **J. Brandstätter:** None. **J. Winkler:** None.

Poster

706. Neurodegenerative Disease Models and Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 706.02

Topic: C.06. Neuromuscular Diseases

Support: FAPESP grant 2017/05264-7
FAPESP grant 2018/23460-0
FAPESP grant 2020/06970-5
FAPESP grant CEPID: 2013/08028-1

FAPESP grant CEPID: 2013/07937-8
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Financial Code 001)

Title: Multiple Sclerosis iPSC-derived astrocytes recapitulate disease-related metabolic alterations

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Abstract: Multiple sclerosis (MS) is a severe multifactorial demyelinating disease that affects more than two million people worldwide and, despite several advances in the field, it still has no cure. Astrocytes compose most of the human brain and a play a key role in MS and, in this sense, mitochondrial dysfunction has recently been indicated as a relevant pathway in astrocyte pathology during MS. However, most studies were performed in the Experimental Autoimmune Encephalomyelitis model, which has several differences to patients, urging the need to study brain resident cells in models that better resemble MS. Accordingly, induced pluripotent stem cells (iPSC) appear as a powerful tool to unravel pathological mechanisms of complex diseases like MS, as they can be differentiated into any resident cell population of the human brain. Here we successfully obtained and characterized iPSC-derived astrocytes from three patients with MS (PwMS) and three age and sex-matched controls and performed functional assays in these cells including electron microscopy, flow cytometry, cytokine and glutamate measurement, gene expression, *in-situ* respiration, and metabolomics. We observed several differences between control and MS astrocytes, with enrichment of genes associated with mitochondrial dysfunction and neurodegeneration in patients' cells. Next, using electron microscopy, we observed a significant increase in mitochondrial fission in the MS astrocytes, which was followed by a decreased mitochondrial to nuclear DNA ratio, indicating disruption of mitochondrial content in these cells. Then, we observed in this same group increased superoxide and MS-related proinflammatory chemokines production along with a decresed sodium-dependent glutamate uptake and increased glutamate release, which can mediate neurotoxicity. Additionally, using Seahorse assays, we observed an increased electron transport capacity and proton leak in patients' astrocytes, which is in line with the increased oxidative stress observed in these cells. Finally, our metabolomics analysis indicated a distinct metabolic profile between the groups, with a deficiency in amino acid catabolism and increased sphingolipid metabolism in the patients' cells, which have already been linked to MS. We validated our findings using a publicly available single-nucleus RNA sequencing dataset consisting of different lesion areas from PwMS and healthy individuals' brains. To our knowledge, this is the first study thoroughly describing

the metabolic profile of iPSC-derived astrocytes from PwMS, validating this model as a very powerful tool to study MS mechanisms and to perform drug targeting assays *in vitro*.

Disclosures: **B. Ghirotto Nunes:** None. **D. Oliveira:** None. **M. Cipelli:** None. **P. Basso:** None. **C. Naffah:** None. **J. de Lima:** None. **H. Ribeiro:** None. **C. Caldeira:** None. **A. Sertié:** None. **A. Oliveira:** None. **M. Hiyane:** None. **E. Caldini:** None. **A. Sussulini:** None. **H. Nakaya:** None. **A. Kowaltowski:** None. **E. Oliveira:** None. **M. Zatz:** None. **N. Camara:** None.

Poster

706. Neurodegenerative Disease Models and Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 706.03

Topic: C.06. Neuromuscular Diseases

Support: TreatHSP consortium BMBF 01GM1905B

Title: Targeting GSK3 signaling to restore neurodevelopmental and neurodegenerative phenotypes of SPG11- and SPG15-hiPSC patients-derived cortical progenitors and neurons

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Abstract: SPG11- and SPG15-related hereditary spastic paraplegias (HSP) are the most common autosomal recessive forms of HSP. In addition to the HSP hallmarks spasticity and paraplegia of the lower limbs, SPG11- and SPG15-related HSP patients exhibit early disease onset, cognitive impairment, and a thin corpus callosum. To date, there is no causal treatment. Interestingly, an interaction of SPG11 and SPG15 could be previously demonstrated on the protein level. This and the clinical overlaps lead us to hypothesize that SPG11 and SPG15-related HSP share common disease mechanisms. We previously reported in SPG11 hiPSC patient-derived cortical progenitors and neurons that impaired GSK3 signaling leads to neurodevelopmental and neurodegenerative phenotypes in vitro. The application of the FDA-approved drug tideglusib was able to restore these phenotypes. Here, we generated cortical progenitors and neurons from SPG11- and SPG15-hiPSC to identify common phenotypic alterations in both forms of HSP. We investigate tideglusib's potential for broader pharmacological use in HSPs and will extend our analyses to test for further compounds targeting the GSK3 signaling.

Disclosures: **T. Börstler:** None. **L. Krumm:** None. **J. Winkler:** None. **H. Houlden:** None. **B. Winner:** None. **M. Regensburger:** None.

Poster

706. Neurodegenerative Disease Models and Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 706.04

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01NS115977
PA State Spinal Cord Injury Grant (4100089343)
Hereditary Spastic Paraplegia Foundation Research Grant

Title: Hdac6 is a novel therapeutic target for spast-based hereditary spastic paraplegia revealed by transgenic mice and hipsc-derived forebrain organoids

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Abstract: Hereditary Spastic Paraplegia (HSP) is a neurodegenerative disorder that manifests as progressive weakness and spasticity of the lower limbs with a unique gait deficiency. The pathological hallmarks of HSP include swelling and degeneration of the corticospinal tracts (CST) projected from the upper motor neurons of the motor cortex. Mutations in the SPAST gene lead to an autosomal dominant form of HSP, namely *SPAST*-HSP or HSP-*SPG4*, which accounts for about 40% of the HSP cases with confirmed gene mutations. *SPAST* encodes a microtubule (MT)-severing enzyme called spastin, which regulates MT behaviors, as well as other important cellular functions. Based on previous studies, we and other groups identified significantly reduced MT acetylation, which is a tubulin modification normally associated with axonal integrity in various disease models. Consistent with reduced MT acetylation, we detected hyperactivity of HDAC6, a major tubulin deacetylase, in the neurons of the transgenic mice, human induced pluripotent stem cell (hiPSC) derived forebrain organoids and postmortem brain tissues from HSP patients. Here, we tested the effects of a highly selective HDAC6 inhibitor, Tubastatin A (Tub A) in (i) transgenic mouse models, namely the “dHET” (double transgenic heterozygous, hSPAST-C448Y$^{+/-}$;mSPAST$^{-/+}$), which encompasses both *SPAST*-haploinsufficiency and gain-of-toxicity mechanisms of HSP-*SPG4* and (ii) deep-layer cortical neurons and forebrain organoids derived from CRISPR-Cas9 based isogenic hiPSCs, including those with a disease relevant truncated mutation of *SPAST* (hiPSC-SPAST^{S245X}). Daily Tub A treatment for 3 weeks reduced the hyperactivity of HDAC6 in the dHET mice and was accompanied by a substantial increase of axonal MT acetylation. Catwalk analyses of gait behavior as well as anatomical studies for CST degeneration reveal therapeutic benefit from this treatment regimen. Treatment with Tub A also rescued several of the degenerative abnormalities that we documented in the hiPSC-SPAST^{S245X} derived organoids. Finally, subcellular fractionation-based analyses demonstrate enhanced cytoplasmic retention of HDAC6 induced by mutant spastin, supporting the possibility that HDAC6 misregulation may be central to the pathological mechanisms of HSP-*SPG4*. Collectively, these results introduce HDAC6 as a novel therapeutic target for HSP-*SPG4*.

Disclosures: **N. Mohan:** None. **E. Piermarini:** None. **S. Ramakrishnan:** None. **L. Ibric:** None. **P.W. Baas:** None. **L. Qiang:** None.

Poster

706. Neurodegenerative Disease Models and Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 706.05

Topic: C.06. Neuromuscular Diseases

Support: NIH grant R01GM118847
NIH grant R01NS111588
A gift from The Hannah's Hope Foundation to Michael Boyce, PhD
A Research Award for Graduate Students by the Ruth K. Broad Biomedical Research Foundation to Duc Huynh

Title: Regulation of human neurofilament-light assembly states by O-GlcNAc and hypoglycosylation of Charcot-Marie-Tooth disease mutants

Authors: *D. T. HUYNH[1], J. HU[1], K. TSOLOVA[1], M. ZORAWSKI[1], E. SODERBLOM[2], C.-C. LIN[3], N. LINHART[1], D. LI[1], J.-T. CHI[3], M. BOYCE[1];
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Abstract: Neurofilaments (NF) are cytoskeletal proteins composed of light, medium, heavy subunits that structurally support axons. These proteins assemble in discrete states, from low-order oligomers to fully assembled filaments, and require the light subunit (NF-L) to form filamentous networks. NF-L mutants in a subtype of Charcot-Marie-Tooth (CMT), an inherited neuromuscular disease, form aggregates and reduce NF-L filament formation in cultured cells, which causes NF-L aggregations and gait defects seen in mouse models. In the rodent brain, NFs are modified post-translationally by O-GlcNAc, an intracellular form of glycosylation on serine/threonine residues. However, how O-GlcNAc regulates human NF-L assembly states is unclear. We used immunoprecipitation to show dynamic O-GlcNAcylation of human NF-L and combined CRISPR-tagged endogenous human NF-L with mass spectrometry to find novel glycosites (S48, S431). When we expressed wild type (WT) NF-L in NF-L$^{-/-}$ 293T cells and biochemically fractionated discrete NF-L assembly states, 89.4 ± 0.7% of the total NF-L was in fully assembled filaments. However, elevating O-GlcNAc levels by expression of O-GlcNAc-transferase (OGT), which adds O-GlcNAc to substrates, reduced this proportion to 48.3 ± 2.2% (n=3), indicating a shift towards lower-order oligomers. We next created an unglycosylatable (S/T-to-A) NF-L mutant, which was less affected by OGT expression, with 86.9 ± 6.2% of the total mutant in the fully assembled state in control cells versus 67.0 ± 5.6% with OGT expression. To extend these results, we expressed WT NF-L in NF-L$^{-/-}$ SH-SY5Y neuroblastoma cells. By immunofluorescence, OGT expression reduced NF-L full-length filaments and increased the prevalence of puncta, representing lower-order states. Notably, the

unglycosylatable mutant partially suppressed this effect. Interestingly, among NF-L CMT mutants, those near glycosites abolished NF-L O-GlcNAcylation. In immunofluorescence and fractionation assays, these mutants formed aggregates that were unaffected by increased O-GlcNAc levels: 91.8 ± 2.0% of total NF-L mutant was in aggregates in control cells, compared to 92.4 ± 0.7% with OGT expression. Therefore, our data indicate that increasing O-GlcNAcylation drives WT NF-L to lower-order assembly states, and NF-L may be hypoglycosylated in CMT disease. We hypothesize that NF-L aggregates found in other neurodegenerative diseases may likewise involve perturbed NF-L O-GlcNAcylation, which we will test in future studies. This work advances our knowledge of the neuronal cytoskeleton and inspires efforts to detect and rationally manipulate O-GlcNAc changes in nervous system disorders.

Disclosures: D.T. Huynh: None. **J. Hu:** None. **K. Tsolova:** None. **M. Zorawski:** None. **E. Soderblom:** None. **C. Lin:** None. **N. Linhart:** None. **D. Li:** None. **J. Chi:** None. **M. Boyce:** None.

Poster

706. Neurodegenerative Disease Models and Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 706.06

Topic: C.06. Neuromuscular Diseases

Support: ALS Association, USA
NIH, USA
DFG, Germany

Title: Als-linked kif5a Δe27 mutant causes neuronal toxicity through gain-of-function

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Abstract: Background: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by loss of upper and lower motor neurons (MNs) leading to paralysis and death within 3-5 years after diagnosis. In 2018, two groups identified *KIF5A* (kinesin-1 family member 5A), which encodes for a motor protein involved in cargo transport, as a causative of ALS. KIF5A is a dimer of heavy chains with three domains - N-terminal motor, hinged stalk, and a C-terminal tail. The *KIF5A* ALS variants are concentrated in tail region, which is responsible for cargo binding, autoinhibition, and microtubule sliding. When not transporting cargoes, kinesin is autoinhibited to prevent ATP squandering. Autoinhibition is achieved by the tail domain binding

to the motor to keep it in a folded autoinhibited state. *KIF5A* ALS variants cause exon 27 skipping (referred to as ΔE27) and produce a neopeptide of aberrant 39 amino acids replacing the normal 34 amino acids. Despite the strong genetic evidence supporting *KIF5A* mutations as a cause of ALS, it is unknown on how such mutations lead to disease.
Methods: In this study, we performed a comprehensive analysis of ALS-associated ΔE27 mutant in various cellular models. We used single-molecule total internal reflection fluorescence microscopy assay to understand the kinetics of wild-type KIF5A and ΔE27 motors. Transgenic flies expressing human KIF5A wild-type and ΔE27 were generated to further investigate the role of KIF5A ALS mutant *in vivo*. We also developed a custom antibody against the neopeptide and generated MNs derived from three iPSCs patient's lines bearing *KIF5A* mutations (c.3020+2T>C, c.2993-1G>A).
Results: Our results show that ΔE27 is prone to form cytoplasmic aggregates and is neurotoxic. Single molecule assay shows that the KIF5A ALS mutation relieves motor autoinhibition and forms a constitutively active kinesin lacking autoinhibition and increases motor self-association. Co-expression of wild-type and mutant protein, lead to aggregation of wild-type protein, suggesting a dominant negative role of the mutation on the disease. Moreover, transgenic flies expressing ΔE27 display wing deficits, motor impairment, and paralysis. Finally, we show for the first time the existence of the ALS-associated KIF5A mutant proteins with a C-terminal neopeptide as well as increased KIF5A inclusions in patient MNs.
Conclusions: In summary, our results show that the ΔE27 protein is expressed in KIF5A ALS patients and leads to neuronal toxicity via gain-of-function caused by constitutive activation and increased motor association and aggregation, suggesting gain-of-function as an underlying disease mechanism in KIF5A-associated ALS.

Disclosures: D.C. Pant: None. **J. Parameswaran:** None. **L. Rao:** None. **I. Loss:** None. **G. Chilukuri:** None. **R. Parlato:** None. **L. Shi:** None. **J.D. Glass:** None. **G.J. Bassell:** None. **P. Koch:** None. **R. Yilmaz:** None. **J.H. Weishaupt:** None. **A. Gennerich:** None. **J. Jiang:** None.

Poster

706. Neurodegenerative Disease Models and Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 706.07

Topic: C.06. Neuromuscular Diseases

Title: Als-associated kif5a mutations result in delayed and decreased motor unit recovery following nerve injury

Authors: *K. A. RICH[1], H. HARRIS[2], A. FOX[2], M. G. PINO[2], M. JONES[2], M. YALVAC[2], D. ARNOLD[2], S. J. KOLB[2];
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Abstract: Background: *KIF5A* encodes kinesin protein KIF5A, which is involved in anterograde transport of cargos in eukaryotic cells. Recently, C-terminal mutations in *KIF5A* have been identified in patients with amyotrophic lateral sclerosis (ALS). The mechanism linking *KIF5A* mutations and ALS pathogenesis is unknown. To investigate this, we created a novel mouse with an ALS-associated C-terminal *Kif5a* mutation (c.3005+1G>A; heterozygous [HET] *Kif5a*$^{+/c.3005+1G>A}$; homozygous [HOM] *Kif5a*$^{c.3005+1G>A/\ c.3005+1G>A}$). Peripheral nerve injury (PNI) is an established paradigm to study mechanisms of axon repair, including axon transport, in rodents. Following PNI, electrophysiology can be used to monitor recovery *in vivo* and is a clinically relevant measure of motor unit integrity. Degradation of the motor unit is a primary biological feature of ALS. We hypothesize that ALS-associated *KIF5A* mutations alter the ability of the motor unit to be maintained or repaired. **Methods**: PNI was induced via sciatic nerve crush in 14-week mice (wildtype [WT], HET and HOM). Before crush and throughout recovery mice were monitored via weekly electrophysiological assessments (compound muscle action potential [CMAP] and estimation of motor unit number [MUNE]) strength (unilateral hindlimb grip strength). At 16 weeks post PNI, we studied motor unit histopathology (motor neurons, sciatic nerve axons and neuromuscular junctions [NMJ]). **Results**: We observed a loss of functional motor units in mutant mice compared to WT during recovery from PNI. CMAP and grip strength did not differ between genotypes. On histopathology, we saw mutant-specific deficits in motor neurons, sciatic nerve axons and at the NMJ. Ipsilateral motor neurons showed decreased area in mutants (HET and HOM) as compared to WT. In sciatic nerve axons, we saw decreased axon fiber diameter in the ipsilateral nerve (as compared to the contralateral nerve) across all genotypes, however the decrease was most pronounced in HOM mice, followed by HET, followed by WT. At the NMJ, we saw decreased pre- and postsynaptic co-localization area as well as nerve terminal area in mutants as compared to WT. **Conclusions**: We have defined a repair defect in motor axons with an ALS-associated *KIF5A* mutation. Our findings suggest *Kif5a* C-terminal mutations result in a loss of normal KIF5A function, impacting the motor unit. Mutant mice demonstrated observable pathological correlates throughout motor unit tissues. This work establishes a model system to develop disease- modifying therapies and understand basic principles of *KIF5A* biology.

Disclosures: K.A. Rich: None. **H. Harris:** None. **A. Fox:** None. **M.G. Pino:** None. **M. Jones:** None. **M. Yalvac:** None. **D. Arnold:** None. **S.J. Kolb:** None.

Poster

706. Neurodegenerative Disease Models and Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 706.08

Title: WITHDRAWN

Poster

706. Neurodegenerative Disease Models and Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 706.09

Topic: C.06. Neuromuscular Diseases

Support: NIH 5R01NS095969
NIH 1RF1MH123237

Title: Tdp-43 overexpression promotes cryptic splicing events

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Abstract: TDP-43 mislocalization is a hallmark feature in neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS) and frontotemporal dementia (FTD). Normally TDP-43 represses cryptic exons and prevents the formation of deleterious mRNAs. However, less is understood about the toxicity induced by cytoplasmic or nuclear TDP-43 overexpression. We analyzed RNA-seq datasets from TDP-43 transgenic mouse models and found several cryptic splicing events that are highly correlated with TDP-43 overexpression, targets that were further verified by RT-PCR. To confirm these overexpression-linked cryptic splicing events in the human context, we used lentiviral delivery of TDP-43 to infect iPSC derived neurons and confirmed the presence of human cryptic splicing events. Finally, we tested human cases with TDP-43 pathology in ALS-FTD postmortem cases and found that these cryptic splicing events could be identified in some cases, but did not correlate with the presence of TDP-43 pathology. Our data helps us understand the mechanisms that underly the cellular toxicity of TDP-43 overexpression.

Disclosures: R.P. Carmen-Orozco: None. **V. Trinh:** None. **Y. Ye:** None. **K. Chang:** None. **J.C. Troncoso:** None. **S. Sun:** None. **P.C. Wong:** None. **S. Blackshaw:** None. **J.P. Ling:** None.

Poster

706. Neurodegenerative Disease Models and Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 706.10

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01NS095969
Target ALS
Packard Center for ALS Research
Karen Toffler Charitable Trust

Title: A fluid biomarker reveals loss of TDP-43 splicing repression in pre-symptomatic ALS

Authors: *K. IRWIN[1], P. JASIN[1], K. BRAUNSTEIN[1], J. BERRY[2], E. OH[1], B. TRAYNOR[3], J. LING[1], P. WONG[1];
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Abstract: Introduction
Nuclear clearance of TDP-43, first identified in amyotrophic lateral sclerosis-frontotemporal dementia (ALS-FTD) (Neumann *et al*, 2006), leads to the protein's failure to repress splicing of nonconserved cryptic exons (Ling *et al*, 2015). While the presence of TDP-43-related cryptic exons has been shown in autopsy brain tissues (Klim *et al*, 2019; Melamed *et al*, 2019; Prudencio *et al*, 2020; Ma *et al*, 2021; Brown *et al*, 2021), whether loss of TDP-43 splicing repression is impacted during early-stage disease remains to be established. As some cryptic exons are spliced in-frame and translated into proteins carrying novel epitopes, we hypothesize that these "cryptic peptides" may be found in patient cerebrospinal fluid (CSF). Using a highly specific and sensitive ELISA, we test whether a cryptic exon-encoded neo-epitope can be detected in CSF of ALS patients.
Methods
We generated novel monoclonal antisera against several TDP-43 cryptic exon targets and then developed a sandwich ELISA using the Meso Scale Discovery (MSD) platform, which we validated in cells deficient in TDP-43 for one cryptic exon target. We then screened CSF samples of C9orf72-mutation carriers (Offit *et al*, 2020) and control individuals for the presence of this cryptic peptide.
Results
The MSD signal for the cryptic peptide was elevated in CSF of C9orf72 mutation carriers with ALS (n=5, mean=1601) as compared to those of controls (n=5, mean=-64.10; $p<0.013$), so we examined a larger cohort of C9orf72 mutation carriers. In symptomatic individuals (n=27), cryptic peptide levels showed a correlation nearing significance with symptom duration ($r=-0.368$, $p=0.059$), suggesting that levels of the cryptic peptide tend to be higher during the earlier symptomatic phase. We also found elevated cryptic peptide levels in CSF of some pre-symptomatic individuals. To clarify cryptic peptide dynamics during disease progression, we began to assess longitudinal CSF samples and found that in 82.35% (14/17) of symptomatic individuals, levels of the cryptic peptide decreased with disease progression. Further analyses will be presented.
Conclusions
Our findings provide the first direct evidence that loss of TDP-43 splicing repression occurs during early-stage disease, including the pre-symptomatic phase. The use of cryptic peptide biomarkers in early-stage disease could facilitate earlier diagnosis and may help predict phenoconversion in familial ALS. Because detection of cryptic peptides in patient biofluids reflects TDP-43 loss of function, evaluating the dynamics of these biomarkers could provide a way of measuring target engagement for new therapeutics aimed at restoring TDP-43 function.

Disclosures: K. Irwin: None. **P. Jasin:** None. **K. Braunstein:** None. **J. Berry:** None. **E. Oh:** None. **B. Traynor:** None. **J. Ling:** None. **P. Wong:** None.

Poster

706. Neurodegenerative Disease Models and Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 706.11

Topic: C.06. Neuromuscular Diseases

Support: DFG 270949263/GRK2162
Interdisciplinary Center for Clinical Research (J92)
Bavarian Research Network ForInter

Title: Link between actin remodeling, mechanical properties, and lipid metabolism of human induced oligodendrocytes upon a-synuclein overexpression

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Abstract: Oligodendrocytes are the primary affected cell type in multiple system atrophy (MSA), a rare and devastating movement disorder with a fast progressive and fatal disease course. The accumulation of α-synuclein (α-syn) within oligodendroglial cytoplasmic inclusions (GCIs) is one of the neuropathological hallmarks of the disease and has been associated with a severe myelin deficit without a concurrent loss of oligodendrocytes. Thus, one hypothesis is that intracellular accumulation of α-syn interferes with the myelinating capacity of oligodendrocytes. A human cellular model for MSA was established to address the underlying pathogenesis. Human induced pluripotent stem cells were derived from healthy donors and oligodendroglial lineage specification was induced by the ectopic expression of the oligodendroglial transcription factors SOX10, OLIG2, and NKX6.2. Oligodendroglial identity was confirmed by a thorough phenotypical characterization based on morphological, transcriptional, and metabolome analyses. Ultimately, oligodendrocytes ensheathed inert nanofibers as wells as human induced neurons *in vitro* supporting the myelinating potential of these cells. Moreover, intraoligodendroglial α-syn accumulation led to a myelin deficit *in vitro*. In particular, oligodendrocytes extended less primary processes to ensheath nanofibers while the length of individual myelin - like segments was unaltered or even increased. These morphological changes were accompanied by an increase in actin filaments and cell body enlargement. Actin remodeling is a critical event during myelination and a widespread polymerization acts as physical barrier by increasing membrane tension. In addition, oligodendrocytes are sensitive to mechanical properties of their environment. Therefore, we investigated the stiffness of oligodendroglial cell bodies. Overexpression of α-syn was leading to an increased cell body stiffness measured by atomic force indentation accompanied by transcriptomic alterations mainly in the actin cytoskeleton and lipid metabolism. In conclusion, the results suggest a pathogenic link between actin remodeling, mechanical properties, and lipid metabolism thus pointing toward a novel pathogenic cascade with a profound impact on myelination. By resembling α-syn induced myelin deficits, the present disease model represents an important tool for MSA research and will help to evaluate promising candidates for future interventional therapies.

Disclosures: **K. Battis:** None. **J. Wihan:** None. **G. Rosso:** None. **J. Guck:** None. **T. Kuhlmann:** None. **J. Winkler:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.01

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: VA Merit I21BX004957

Title: Fingolimod decreases inflammation and the interferon-gamma induced protein kinase R in a mouse model of Gulf war illness

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Abstract: Gulf War illness (GWI) is a chronic multi-symptomatic disease affecting one third of Veterans of the Gulf War (GW) (1990-1991) for which treatment is lacking. Neurological symptoms are a top complaint among GWI patients. Aberrant immune system and chronic inflammation appears to be components of the pathology of GWI. Altered lipid profiles, with the accumulation of those that promote inflammation, have been found in plasma and brain of GWI patients and in animal models of the disease. Specifically, increased ceramide level in plasma of female patients has been reported. Here we hypothesized that as ceramide increases in GWI, sphingosine-1 phosphate (S1P) decreases and that treatment with fingolimod, a structural analog of sphingosine known for its neuroprotective effects, is beneficial to GWI model mice. To test this hypothesis, we used a well-established mouse model of GWI based on 1 month daily exposure to chemicals used to protect GW military personnel (pyridostigmine bromide, permethrin, and DEET). To allow for the pathology to develop, 3 months after exposure mice were orally treated with fingolimod at 0.03 or 1 mg/kg/day for 1 month. Immunoblot analysis of brain cortical samples from female GWI-model mice showed decreased S1P levels compared to non-exposed controls. In GWI-model mice treated with either dose of fingolimod, the level of S1P was restored to that of control mice. To determine the effect of the chemical exposure and fingolimod treatment on neuroinflammation, brain sections were immunostained using antibodies to Iba1, specific to microglia. Microglia activation, as a measure of neuroinflammation, was quantified in the dentate gyrus using the Area Fraction Fractionator probe. We found increased Iba1 staining in GWI-model mice compared to controls that was restored in fingolimod treated GWI-model mice. Quantitative real-time PCR analyses of RNA cortical brain samples revealed that interferon-gamma (IFN-γ), a prominent pro-inflammatory cytokine, was increased in GWI-model mice and restored back down to control levels with

fingolimod treatment. Further, we measured mRNA levels of the IFN-γ induced protein kinase R (PKR), a major regulator of central cellular processes and a marker of stress. PKR mRNA levels increased in exposed mice and decreased in fingolimod treated mice, mirroring the effect of IFN-γ. Relevant to GWI, suppression of PKR has been shown to promote network excitability and enhance cognition by an IFN-γ mediated selective reduction of GABAergic synaptic action. In conclusion, the equilibrium of the ceramide/S1P system appears to be central to GWI and a target for therapy.

Disclosures: I. Carreras: None. **J. Lopez-Benitez:** None. **Y. Jung:** None. **C.M. Tognoni:** None. **A. Dedeoglu:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.02

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Research Foundation of Korea funded by the Ministry of Science and ICT 2018R1A5A2025964
National Research Foundation of Korea funded by the Ministry of Science and ICT 2018R1A5A2025964
National Research Foundation of Korea funded by the Ministry of Education 2022R1A6A3A13072676

Title: Neurotoxicity of phenylalanine in phenylketonuria using patient-derived cerebral organoids

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Abstract: Phenylketonuria (PKU) is a common genetic metabolic disorder that causes phenylalanine accumulation in the blood. The most serious symptoms are related to the brain, as intellectual disability, seizure, and microcephaly that are commonly found in poorly treated PKU patients. However, the mechanism of hyperphenylalaninemia on human neurodevelopment is still unclear. Previously, we used human induced pluripotent stem cell (iPSC)-derived cerebral organoids to investigate the neurotoxicity of hyperphenylalaninemia. Cerebral organoids at days 40 or 100 were treated with different concentrations of phenylalanine for 5 days. After phenylalanine treatments, the cerebral organoids displayed alterations in organoid size, induction of apoptosis, and depletion of neural progenitor cells. Remarkably, a reduction in the thickness of the cortical rosettes and a decrease in myelination at the intermediate zone were inspected with the elevated phenylalanine concentrations. RNA-seq of phenylalanine-treated organoids revealed that gene sets related to apoptosis, p53 signaling pathway, and TNF signaling pathway

via NF-kB were enriched in upregulated genes, while those related to cell cycle and amino acid metabolism were enriched in downregulated genes. In addition, there were several microcephaly disease genes, such as *ASPM*, *LMNB1*, and *CENPE*, ranked at the top of the downregulated genes. Here we utilized PKU patient iPSC-derived cerebral organoids to inspect the impact of hyperphenylalaninemia in PKU patients' brains and explored the differences in its neurotoxic effects between PKU patients and controls. These findings indicate that the high levels of phenylalanine may induce brain damage in not only PKU patients but also normal humans.

Disclosures: **J. Kim:** None. **K. Kim:** None. **J. Lee:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.03

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: University of Georgia ITP stipend award to NEK

Title: Hippocampal Neurotoxicity in Three Generations of Brominated Flame Retardants

Authors: N. E. KRAMER[1], *J. J. WAGNER[2], B. S. CUMMINGS[3];
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Abstract: Brominated Flame Retardants (BFRs) are ubiquitously utilized to reduce flammability in a wide range of household products including carpets, upholstery, and paints. While useful chemicals, BFRs also migrate from their products into the environment. This has resulted in continuous, population-level exposure that has been correlated to impaired learning and memory. To determine the effects of different BFR generations on hippocampal cells, HT-22 cells were exposed to tetrabromobisphenol-A (TBBPA), hexabromocyclododecane (HBCD), or 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) (current, phasing out, and phased out BFRs, respectively). Cell viability analysis was assessed by MTT staining, as well as nuclear morphology after 48 hr of exposure. HBCD exposure resulted in lower IC_{50} values in HT-22 cells (15 μM IC_{50}), as compared to TBBPA (70 μM) and BDE-47 (60 μM). HT-22 cellular and nuclear morphology suggested the presence of apoptosis after exposure to the IC_{50} for each BFR after both 24 and 48 hr exposure. To understand the mechanisms of toxicity, cell cycle and cell death were evaluated. Each BFR induced cell cycle alterations with increasing exposure time. Upon 24 hr exposure, HBCD (50 or 100 μM) induced significant S-phase arrest which was maintained upon 48 hr exposure. However, only upon 48 hr exposure did BDE-47 (50 and 100 μM) and TBBPA (100 μM) induce significant S-phase arrest. Annexin-PI staining verified a time and concentration-dependent neurotoxic effect, as evidenced by an increase in annexin V staining in cells, indicating the presence of apoptotic cell death. Both 24 and 48 hr exposure to HBCD (50 or 100 μM) or BDE-47 (100 μM) induced significant increases in apoptosis, although 100 μM TBBPA

only induced apoptosis and necrosis after 48 hr. Further evaluation of the mechanisms of toxicity indicates that p53 and p21 activation may play a central role in the onset of cell cycle arrest and apoptosis. These data demonstrate that BFRs can induce chemical-dependent toxicity in neural cells *in vitro*; however, additional study will be necessary to determine if BFR-induced neural cytotoxicity would adversely affect learning and memory *in vivo*.

Disclosures: **N.E. Kramer:** None. **J.J. Wagner:** None. **B.S. Cummings:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.04

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: The exposure to lead in mice from birth induces a tendency to aggressiveness: preliminary study

Authors: A. MENDOZA MARTÍNEZ[1], F. PEREZ[2], *E. GONZÁLEZ-GUEVARA[3];
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Abstract: The exposure to lead (Pb) in mice from birth induces a tendency to aggressiveness: preliminary study Mendoza-Martínez A, Pérez-Severiano F. González-Guevara E Lead (Pb) is used in several anthropogenic activities such as mining, metallurgy and industry and could be toxic due to its use in products such as glazed ceramics, car batteries, vinyl paints, ammunition, and tobacco. Pb does not have a biological function in the body, but it is harmful when it accumulates in different body organs such as in nails, bones and teeth. The concentration of 5 µg/dL of Pb is already toxic and this way Pb can be transmitted to the fetus of pregnant women and can even cause abortions. Early exposure to Pb affects the Central Nervous System (CNS), causing disorders such as attention deficit, language disorders, antisocial, depressive and aggressive behaviors in children and adolescents. Aggressive behavior is regulated by serotonin (5-hydroxytryptamine). Interaction of serotonin with 5-HT1A or 5-HT1B receptors modulates aggressive behavior. However, the molecular mechanism that describes the serotonergic signaling pathway that involves a punctual alteration of serotonin receptors induced by Pb exposure remains unclear. In this study were exposed mice to Pb (250 ppm) since prenatal to postnatal stage, and after 56 or 74 postnatal days of exposure, the aggressive behavior was analyzed with the modified resident-intruder paradigm, where different parameters were evaluated among them the attacks latency and the number of attacks. At 56 days of age, the latency to attack in the control group versus the exposed group was 337 sec and 323 sec, respectively (z=-0.59, p=0.278, n=4); at 76 days it was 333 and 191 respectively (z=-0.94, p= 0.173, n=4). While the number of attacks at 56 days for the control and exposed group was 7 and 12 events respectively (z=-0.48 p= 0.316, n=6). These results demonstrated a tendency to

aggressiveness. We expect that the analysis in the expression of the 5HT1A and 5HT1B receptors after the 56 or 74 days, allow us to confirm that the animals exposed to Pb could be more aggressive.

Disclosures: **A. Mendoza Martínez:** None. **F. Perez:** None. **E. González-Guevara:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.05

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: PAPIIT, UNAM, IN228420

Title: Contribution of AMPA-Kainate ionotropic glutamatergic receptors to excitotoxicity of hippocampal neurons: role of prolactin in neuroprotection

Authors: *V. RODRIGUEZ CHAVEZ[1], G. MOLINA-SALINAS[1], E. FLORES-SOTO[2], J. MORAN[3], L. MONTAÑO RAMÍREZ[2], M. CERBON[1];
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Abstract: Glutamate is the main excitatory neurotransmitter in the central nervous system. To carry out its functions, glutamate acts via interaction with its cognate receptors, which are ligand dependent. It is well known that excitotoxicity by glutamate induces overstimulation of ionotropic glutamatergic receptors (iGluRs), leading to neuronal damage and cell death. Therefore, the continuous elucidation of the molecular mechanisms underlying excitotoxicity in order to prevent damage or neuronal death is essential. In that regard, prolactin has been shown to have a neuroprotective effect against excitotoxicity *in viv*o and *in vitro* models. The aim of this study was to determine the expression of ionotropic glutamatergic receptors in primary cultures of hippocampal neurons and to evaluate their functionality, as well as to study the protective action of prolactin on excitotoxicity. To determine iGluRs we used primary cultures of hippocampal neurons obtained from 17.5 day old rat embryos. The cultures were divided in six groups: Control (CTRL, saline), prolactin (PRL, 20 ng/ml), glutamate (Glu, 20 μM), PRL+Glu (20 ng/ml/ 20μM), kainic acid (KA 20 μM) and PRL+AK (20 ng/ml/ 20μM). The cell viability was evaluated by means of MTT assay. The presence of the iGluRs and the intracellular calcium (Ca^{2+}) concentration assays were evaluated by Fura-2 assays. We found that treatments with Glu and AK decreased cell viability of primary cultures of hippocampal neurons and induced a significantly increase in neuronal intracellular Ca^{2+}. The independent and simultaneous administration of NMDA or AMPA-KA receptor inhibitors reverted cell death and Ca^{2+} increase. Interestingly, the treatment with prolactin (20 ng/ml) prevented cell death and induced a

significant reduction in Ca^{2+} entrance. The diversity of NMDA, AMPA and KA receptors assessed by RT-qPCR indicated that both NMDA and AMPA-KA receptors expression are present in hippocampal neurons. With this information it is concluded that both AMPA/KA and NMDA receptors may have key role in the physiopathological processes of hippocampal excitotoxicity and that PRL could participate in the regulation of the glutamatergic signaling during excitotoxic neuronal death.

Disclosures: V. Rodriguez Chavez: None. **G. Molina-Salinas:** None. **E. Flores-Soto:** None. **J. Moran:** None. **L. Montaño Ramírez:** None. **M. Cerbon:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.06

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIAAA Intramural program

Title: Gpr110 activation ameliorates lps induced neuro-inflammation neuroinflammation enhanced by single binge ethanol

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Abstract: Research objective- Neuroinflammation is a widely studied phenomena underlying various neurodegenerative diseases. Earlier study demonstrated that pharmacological activation of GPR110 in both central and peripheral immune cells cooperatively ameliorates neuroinflammation caused by systemic lipopolysaccharide (LPS) administration. Ethanol consumption has been associated with exacerbation of neurodegenerative and systemic inflammatory diseases. In this study, our goal is to investigate the effects of GPR110 ligands on the neuro-inflammatory mechanisms aggravated by ethanol consumption**.Methods:** For *in vivo* studies, WT and GPR110 KO mice (10 to12 weeks of age) were given an oral gavage of ethanol (3 g/kg) or maltose (5.4 mg/kg) at 4 h prior to the injection of LPS (1 mg/kg, i.p.) followed by GPR110 ligands, synaptamide (5 mg/kg) and A8 (1mg/kg). After 2 or 24 h brains were collected for gene expression analysis by RT-PCR or protein expression by western blotting and enzyme-linked immunosorbent assay (ELISA). For in vitro studies, microglia and peritoneal macrophages were isolated from adult WT mice and treated with 25 mM ethanol for 4 h and with100 ng/µL of LPS followed by 10 nM of synaptamide for 2 h for gene expression and 12 h for ELISA. Microglial activation *in vivo* was assessed by both western blotting and immunohistochemistry.**Results:** Single binge administration of ethanol before LPS injection upregulated pro-inflammatory cytokine expression in the brain and plasma. The LPS-induced iba-1expression in the brain was significantly higher after ethanol treatment in both WT and

GPR110KO mice. GPR110 ligands decreased the expression of these cytokines as well as iba-1 in the WT but not in GPR110KO mice. In the isolated microglia and peritoneal macrophages, synaptamide also reduced the LPS-induced expression of pro-inflammatory cytokines exacerbated by ethanol. The expression of an inflammasome marker NLRP3 induced by LPS was significantly higher after single ethanol binge, especially in the brains of GPR110KO mice. Both ethanol and LPS reduced adenylate cyclase 8 expression which was prevented by the GPR110 activation by its ligands. PDE4B mRNA expression was upregulated after ethanol and LPS treatment in the brain tissue and synpatamide was able to suppress its expression in a GPR110-dependent manner.**Conclusion:** GPR110 ligand, synaptamide, ameliorated LPS-induced neuro-inflammation exacerbated by single binge ethanol exposure by targeting common targets in cAMP signaling.

Disclosures: S. Banerjee: None. **T. Park:** None. **Y. Kim:** None. **H. Kim:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.07

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: UNAM-DGAPA- PAPIIT Grant # IN212522
CONACYT #251510

Title: Neurotoxic effects of chronic atrazine exposure in female albino rats

Authors: J. SANCHEZ-YEPEZ, T. ACEVEDO-HUERGO, M. MENDOZA-TREJO, R. CORONA, V. VIÑUELA-BERNI, M. GIORDANO, ***V. M. RODRIGUEZ**;
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Abstract: Several studies have shown that chronic exposure to the herbicide atrazine (ATR) causes alterations in locomotor activity and markers of dopaminergic systems of male rats. However, few studies have evaluated the sex-dependent effects of atrazine exposure. This study's objective was to evaluate whether chronic ATR exposure causes alterations in female rats' behavioral performance and dopaminergic systems. Two groups of rats were exposed to 1 or 10 mg ATR/kg body weight daily, while the control group received food without ATR for 14 months. Spontaneous locomotor activity was evaluated monthly for 12 months, while anxiety, egocentric and spatial memory, motor coordination, and olfactory function tasks were evaluated between 13 and 14 months of ATR exposure. Tissular monoamine content was assessed at the end of ATR treatment. Female rats treated with 1 or 10 mg ATR showed vertical hypoactivity compared to the control group only at the first month of ATR exposure. Impairments in olfactory functions were found due to ATR exposure. Nevertheless, no alterations in anxiety, spatial and egocentric memory, or motor coordination tasks were observed, while the tissue dopamine and its metabolites levels were similar among groups. These results suggest that female rats could

present greater sensitivity to the neurotoxic effects of ATR on spontaneous locomotor activity in the early stages of development. Furthermore, they are unaffected by chronic ATR exposure later in life compared to male rats. More studies are necessary to unravel the sex-related differences due to ATR exposure.

Disclosures: J. Sanchez-Yepez: None. **T. Acevedo-Huergo:** None. **M. Mendoza-Trejo:** None. **R. Corona:** None. **V. Viñuela-Berni:** None. **M. Giordano:** None. **V.M. Rodriguez:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.08

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: A model for therapeutic screening of chemotherapy-induced peripheral neuropathy using a nerve-on-a-chip microphysiological system

Authors: J. L. CURLEY[1], L. KRAMER[1], H. NGUYEN[1], E. JACOBS[1], L. MCCOY[1], A. D. SHARMA[1], C. ROUNTREE[1], M. MOORE[1,2,3];
[1]AxoSim, Inc., New Orleans, LA; [2]Dept. of Biomed. Engin., [3]Brain Inst., Tulane Univ., New Orleans, LA

Abstract: Organs-on-Chip mimicking *in vivo* physiology can identify neuroprotection and neuroregeneration following drug exposure without relying on animal models. Toxicity is a leading reason drugs are withdrawn from the market, with neurotoxicity responsible for 16%. Peripheral nerves are particularly susceptible to off-target effects resulting in permanent sensory-motor deficits, and chemotherapy-induced peripheral neuropathy (CIPN) occurs with a 68% incidence rate and 30% retaining effects after 6 months. CIPN can also affect clinical outcomes, with 91% of cases leading to dose reduction and a 45% discontinuation rate. Increasingly, therapeutic development is focusing on mitigation or recovery for peripheral neuropathies. We designed a biomimetic nerve-on-a-chip construct with axon growth analogous to mature nerve anatomy and the first 3D *in vitro* platform to collect electrophysiological and histomorphological metrics, gold standard methods for *in vivo* neuropathophysiology. Here, we cultured embryonic rat dorsal root ganglia in a hydrogel construct to screen for nerve dysfunction in CIPN. After 28 days of growth *in vitro*, myelinated nerve-on-a-chip constructs were exposed to bortezomib, oxaliplatin, paclitaxel, or vincristine for 7 days. Then, axons were electrically stimulated to elicit compound action potentials, used to assess nerve conduction velocity (NCV) and peak amplitude (AMP), which are clinically analogous metrics. Histological analysis and cell viability assays were also performed to observe underlying mechanistic changes in the tissue. All chemotherapeutics showed a concentration-dependent decrease in NCV and AMP. Histopathology revealed hallmarks of peripheral neuropathy, including decreases in myelinated fiber density and increased degenerated fibers. IC50 values indicate significant decreases in

electrical function occurred before decreased viability. Data suggest that electrophysiology collected from our platform tracks pathological changes in nerve function, with distinction between electrical deficits and general cytotoxicity. The ability to collect clinically relevant data is an effective tool for *in vitro* modeling of CIPN towards screening of therapeutics for neuroprotection and neuroregeneration.

Disclosures: J.L. Curley: None. **L. Kramer:** None. **H. Nguyen:** None. **E. Jacobs:** None. **L. McCoy:** None. **A.D. Sharma:** None. **C. Rountree:** None. **M. Moore:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.09

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NINDS R01NS115800
Iowa Neuroscience Institute

Title: Neuronal excitotoxic injury alters nuclear dynamics in the neonatal period through a calpain-mediated process

Authors: *P. S. SURYAVANSHI[1,2], R. LANGTON[1,2], K. FAIRHEAD[3], J. GLYKYS[1,2,4]; [1]Dept. Pediatrics, [2]Iowa Neurosci. Inst., [3]Col. of Liberal Arts and Sci., [4]Dept. Neurol., The Univ. of Iowa, Iowa city, IA

Abstract: Neuronal swelling occurs in different brain insults, including stroke, hypoxia, traumatic brain injury, and seizures. While osmotic agents and neurosurgical treatments effectively mitigate brain swelling, the outcomes continue to be poor, prompting an urgent need to understand the downstream consequences of excitotoxic edema. Apart from swelling, Ca^{2+} signals elicited by neuronal excitation during insults can induce long-lasting structural and functional changes. However, the role of nuclear dynamics in neuronal excitotoxic edema remains elusive, especially during the neonatal period. Using multiphoton microscopy, we examined the interaction between neuronal swelling and Ca^{2+} dynamics following brief excitotoxic injury in neonatal mice (postnatal day 8 to 12) expressing neuron-specific fluorophores (YFP, mRuby2) and a Ca^{2+} sensor (GCaMP6s). We induced excitotoxic edema in acute brain slices by transient activation of NMDA receptors and used an automated neuronal morphology analysis framework based on convolutional neuronal networks (ANMAF) to measure neuronal areas. We observed long-lasting neuronal swelling following brief activation of NMDA receptors. After a transient increase in cytosolic Ca^{2+} during NMDA activation, neurons exhibit a delayed elevation in nuclear Ca^{2+} signal, increasing the nucleus to cytosolic Ca^{2+} ratio (N/C ratio). Elevation of N/C ratio was confirmed in slices with other excitotoxic insults, including seizures and short, repeated pressure-ejected pulses of NMDA. A robust increase in N/C ratio was not induced by osmotic swelling of neurons, nor was it rescued by

hypertonic conditions following excitotoxic edema. However, inhibition of calpains (calcium-dependent proteases) prevented the elevation of the N/C ratio. In summary, our results show hyperexcitation-induced, calpain-mediated changes in neuronal nuclear dynamics in the neonatal period. Since GCaMP6s is predominantly localized to the cytosol, nuclear translocation of GCaMP6s suggests “leaky” nuclear envelopes. Therefore, an elevated nuclear GCaMP signal may be an early marker for long-term neuronal damage.

Disclosures: **P.S. Suryavanshi:** None. **R. Langton:** None. **K. Fairhead:** None. **J. Glykys:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Minciencias (Colombia) Grant 11180763133

Title: Paclitaxel-induced neurotoxicity involves TRPV4 activation through IP3K, but not through PKA or PKC

Authors: *J. C. SÁNCHEZ, L. V. MUÑOZ, A. VALENCIA-VÁSQUEZ, J. C. OLAYA-GÓMEZ, J. F. HENAO-MARTÍNEZ, A. ALEMÁN-CASTELLANOS, J. GUERRERO-APRÁEZ, L. F. MARTÍNEZ-MURILLO;
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Abstract: Transient receptor potential vanilloid 4 (TRPV4) is a calcium channel involved in physiological and pathological processes, such as chemotherapy-induced peripheral neuropathy (CIPN), which is a disabling complication that encompasses cognitive, sensory, and motor alterations caused by antineoplastic drugs such as paclitaxel (PTX), a taxane used to treat several malignancies. TRPV4 has been associated with the development of CIPN by PTX in rodent models. Protein kinase C (PKC), cyclic AMP-dependent protein kinase (PKA), and protein kinase B (PKB/Akt) act as regulatory mechanisms in neurons and have been associated with TRP channels function. TRPV4 channels are directly associated with the N-terminal domain in the phosphorylation sites of PKA and PKC and modulate the pathway associated with PKB/Akt. Nonetheless, the interaction between TRPV4 and these PKs in PTX-induced neurotoxicity is still debated. This study evaluated the effect of PKA, PKB/Akt, and PKC on TRPV4 channels in the neurotoxic conditions induced by the PTX in a neuronal cell model. We used the SH-SY5Y cell line as a neuronal model to perform the experiments, which were cultured following established protocols. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to determine cell viability. Changes in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) were assessed employing spectrofluorometry in Fura-2-loaded cells; variations of $[Ca^{2+}]_i$ dynamics and the maximal percentage of increase were recorded and analyzed. TRPV4 channels

electrophysiology was also evaluated using the whole-cell patch-clamp technique. All these tests were performed in cells under treatment with GSK1016790A (GSK101, 100 nM), a specific TRPV4 agonist and HC-067047 (50 nM), a specific TRPV4 inhibitor. In all cases, the effects of PKA (H89, 10 µM), PKB/Akt (Wortmannin, WOR, 100 nM), and PKC (Chelerythrine, CHEL, 25 µM) inhibitors on PTX-treated cells were tested. PTX (1 uM, 6 h) decreased cell viability, increased TRPV4 currents (I_{TRPV4}), and intensified TRPV4-mediated $[Ca^{2+}]_i$ increase (GSK101-induced $[Ca^{2+}]_i$ increase). WOR treatment neutralized both effects of PTX, but H89 and CHEL treatment had no effect. In conclusion, the PI3K pathway (but not PKA and PKC pathways) was involved in the regulation that PTX exerts on TRPV4 channels to induce cellular neurotoxicity. Pharmacological inhibition of PI3K or direct inhibition of TRPV4 channels could be helpful to prevent and treat PTX-induced neurotoxicity, but further studies are required to enlighten the signaling mechanisms involved and thus proceed to design preclinical models to test that hypothesis.

Disclosures: J.C. Sánchez: None. **L.V. Muñoz:** None. **A. Valencia-Vásquez:** None. **J.C. Olaya-Gómez:** None. **J.F. Henao-Martínez:** None. **A. Alemán-Castellanos:** None. **J. Guerrero-Apráez:** None. **L.F. Martínez-Murillo:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Irish Research Council Laureate Award (IRCLA/2017/78)
Supported by Ministerio de Ciencia, Innovación y Universidades (PID2019-111510RB-I00)
Comunidad Autónoma de Madrid funded YLT (PEJD-2017-PRE/BMD-3924)

Title: Analysis of the short-term consequences of two pharmacological treatments with chemotherapy drugs in the endocannabinoid system of cognitive-related brain areas in male Wistar rats

Authors: Y. LÓPEZ-TOFIÑO[1,2], M. HOPKINS[3,4], A. BAGÜÉS[1,2], K. MOLONY[3], R. ABALO[1,2], ***Á. LLORENTE-BERZAL**[3,4,1];
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Abstract: Chemotherapy is still the main therapeutic approach to treat cancer regardless of its neurotoxic effects. Chemotherapy-related neurotoxicity can lead to cognitive deficits in a process known as chemotherapy-induced cognitive impairment (CICI). Cannabinoid drugs, i.e. drugs that

target the endocannabinoid system (ECS), not only alter cognition, but they also show neuroprotective properties. Thus, pharmacological manipulation of the ECS could potentially become a valuable therapeutic approach to treat CICI. In these experiments, we aimed to analyse the short-term consequences of the treatment with two different chemotherapy drugs, commonly used in cancer patients, in the ECS of brain regions related to cognition such as prefrontal cortex (PFC), hippocampus (HIP) and amygdala (AMY). Male Wistar rats were used in two different experiments. In experiment 1, animals were acutely injected with cisplatin (CS; n=6; 5mg/kg; i.p.) or saline (n=6), while in experiment 2, animals received two cycles of five injections (Monday to Friday for two consecutive weeks) of vincristine (VC; n=8; 0.1 mg/kg/day; i.p.) or saline (n=9). Animals were exposed then to a battery of tests to measure pain-related behaviours, locomotor activity and gastrointestinal functionality and they were euthanized between 3 and 7 days after the last day of treatment. Levels of endocannabinoids and related *N*-acylethanolamines were assessed in PFC, HIP and AMY using liquid chromatography tandem mass spectrometry. Rt-PCR was used to analyse gene expression of cannabinoid receptors (CB_1 and CB_2), catabolic enzymes (FAAH and MAGL) as well as that of the 3 subtypes of peroxisome proliferator-activated receptors (PPARα, PPARβ/δ and PPARγ) in PFC, HIP and AMY. Significant differences between saline and CS- or VC-treated animals were assessed using a t-student analysis (Pvalue<0.05 was considered significant). CS induced a significant increase in the gene expression of CB_2, MAGL and PPARα in the PFC and a significant decrease of CB_1 and MAGL in the AMY, but failed to alter levels of endocannabinoids and related *N*-acylethanolamines. In the other hand, VC induced a significant increase in the levels of these analytes in the PFC with no changes in gene expression. No significant alterations were observed in the HIP of animals treated either with CS or VC. Our results show short-term alterations in the ECS in the PFC and AMY. These changes were dependent on the region analysed and on the chemotherapy drug used. Further studies are required to analyse the potential therapeutic effect of cannabinoid drugs to treat CICI.

Disclosures: **Y. López-Tofiño:** None. **M. Hopkins:** None. **A. Bagüés:** None. **K. Molony:** None. **R. Abalo:** None. **Á. Llorente-Berzal:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R01AG061188
Alzheimer's Association AARF-22-926617

Title: Neuronal vulnerability in response to AD-relevant insults is alleviated by tau reduction

Authors: *J.-H. TSENG, C. ISEMANN, T. COHEN;
Univ. of North Carolina at Chapel Hill, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Mounting evidence suggests tau reduction provides neuronal resiliency against not only Alzheimer's disease (AD), but also a wide variety of neurological disorders, indicating a potential detrimental role of physiological tau in response to pathological triggers. However, the detailed protection mechanism in which tau reduction involved is still unclear. Our previous work has shown that oxidative stress leads to altered global acetylation profile and induces insoluble protein aggregation in neurons. Such aberrant protein acetylation and aggregation is a characteristic in neurodegenerative diseases, and surprisingly is alleviated in $Tau^{-/-}$ neurons. Here, we employed multiple AD-relevant insults, including an AD-associated inflammatory trigger, oxidative stress, and DNA damage reagents, that target distinct cell death pathways in $Tau^{+/+}$ and $Tau^{-/-}$ neurons to investigate the mechanism of physiological tau-mediated neuronal vulnerability. We show that metabolic activity is remarkably impaired in response to all insults, in parallel with acetylated protein accumulation. Moreover, in line with our hypothesis, this metabolic deficit and acetylated protein accumulation are significantly recovered in $Tau^{-/-}$ neurons, illustrating that tau reduction is a promising strategy to combat triggers that lead to neurodegeneration. To further dissect the mechanisms, we suspect particular human deacetylases (HDACs or SIRTs) could be the primary mediator for the protection, since they are major protective deacetylase machineries within cells and from previous studies, deacetylase activity of particular HDACs/SIRTs can be suppressed by tau in vitro. In summary, our study reveals valuable insights into the molecular regulation that could underlie physiological tau reduction, as well as shed light on the emerging idea of tau reduction as a therapeutic strategy in AD and related neurological disorders.

Disclosures: J. Tseng: None. **C. Isemann:** None. **T. Cohen:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: AvH GF Fellowship 2021

Title: p38- and ERK-MAPK signalling modulate developmental neurotoxicity of nickel and vanadium in the *Caenorhabditis elegans* model

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Abstract: Nickel (Ni) and vanadium (V) are characteristic heavy metal constituents of many crude oil blends in Sub-Saharan Africa, and we have previously demonstrated their neurotoxic impact. However, molecular mechanisms driving Ni and V neurotoxicity are still being

elucidated. The p38- and ERKs-MAPK pathways, which are mostly known for their involvement in human immune and inflammatory signalling, have been shown to influence an array of neurodevelopmental processes. In the present study we attempt to elucidate the role of p38- and ERK-MAPK in neurodevelopmental toxicity after early life exposures to Ni and V using the *Caenorhabditis elegans* model. Synchronized larvae stage-1 (L1) worms were treated with varying concentrations of Ni and V for 1 hour. We then performed survival and developmental assays, metal bioavailability via optical emission spectrometry, MitoTracker Red assay, and neurotransmitter measurement via tandem mass spectrometry. All experiments were repeated 3 independent times. Our results show Ni induces lethality in *C. elegans* even at very low concentrations. On the other hand, V exposure requires very high concentrations to induce lethality. Furthermore, we see that loss-of-function of *pmk-1* and *pmk-3* which are both homologous to human p38-α (MAPK14) are differentially affected by Ni and V exposures. Our data show that lethality of Ni or Ni + V exposures is attenuated in *pmk-3* mutant worms, while on the other hand, *pmk-1* mutations increase lethality of V exposures. However, loss-of-function mutations in *mpk-1* which is homologous to human MAPK1 (ERK2), consistently attenuate lethality across all exposure scenarios. Also, all exposure scenarios triggered significant developmental delays in both wild-type and mutant strains. We also see increased mitochondrial-derived reactive oxygen species following Ni and V exposures in wild-type worms with differential responses in mutant strains. Inductively coupled plasma mass spectrometry showed significantly increased Ni content after Ni exposure in *pmk-1* and *mpk-1* strains and increased V content for all strains following V exposure. Additionally, we see significant changes in dopamine and serotonin levels after metal exposures, particularly in the *pmk-1* strain. Overall, our results suggest the p38- and ERK-MAPK signalling pathways may modulate Ni and V neurodevelopmental toxicity via influence on mitochondrial health, metal level dynamics and neurotransmitter regulation.

Disclosures: O.M. Ijomone: None. **A. Weishaupt:** None. **V. Michaelis:** None. **J. Bornhorst:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Randolph-Macon College Chenery and Craigie Research grants to E.C
Hampden-Sydney College Honors program summer research fellowships to J.I. and T.R.

Title: Acute Ethanol during Synaptogenesis Rapidly Alters Neuronal Morphology and Synaptic Proteins in Dorsal Striatum

Authors: *E. CLABOUGH[1], J. INGERSOLL[2], T. H. REEKES[3], A. GLEICHSNER[4], A. RYAN[4];
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Abstract: Fetal alcohol spectrum disorders are caused by the disruption of normal brain development in utero. The severity and range of symptoms is dictated by both the dosage and timing of ethanol administration, and the resulting developmental processes that are impacted. In order to investigate the effects of an acute, high-dose intoxication event on the development of medium spiny neurons (MSNs) in the striatum, mice were injected with ethanol on P6, and neuronal morphology was assessed after 24 h, or at 1 month or 5 months of age. Data indicate an immediate increase in MSN dendritic length and branching, a rapid decrease in spine number, and increased levels of the synaptic protein PSD-95 as a consequence of this neonatal exposure to ethanol, but these differences do not persist into adulthood. These results demonstrate a rapid neuronal response to ethanol exposure and characterize the dynamic nature of neuronal architecture in the MSNs. Although differences in neuronal branching and spine density induced by ethanol resolve with time, early changes in the caudate/putamen region have a potential impact on the execution of complex motor skills, as well as aspects of long-term learning and addictive behavior.

Disclosures: E. Clabough: None. **J. Ingersoll:** None. **T.H. Reekes:** None. **A. Gleichsner:** None. **A. Ryan:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.15

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: The translocator protein(18kD; TSPO) ligand XBD173 reduces glutamatergic synaptic transmission in slices and increases astrocytic calcium transient monitored by in-vivo microscopy

Authors: *N. KASSAB[1], P. L. FEYEN[2], K. PRATSCH[3], J. W. HERMS[4], G. RAMMES[5], G. SCHNEIDER[1];
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Abstract: The accumulation of neurotoxic proteins such as Aß in Alzheimer's (AD) and α-synuclein in Parkinson’s (PD) disease disrupts glutamate reuptake at the synaptic cleft leading to

overactivation of their receptors and excitotoxicity. In those diseases, the mitochondrial protein TSPO is overexpressed in glia and neurons. TSPO activation promotes the release of neurosteroids, which are known modulators of neurotransmitter receptors. While the effects of these neurosteroids on GABAA receptors are well documented, only a few studies have addressed the modulation of glutamatergic synaptic and astrocytic receptors, and whether it can be neuroprotective. In this study, we used the TSPO agonist XBD173, known to promote neurosteroids synthesis and release, for ex-vivo and in-vivo experiments to answer that hypothesis. We recorded spontaneous and evoked excitatory postsynaptic pharmacologically isolated glutamatergic currents (sEPSC and eEPSCs) from CA1 pyramidal neurons of wt and TSPO-KO mice in the whole-cell patch-clamp configuration. Astrocyte calcium transients were recorded from the somatosensory cortex of awake wt mice under 2-photon microscopy. Application of XBD173 (3µM) reduces eEPSC amplitude mediated by AMPA and NMDA receptors significantly by 17% ± 6 (p=0.007 Wilcoxon test, n=7). NMDA-eEPSC were more prominently affected and the amplitude decreased by 35% ± 20 (p=0.007 Wilcoxon test, n=7). In contrast, the same application had no significant effect on the eEPSC amplitude of TSPO-KO neurons (1% ± 17; p=0.2344 Wilcoxon test, n=7). We further analyzed the pathway mediating this effect by applying a GABAA neurosteroid the 3α5α-tetrahydrodeoxycorticosterone (THDOC 100nM). NMDA spontaneous sEPSCs amplitude was reduced to a similar extent as XBD (30% ± 25; p=0.015 Wilcoxon test, n=6). *In-vivo* recordings showed an increase in frequency and kinetics of astrocytic calcium transient after XBD IP injection (1mg/kg) by 127% ± 23 (p=0.05, Mann-Whitney test (MW), Cohen's d=2.317, n=3) and 30% ± 10 (p=0.0248 MW test, Cohen's d=4.292, n=3), respectively, compared to saline injection. Our results suggest that XBD acts via TSPO-dependent neurosteroids to inhibit AMPA and NMDA receptors and increase astrocyte calcium transient frequency and duration. The latter effect might reflect an increase in astrocytes activities that either require or generate calcium transients such as gliotransmitter release and glutamate reuptake respectively. Thus, neurosteroid release can modulate synaptic transmission and might protect against receptor overactivation by glutamate such as seen in AD. Our next step is to show the neuroprotective effect of XBD in an AD mouse model.

Disclosures: **N. Kassab:** None. **P.L. Feyen:** None. **K. Pratsch:** None. **J.W. Herms:** None. **G. Rammes:** None. **G. Schneider:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.16

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Standardization of white and blue light-induced retinal phototoxicity models in pigmented mice

Authors: *M. BACELLAR-GALDINO, N. E. PAPPENHAGEN, S. KAJA, J. A. JAMISON; Experimentica Ltd., Forest Park, IL

Abstract: Retinal phototoxicity induced by light in laboratory rodents is a well-established model to mimic aspects of human retinal degeneration, such as occurs in age-related macular degeneration (AMD). Induction of this model is usually performed in albino rodents lacking ocular pigmentation, thereby facilitating absorbance of light by photoreceptors and retinal pigment epithelium cells. However, assessing possible confounding effects of experimental therapeutics binding to melanin is desirable for drug discovery studies in light-induced phototoxicity models. The purpose of this study was, therefore, to evaluate feasibility of induction of white and blue light damage in pigmented mice. Male C57BL/6J mice were dark-adapted overnight and pupils were dilated by bilateral instillation of 1% atropine in both eyes at least 15 minutes prior to light induction. Mice were randomized into two groups, receiving either 20 kLux of spectrally-filtered blue light or 29 kLux of white light, each for 6 h. Flash electroretinography (ERG) was performed prior to light exposure and five days after light exposure to assess retinal function. Retinal thickness was quantified by *in vivo* spectral-domain optical coherence tomography (SD-OCT) imaging and histological analysis. Pupil dilation by the muscarinic antagonist, atropine, provided lasting mydriasis in pigmented mice, advantageous over short-lasting mydriasis induced by the parasympathetic antagonist, tropicamide. Baseline ERG amplitudes acquired at 1,000 cd.s/m^2 averaged ~ 160 µV for a-waves and ~ 800µV for b-waves, typical for young C57BL/6J mice. Exposure to white or blue light resulted in significant reduction of b-wave amplitudes by ~50% and ~60%, respectively. The observed functional impairment after light exposure was reflected by significant reductions in retinal thickness, contributed by loss of outer nuclear layer integrity. Photoreceptor loss was confirmed by histological analysis. Our data provide feasibility for the use of pigmented mice in white and blue light-induced retinal phototoxicity studies for the evaluation of drug candidates for the treatment of AMD and related retinal degenerative diseases. The models presented here can be readily transferred to transgenic strains that are typically maintained on pigmented genetic backgrounds.

Disclosures: M. Bacellar-Galdino: A. Employment/Salary (full or part-time):; Experimentica Ltd.. F. Consulting Fees (e.g., advisory boards); AcuiSee, Inc. **N.E. Pappenhagen:** A. Employment/Salary (full or part-time):; Experimentica Ltd. **S. Kaja:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Experimentica Ltd., K&P Scientific LLC, eyeNOS, Inc. **J.A. Jamison:** A. Employment/Salary (full or part-time):; Experimentica Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ONL Therapeutics, Inc., AcuiSee, Inc..

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.17

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant MH128022
NIH Grant MH122235
NIH Grant MH072567
NIH Grant HL126559
NIH Grant DA044579
NIH Grant DA039576
NIH Grant DA040537

Title: Bmal1 disruption potentiates PCB-induced alterations of tight junctions

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Dept. of Biochem. and Mol. Biol., Univ. of Miami, Miami, FL

Abstract: The circadian clock is ubiquitously present in every cell and is critical in coordinating internal physiological rhythms on a 24h light-dark cycle. At the molecular level, positive (brain and muscle ARNT-like 1: Bmal1, and circadian locomotor output cycles kaput: Clock) and negative (period 1/2: Per1/2 and cryptochrome 1/2: Cry1/2) regulatory feedback loops make up the central circadian clock. In a fast-paced, modern world, poor sleep quality and quantity results in a disruption of day-night balance, and this disruption contributes to the development of several diseases, such as type 2 diabetes, cancer, vascular disease, and other metabolic disorders. Polychlorinated biphenyls (PCBs) are lipophilic and highly toxic environmental pollutants. Although the production and use of PCBs has been prohibited, they are still present in the environment, and accumulate in human and animal tissues, which includes all classes of animal products. In this study, we aim to investigate if *Bmal1* gene silencing affects the blood-brain barrier (BBB) integrity through alterations in expression of the main tight junction proteins. Briefly, we transfected the hCMEC/D3 cells with either *Bmal1* or negative control siRNAs for the modeling of circadian rhythm disruption. After 24 hours from the beginning of transfection, we continued the experiments by examining the effects of coplanar and/or non-coplanar PCBs on hCMEC/D3 cells at different time points. We studied transmembrane (Occludin and Claudin-5), adhesion (Jam-2), and scaffolding (ZO-1 and ZO-2) tight junction proteins, as well as the adherens junction protein ß-catenin. We found significantly lower protein levels of Occludin and Jam-2 after *Bmal1* disruption and 48h PCB exposure. In addition, our results indicated that the ZO-1 and ZO-2 protein expression has been markedly modulated by the silencing of *Bmal1* and 48h PCB exposure. We found the same trend present with a decrease in adherens ß-catenin protein expression. In summary, we demonstrate that the exposure to PCBs can modulate endothelial cell functions by altering TJ protein expression after *Bmal1* disruption. Thus, our study indicates that *Bmal1* silencing can potentiate PCB-induced alterations in BBB integrity via altered expression of tight junction proteins, especially occludin, ZO-1, ZO-2 and ß-catenin.

Disclosures: T. Teglas: None. **S. Torices:** None. **D. Coker:** None. **M. Toborek:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.18

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: An In Vitro Assay to Determine the Neurotoxic Effects of Pharmacological Compounds

Authors: *C. K. H. MAK[1], K. MCCORMACK[1], A. C. EAVES[1,2], S. A. LOUIS[1], E. KNOCK[1,3];
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Abstract: Early drug development typically requires screening compounds of interest for neurotoxic effects in order to determine how they may alter the activity of the nervous system, traditionally through use of in-vivo animal models. Microelectrode array (MEA) systems are non-invasive and allow for high-throughput monitoring of in-vitro changes in neuronal activity caused by exposure to drugs and toxins. In order to set up a physiologically relevant MEA assay, it is important to culture neurons in a microenvironment that is representative of the in-vivo environment of the brain. Here, we cultured primary rodent neurons in BrainPhys™ Neuronal Medium (BP) and treated the neurons with picrotoxin (seizurogenic compound) and GABA (inhibitory neurotransmitter) to determine whether neuronal activity would be predictably stimulated or inhibited, respectively. Single cells dissociated from E18 rat cortices were plated at 50,000 cells/well of a 96-well MEA plate in 10 µL droplets of NeuroCult™ Neuronal Plating Medium supplemented with NeuroCult™ SM1 Neuronal Supplement (SM1). After 5 days of incubation, cultures were gradually transitioned to BP supplemented with SM1 and 12.5 mM glucose by performing half-medium changes every 2 - 3 days until the end of the assay. On day 14, baseline neuronal activity was recorded for 15 minutes using the MEA system. Picrotoxin and GABA were then added to the culture at concentrations ranging from 0.3 to 300 µM. After 1 hour of incubation at 37°C, neuronal activity was recorded again. Changes in activity were reported as percent change of baseline activity and were normalized to vehicle controls (VC). In 2 individual experiments, picrotoxin produced an increase in mean firing rate (MFR) across all concentrations tested, with the highest percent increases recorded for neurons treated with 3 µM, at 204.7 ± 23.7% (mean ± SE, 3 replicate wells) and 158.2 ± 30.0% (mean ± SE, 4 replicate wells) of VC. In contrast, GABA produced a consistent decrease in neuronal activity, with the MFR dropping from 90.0 ± 11.8% (mean ± SE, 3 replicate wells) and 102.5 ± 13.0% (mean ± SE, 4 replicate wells) of VC at 3 µM to 7.7 ± 3.8 and 14.7 ± 5.2% of VC at 10 µM, respectively. Additional parameters for neuronal activity, including synchrony index, network burst frequency, and interburst intervals were also analyzed for each condition (data not reported here). This study has shown that primary rodent neurons cultured in physiological conditions within a high-throughput format are functional and can be used in an in-vitro assay to predict neurotoxic effects of pharmacological compounds.

Disclosures: C.K.H. Mak: None. **K. McCormack:** None. **A.C. Eaves:** None. **S.A. Louis:** None. **E. Knock:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.19

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Synthetic dye yellow no. 5 (Tartrazine) short-term exposure lowers Sod1 mRNA expression in mouse Neuro2A neurons in vitro.

Authors: *J. L. FARNUM, A. L. HAWTHORNE;
Univ. of Central Florida, Orlando, FL

Abstract: Yellow Dye No. 5, also known as tartrazine (TRZ), is widely used (Matsyura et al., 2020) and has an accepted daily intake (ADI) of 0-7.5 mg/kg of body weight per day (JEFCA, 2017). Consuming TRZ dosages greater than the ADI can lead to reduced levels of antioxidant enzymes in the brain, chromosomal alterations, or decreased neuronal dendritic lengths after 90 days (Mpountoukas et al., 2010 and Abd-Elhakim et al., 2019), which can result in oxidative stress, impaired neuronal functioning and potential mutagenic effects. Within the ADI, there have been observed reductions of the copper zinc superoxide dismutase-1 (SOD1) enzyme level (Albasher et al., 2020). We hypothesize that TRZ interacts pre-translationally inside the cell, resulting in the reduction of Sod1 mRNA. In this study, differentiated Neuro2A-derived neurons were exposed to TRZ for 3 or 7 days. We tested a concentration curve from 0 to 11 μg/mL. Treated cells were grown on poly-L-lysine (PLL)- and laminin-coated glass coverslips, immunostained with anti-β-tubulin III and phalloidin, imaged, and analyzed using NeuronJ/ImageJ (NIH). Neurons were traced to analyze the morphological impacts of TRZ. Sod1 mRNA was quantified using reverse transcription quantitative polymerase chain reaction (RT-qPCR). We analyzed the differences in Sod1 mRNA levels of the controls vs. experimental cells, using the 2-ΔΔCT method. TRZ caused an acute increase in neurite length after 7 days of TRZ exposure. Additionally, there was a general decreasing trend of Sod1 mRNA expression within the ADI at 3 and 7 days, but there was a significant reduction in the mRNA expression above the ADI at 7 days of exposure. The reduction in Sod1 mRNA expression could indicate pre-translational modifications, which could be a result of TRZ's ability to bind DNA. These findings help fill the gap in understanding the mechanism of SOD1 downregulation due to TRZ exposure. Further studies are needed to examine the mechanism of TRZ's effects and the impacts on human health.

Disclosures: J.L. Farnum: None. **A.L. Hawthorne:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.20

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: 2021R1A2C2006110
2021M3E5D9021364
2019R1A5A2026045

Title: Characterizing phenotypic diversity of macrophages contributing to regeneration or degeneration in PNS and CNS

Authors: *Y. SEO[1,2], M. KWON[2], B. KIM[1,3];
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Abstract: Macrophages dynamically change their molecular characteristics following injuries and their distinct phenotypes can have consequential effects on the outcomes of neural injuries. Although macrophages are classically divided into M1 or M2 type cells, it is increasingly recognized that macrophage phenotypes are diverse. Therefore, it would be important to understand the spectrum of phenotypic diversity of post-injury macrophages and how to regulate their phenotypes to drive regeneration while curbing secondary degeneration concurrently. The present study sought to identify the phenotypic diversity in cultured macrophages and to examine the functional influence of macrophage phenotypes on the regeneration or degeneration of PNS or CNS neurons. Cultured bone marrow-derived macrophages (BMDMs) were treated with factors that are known to induce regeneration or degeneration phenotype: lipopolysaccharide (LPS)/ IFN-γ (M1), IL-4 (M2), zymosan, CCL2, and curdlan. Zymosan treatment induced both M1 and M2 genotype, whereas CCL2 imparted strong and curdlan weak M2 genotype. When conditioned medium (CM) from BMDMs were treated to cultured dorsal root ganglion (DRG) neurons, M2 and CCL2-treated CMs increased DRG neurite outgrowth, and zymosan-treated CM exhibited the strongest neurite-outgrowth activity. CMs collected from all the conditions did not show evidence of toxicity to DRG neurons. However, CM obtained from BMDMs, regardless of treatments, induced neurite degeneration when treated to cultured cortical neurons, indicating BMDMs may be inherently toxic to CNS neurons. We previously reported that neuron-macrophage interaction can drive macrophages to a pro-regenerative phenotype. When BMDMs were co-cultured with DRG neurons and treated with cAMP, which mimics injury signals, collected CM exhibited neurite-outgrowth activity without any sign of toxicity for DRG neurons. Surprisingly, CNS neurotoxicity of BMDM-derived CM was markedly reduced by the BMDM + neuron cocultures. The chemokine array revealed a significant decrease in CCL5 in the coculture CM and blocking CCL5 significantly reduced the inherent toxicity of BMDM-derived CM for CNS neurites. Our results indicate that diverse macrophage phenotypes can influence the regeneration and degeneration in PNS and CNS, respectively. Furthermore, interaction with neurons could reduce the neurotoxicity of BMDMs via a CCL5-dependent mechanism. We are currently examining in vivo consequences of the diverse BMDM phenotypes in the mouse brain. Precise reprogramming of macrophage phenotypes could be exploited to prevent degeneration or induce regeneration following CNS or PNS injury.

Disclosures: Y. Seo: None. **M. Kwon:** None. **B. Kim:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.21

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NIEHS Grant R01ES031823
NIH/NIEHS Grant P30 ES006676
NIH/NIEHS Grant P30 ES030285
NIH/NIEHS Grant T32ES007254

Title: Neurodevelopmental changes induced by early-life exposure to the pyrethroid pesticide deltamethrin

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Abstract: Epidemiological studies indicate that early-life exposure to deltamethrin (DM), a member of the pyrethroid pesticide family, may be linked to neurodevelopmental disorders, including attention deficit hyperactivity disorder (ADHD). An animal model of early-life exposure to DM recapitulates ADHD-like behavior through alterations in the striatum and hippocampus. However, the cellular and circuit mechanisms underlying these ADHD-like phenotypes are not fully understood. We evaluated the effect of DM using an early-life exposure mouse model where dams were exposed to the No Observed Adverse Effect Level (NOAEL) dose of DM from pregnancy to weaning time. Using LC-MS/MS, we detected DM in the brain of exposed mice after cessation of exposure, corroborating the idea that due to its lipophilic nature DM can cross the blood-brain barrier during development and accumulate in the brain. Next, exposed mice were analyzed with a battery of behavioral tests complemented by electrophysiological studies and targeted lipidomic analysis. Consistent with alterations of the reward circuit, we show that consummatory behavior for highly palatable food is disrupted in the DM early-life exposure model, resulting in DM animals consuming significantly more food than their non-exposed counterparts. Intriguingly, this phenotype is accompanied by changes in the firing of parvalbumin-positive interneurons in the striatum that express the voltage-gated Na+ Nav1.1 and as such are uniquely susceptible to DM. Additionally, following cessation of exposure at PND 30, we also observed upregulation of lipid species involved in myelin biosynthesis, a change that was specific for the striatum. Complementary electrophysiological studies in the hippocampus revealed a reduction of long-term potentiation (LTP) at CA3-CA1 synapses in the DM mice compared to their non-exposed counterparts, with no changes in basal synaptic transmission. Our results indicate that early-life exposure to DM leads to complex alterations in the striatum and hippocampus, resulting in neuronal network and behavioral

deficits that have been previously associated with disruption of the reward circuit and cognitive function in ADHD-like animal models.

Disclosures: **M. Marosi:** None. **J. Di Re:** None. **M. Bernabucci:** None. **L. Koff:** None. **I. Bernbucci:** None. **S. Ranaldi:** None. **Y. Avchalumov:** None. **J. Linares:** None. **T. Romsdahl:** None. **W. Russell:** None. **L.M. Hallberg:** None. **B.T. Ameredes:** None. **G. Thomas:** None. **F. Laezza:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.22

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: OCS/FDA Funding 7731.02

Title: Assessing the Developmental Neurotoxicity of Perinatal Exposure to Purified Cannabidiol in Sprague Dawley Rats

Authors: *W. D. GILL, T. FLANIGAN, A. N. SHEN;
Div. of Neurotoxicology, NCTR, FDA, Jefferson, AR

Abstract: Cannabidiol (CBD) is a non-intoxicating chemical component of the cannabis plant, and it is the active ingredient in Epidiolex, which is FDA-approved to treat seizures in rare childhood disorders. Recently, non-drug CBD usage has increased across the US, as CBD is often perceived as a safe and natural product that purportedly relieves anxiety, pain, and sleeplessness, among others. This is concerning because these issues are often associated with pregnancy, and pregnant women may use CBD because of its perceived safety. Yet, cannabis use during pregnancy has been linked to poor developmental outcomes, and CBD cannot currently be excluded as a contributing factor. The endocannabinoid system influences neurodevelopment and immune function, and the effects of developmental exposure to CBD on those systems is currently unclear. The current study investigated the developmental neurotoxicity of purified CBD in Sprague Dawley rats. Pregnant dams were orally gavaged with vehicle, 15, 30, 100, 250 mg/kg/day CBD from gestational day 6 to the day prior to parturition. Pups were orally gavaged with the same dose as their respective dam from postnatal day (PND) 1 to 21. Offspring underwent a series of neurobehavioral tests from PND 21-180, which included tests of motor function, anxiety-like behavior, and cognition. Neurochemistry assays and IHC using brains from PND21 and PND180 were conducted with a particular focus on the dopamine system. Neurobehavioral tests showed that CBD had no dose-dependent effect on motor function, anxiety-like behavior, and performance in the Morris water maze. Adolescent female rats in the high dose group demonstrated a prepulse inhibition deficit to an acoustic startle, but no deficit was found in any other groups. There were no systematic effects of CBD on operant tasks of motivation and cognition. There were no observed differences in neurotransmitter levels and

brain protein concentrations within dopamine systems, and this was also true of select markers within serotonin and acetylcholine systems. Results from this study indicate that high doses of perinatal CBD may result in sensorimotor gaiting deficits in adolescent female rats, which is relatively consistent with publicly available data released along with the approved FDA label for Epidiolex. No other dose-dependent behavioral effects were noted. Similarly, no alterations to dopaminergic systems were demonstrated in any CBD treatment groups. Additional behavioral and neurochemical tests will be analyzed and conducted to further investigate the effects of CBD on neurodevelopment.

Disclosures: W.D. Gill: None. **T. Flanigan:** None. **A.N. Shen:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.23

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 1K08NS118138-01

Title: Integrin a4b1 blockade improves locomotion in mice with CD19-CAR T cell neurotoxicity

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Abstract: Background: Neurotoxicity remains a serious concern in chimeric antigen receptor (CAR) T cell treatment for hematologic malignancies. It affects ~40% of patients and can lead to seizures, coma, and in rare cases death from cerebral edema, likely via disruption of the neurovascular unit. To better understand the underlying mechanisms, we created a mouse model where syngeneic CD19-CAR T cell treatment induces neurotoxicity in wild type mice. We have previously shown via in-vivo two photon imaging that >10% of brain capillaries become plugged by leukocytes 6 days after CAR T cells infusion. This is associated with impairment in exploration and motor function. We hypothesized that neurotoxicity could be ameliorated by blocking the adhesion molecule interaction between circulating leukocytes and the brain endothelium, thus restoring capillary blood flow. Since the interaction of integrinα4β1 with VCAM1 is key to T cell neuro-autoimmunity, we tested whether blocking integrin α4 can decrease brain capillary plugging and improve behavioral neurotoxicity.
Approach: Integrin α4 antibodies (2mg/kg) were given intravenously to mice on days 1,3, and 5 after CAR T cell infusion. We measured neurologic symptom scores daily and open field behavior on day 5. We used in-vivo two photon imaging via a thinned skull window to measure the number of nonflowing cortical capillaries in predefined areas of the somatosensory cortex on day -1 (prior to CAR T cells), and days 4 and 6 post CAR T cells.
Results: Mice treated with anti-integrin α4 antibodies had no improvement in neurologic

symptom scores, but their locomotion speed in the open field was 46% higher compared to mice treated with isotype control antibodies (P=0.0199). On day 4 after CAR T cell infusion, a mean of 3.7% of cortical capillaries were obstructed in mice treated with anti-integrin α4 antibodies, vs 6.2% in mice treated with isotype control. On day 6, 3.6% and 2.5% of capillaries were nonflowing, respectively.
Conclusions: Integrin α4 blockade improved locomotion speed on day 5 and reduced capillary plugging on day 4, but not day 6 after CAR T cell infusion. We show evidence that leukocyte-endothelial interaction via integrina4b1/VCAM interaction plays a role in the pathophysiology of CAR T neurotoxicity, but other mechanisms are likely contributing as well.

Disclosures: L. Faulhaber: None. **O. D'Costa:** None. **J. Gust:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.24

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R21 MH106441
NIH R01 MH109382

Title: Global analysis of excitotoxicity-induced alterations in RNA-protein interactions and RNA structure in primary cortical neurons

Authors: *E. ALVAREZ PERIEL[1], M. C. KRAMER[2], D. P. JACKSON[1], C. AKAY-ESPINOZA[1], J. TASCA[3], B. A. GARCIA[3], K. L. JORDAN-SCIUTTO[1], B. D. GREGORY[2]; [1]Dept. of Oral Medicine, Sch. of Dent. Med., [2]Dept. of Biology, Cell and Mol. Biol. Grad. Group, [3]Epigenetics Institute, Dept. of Biochem. and Biophysics, The Perelman Sch. of Med., Univ. of Pennsylvania, Philadelphia, PA

Abstract: RNA-binding proteins (RBPs) participate in virtually all steps of RNA metabolism regulation, which is particularly relevant in neurons and in cellular responses to stressors. One important stressor for neurons is excitotoxicity, which is caused by excessive excitatory amino acids signaling leading to intracellular calcium overload and eventually to neuronal death. Importantly, excitotoxicity has been implicated in neuronal dysfunction and degeneration in many pathologies including Alzheimer's disease, Huntington's disease, and HIV-associated neurocognitive disorders, among others. However, to our knowledge, global analysis of changes in RNA structure and protein binding in an excitotoxic context has not been assessed. To this end, we have identified global changes in RNA-protein interactions and in RNA secondary structure in an *in vitro* model of excitotoxicity using primary rat cortical neurons exposed to NMDA. We have applied the novel protein interaction profile sequencing (PIP-seq) method to identify sites within RNA molecules that are bound by RNA-binding proteins (RBPs), termed protein protected sites (PPS). Our data show relevant shifts in RNA secondary structure between

untreated and NMDA-treated neurons near the start and stop codons of protein-coding genes. Additionally, we have identified sets of genes that have PPSs specifically in the control condition, specifically after NMDA treatment, or in both conditions but at different intragenic regions. Interestingly, the gene ontology analysis of these gene sets shows that transcripts that are protein-bound only in NMDA-treated samples are associated with several neurodegenerative disorders. Finally, using these data we have found RNA motifs enriched in protein-binding after NMDA treatment and have used them to identify specific RBPs that bind them. Overall, we have described the global landscape of RNA secondary structure and the RBP-ome of primary cortical neurons in an *in vitro* model of excitotoxicity, providing a link between two major hallmarks common in multiple neurodegenerative disorders: excitotoxicity and RNA regulation by RBPs.

Disclosures: E. Alvarez Periel: None. **M.C. Kramer:** None. **D.P. Jackson:** None. **C. Akay-Espinoza:** None. **J. Tasca:** None. **B.A. Garcia:** None. **K.L. Jordan-Sciutto:** None. **B.D. Gregory:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.25

Title: WITHDRAWN

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.26

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Building Strength Grant - Bowling Green State University

Title: Corn grown on dredge-amended soils affects hippocampal development and behavior

Authors: *K. A. S. FLANIGAN[1], M. I. CZUBA[1], M. A. RÚA[2], J. WILLING[1];
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Abstract: The significant depletion of agricultural soil nutrients is of increasing concern and requires novel amendment practices to increase crop yield. The sediment in Lake Erie, which is to be dredged annually to ensure efficient trade and transportation, seems to provide a solution as dredge material is known to improve soil fertility and water absorption. However, this proposed agricultural amendment process may be exposing mammals to compounds known to alter

neurodevelopment. These Contaminants of Concern (COC) can include heavy metals, bisphenol-A, polyaromatic hydrocarbons, pesticides, pharmaceuticals and others. COC bioaccumulate within the agricultural crops and biomagnify in the tissues of organisms consuming them, including both livestock and humans. COC within the dredged sediment can be of particular concern for the developing brain and could potentially alter neurodevelopment and the development of behavior. The current study investigated the neurodevelopmental and behavioral impact of corn grown on dredge-amended soil in Long Evans rats. Female rats were exposed to corn grown on dredge-amended soil (or a non-dredge amended source of corn) during gestation and lactation (E0-P25), and male and female progeny were tested in the elevated plus maze, open field, and novel object recognition tests. In addition, we assessed hippocampal volume in adult offspring. Results suggest that gestational and lactational exposure to dredge-amended corn can affect adult anxiety-like and exploratory behavior and can lead to sex-specific effects on hippocampal neuroanatomy. These data suggest that more research may be needed to determine the effects of soil amendment processes. Continued study of corn grown on dredge-amended soil will help to determine the safety of this agricultural practice on mammalian brain development.

Disclosures: K.A.S. Flanigan: None. **M.I. Czuba:** None. **M.A. Rúa:** None. **J. Willing:** None.

Poster

707. Neuronal Injury and Death II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 707.27

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R01CA242158
NIH R01AG058560
R50CA116201
19-40-60-OLIV

Title: Nicotinamide mononucleotide prevents cisplatin-induced mitochondrial defects in cortical neurons derived from human induced pluripotent stem cells

Authors: *M. RASHID, A. OLIVEROS, J. MI-HYEON;
Rutgers, The State Univ. of New Jersey, Piscataway, NJ

Abstract: Chemotherapy-induced cognitive impairment (CICI or chemobrain) is a neurotoxic side effect of chemotherapy that has yet to have an effective treatment. Using cisplatin, a platinum-based chemotherapy to the model of CICI, our recent study demonstrated that dysregulation of brain NAD^+ metabolism contributes to cisplatin-induced impairments in neurogenesis and cognitive function, which was prevented by administration of the NAD^+ precursor, nicotinamide mononucleotide (NMN). However, it remains unclear how cisplatin causes neuronal dysfunction and the mechanism by which NMN prevents cisplatin-induced cognitive impairment. Given that mitochondrial dysfunction is thought to play a prominent role

in age-related neurodegenerative disease and chemotherapy-induced neurotoxicity, we sought to explore if NMN prevents chemotherapy-related neurotoxicity by attenuating cisplatin-induced mitochondrial damage. Using excitatory cortical neurons derived from human-induced pluripotent cells (iPSCs), we demonstrate that cisplatin increases the generation of mitochondrial reactive oxygen species and decreases ATP production, all of which are indicative of oxidative DNA damage resulting in mitochondrial functional defects. Ultrastructural analysis revealed that cisplatin caused loss of cristae membrane integrity and matrix swelling in conjunction with a reduction in expression of the pre- and post-synaptic markers PSD95 and SYP in human cortical neurons. Notably, pretreatment with NMN prevents cisplatin-induced adverse defects in mitochondria and synapse formation of human cortical neurons. Taken together, our results suggest that increased mitochondrial oxidative stress and dysfunction play key roles in cisplatin-induced neurotoxicity. Thus, NMN may be an effective therapeutic strategy to prevent cisplatin-induced deleterious effects on mitochondria, making this organelle a key factor in the amelioration of cisplatin-induced cognitive impairments.

Disclosures: **M. Rashid:** None. **A. Oliveros:** None. **J. Mi-Hyeon:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.01

Topic: C.10. Brain Injury and Trauma

Support: NINDS, R01-NS118037

Title: Interleukin 1 Receptor 1 Signaling in the Hippocampus Mediates Impaired Neuronal Homeostasis and Cognitive Decline Following Traumatic Brain Injury

Authors: *C. BRAY[1], A. DAVIS[2], K. BAETZ[2], N. BECKMAN[2], J. PACKER[2], L. WANGLER[2], E. GOODMAN[2], J. SHERIDAN[2], J. GODBOUT[2];
[1]Col. of Med., [2]Ohio State Univ., Columbus, OH

Abstract: Traumatic Brain Injury (TBI) causes neurodegenerative pathologies and neurological dysfunction, which may develop years after injury. Mounting evidence indicates neuroinflammatory processes post-TBI are mediated by microglia. For example, microglia elimination and forced turnover approaches (with CSF1R antagonism) in mice, attenuated TBI-dependent neuroinflammation and reversed deficits in neuronal plasticity and cognitive impairment at 30 dpi. Moreover, our recent scRNAseq analysis showed unique Trauma Associated Microglia (TRAMs) present 7 dpi in the cortex. Type I interferon and Interleukin (IL) 1 signaling pathways were prominently enhanced in these microglia 7 dpi. Furthermore, there are several lines of evidence across TBI models that IL1 signaling persists chronically in the brain after TBI. Based on these data, we hypothesize that reducing IL1R1 signaling after TBI reduces inflammation, prevents neuronal dysfunction, and restores cognition. Therefore, the goal of this

study was to better understand the potential cellular targets of this increased IL1 signaling in the brain after TBI. In the first study, $IL1R1^{tdTom}$ reporter mice were uninjured or subjected to midline fluid percussion injury. Histological analyses show that IL1R1 was markedly increased on neurons in the dentate gyrus of the hippocampus 7 days after TBI compared to controls. IL1R1 expression was highly concentrated in neurons of the HPC compared to all other cell types and CNS regions examined. To further investigate the potential role of IL1 signaling in the HPC, $IL1R1^{WT}$ and $IL1R1^{KO}$ transgenic mice were uninjured or subjected to midline fluid percussion injury (mFPI) and hippocampal dependent memory was assessed. TBI caused deficits in novel objection recognition (NOR), novel object location NOL and conditioned fear memory at 7 dpi. All HPC dependent deficits in memory were absent in IL-$1R1^{KO}$ subjected to TBI. Consistent with these results, there was less TBI-associated inflammation (*Irf7, IL1b, Tnfa*) in the HPC and CTX in the $IL1R1^{KO}$ TBI compared to WT TBI groups. TBI also increased the morphological restructuring of $Iba1^{+}$ microglia, independent of IL1R1. In order to explore the influence of IL1 signaling concomitant with TBI in the HPC directly, mice were injected bilaterally in the HPC with an AAV2-IL1RA designed to infect neurons and overexpress IL1 receptor antagonist (RA). Diffuse TBI again promoted deficits in NOR/NOL at 7 dpi and these deficits were prevented by neuronal overexpression of IL1RA in the HPC. Taken together, these data indicate that IL1R1 mediated signaling in neurons after TBI is important in HPC-dependent neuronal dysfunction and cognitive impairment.

Disclosures: C. Bray: None. **A. Davis:** None. **K. Baetz:** None. **N. Beckman:** None. **J. Packer:** None. **L. Wangler:** None. **E. Goodman:** None. **J. Sheridan:** None. **J. Godbout:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.02

Topic: C.10. Brain Injury and Trauma

Support: RO1-AG-051902
P30-NS-045758

Title: Traumatic Brain Injury Induced Chronic Inflammation and Cognitive Impairment is Attenuated by Inhibition of the Type 1 Interferon Pathway

Authors: *J. PACKER[1], C. E. BRAY[3], N. BECKMAN[2], M. WITZEL[2], M. OUVIÑA[2], D. ADEKUNLE-ADEGBITE[2], A. DAVIS[2], J. P. GODBOUT[4];
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Abstract: Neuropsychiatric complications including depression and cognitive decline develop, persist, and even worsen in the years after traumatic brain injury (TBI), negatively affecting the

quality of life and lifespan. Chronic inflammatory processes persist after TBI, but the mechanism that drives this response is unclear. We previously reported that microglia, innate immune cells in the brain, drove chronic inflammation following diffuse TBI in mice. Moreover, the subacute phase of cortical inflammation 7 days post injury (dpi) was dominated by a robust type 1 interferon (IFN) response. Thus, we hypothesize that increased type I IFN signaling is critical in promoting microglial priming and the subsequent transition from acute to chronic neuroinflammation after brain injury. In the current study, the type 1 IFN pathway was targeted for intervention using knock out mice for the transmembrane protein stimulator of IFN genes (STING). In these experiments, adult male wildtype (WT) C57BL/6 or $STING^{KO}$ mice received a diffuse brain injury and neuroinflammation and functional recovery were assessed 7 and 30 dpi. As expected, inflammatory/priming related genes (TNF, Cd68, H2-Eb1) and type 1 IFN associated genes (Tmem173, Irf3, Irf7, Ifi27) were increased 7 dpi in the cortex of TBI mice compared to controls. These TBI induced increases in the IFN and inflammatory/priming associated genes 7 dpi were attenuated in $STING^{KO}$ mice. These changes in the cortex were mirrored in whole brain percoll enriched microglia. In $STING^{KO}$ mice there was reduced microglial activation (Iba1) within the somatosensory cortex and hippocampus (7 dpi) In addition, there was reduced microglial priming related mRNA (H2-Eb1, ITGAX, Clec7a) as well as inflammatory (Ccl2) expression 30 dpi in $STING^{KO}$ compared to WT TBI controls. Last, the TBI associated deficits in cortical and hippocampal dependent memory in the novel object recognition and location tasks 7 and 30 dpi were attenuated in the TBI- $STING^{KO}$ mice. Taken together, reducing type I IFN signaling after TBI intervention is effective at reducing acute and chronic inflammation, microglial priming, and improving functional recovery post-TBI.

Disclosures: **J. Packer:** None. **C.E. Bray:** None. **N. Beckman:** None. **M. Witzel:** None. **M. Ouviña:** None. **D. Adekunle-Adegbite:** None. **A. Davis:** None. **J.P. Godbout:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.03

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R01-AG051902
NIH Grant R01-NS118037
NINDS Training Grant T32-NS-105864
NINDS Core Grant P30-NS-045758
OSU Distinguished University Fellowships
OSU Dean's Distinguished University Fellowship

Title: Amplified gliosis and interferon-associated inflammation in the brain following diffuse traumatic brain injury in aged mice

Authors: *L. WANGLER[1], C. E. BRAY[3], J. PACKER[1], Z. TAPP[4], A. DAVIS[1], S. O'NEIL[1], K. BAETZ[2], M. OUVIÑA[2], M. WITZEL[2], J. GODBOUT[5];
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Abstract: Traumatic brain injury (TBI) is associated with an increased risk of cognitive, psychiatric, and neurodegenerative complications that may develop and persist years after injury. Aged individuals are especially vulnerable to fall-related TBI and account for a high proportion of TBI-related hospitalizations and deaths. Nonetheless, the neurobiological mechanisms that underlie worse functional outcomes after TBI in the aged are unclear. Therefore, the purpose of this study was to identify pathways that govern the differential responses to diffuse brain injury with age. Here, adult (2 mo) and aged (16-18 mo) C57BL/6 mice were subjected to a diffuse brain injury (midline fluid percussion) and cognition, gliosis, and brain inflammation were determined 7 or 30 days post injury (dpi). Acute cognitive impairment was evident in both adult and aged mice 7 dpi. There was enhanced morphological restructuring of microglia and astrocytes 7 dpi in the cortex and hippocampus of aged mice compared to adults. mRNA analysis (nCounter NanoString Neuropathology panel) revealed robust age-dependent amplification of cytokine/chemokine, complement, innate immune, and interferon-associated gene expression in the cortex 7 dpi. Ingenuity Pathway Analysis of the transcriptional data showed that type I (IFN) signaling was significantly enhanced in the aged brain after TBI compared to adults. Evidence of prolonged inflammatory signaling and microgliosis persisted in aged mice 30 dpi. Based on these results, a STING (stimulator of interferon genes) agonist DMXAA was used to determine if augmenting IFN signaling worsened cortical inflammation and gliosis after TBI. Adult mice administered the STING agonist after TBI had amplified expression of myriad genes in the cortex that were overexpressed in Aged-TBI mice, including IRF7, Clec7a, Cxcl10, and Ccl5. Overall, diffuse TBI promoted amplified IFN signaling in aged mice resulting in extended inflammation and gliosis.

Disclosures: L. Wangler: None. **C.E. Bray:** None. **J. Packer:** None. **Z. Tapp:** None. **A. Davis:** None. **S. O'Neil:** None. **K. Baetz:** None. **M. Ouviña:** None. **M. Witzel:** None. **J. Godbout:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.04

Topic: C.10. Brain Injury and Trauma

Support: NHI grant R01-AG051902

Title: Cuprizone induced demyelination causes robust formation of rod microglia in he cortex

Authors: *A. DAVIS[1], J. PACKER[3], L. WANGLER[2], G. K. MATSUSHIMA[4], J. P. GODBOUT[5];
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Abstract: Traumatic brain injury (TBI) promotes unique morphological and transcriptional responses in microglia that are critical in mediating inflammatory and repair processes in response to injury. One group of microglia are “rod microglia” defined by their elongated morphology and processes that align linearly. Rod microglia are present after TBI and are also detected in many pathological conditions including: CNS autoimmune diseases, neurodegenerative diseases and advanced age. Moreover, we have reported that diffuse TBI in mice caused the formation of rod microglia in the cortex 7 days-post-injury (dpi). These rod-microglia aligned with apical dendrites of cortical neurons and overlapped with dense astrogliosis. While these rod microglia were markedly evident 7 dpi, they were no longer detectable by 30 dpi. Nonetheless, the function and biochemical etiology of these microglia is unclear. TBI causes axonal sheering and injury to the white matter that likely increases the amount of myelin debris. Therefore, the objective of this study was to investigate the spatial and temporal formation of rod microglia after demyelination and subsequent re-myelination. Here dietary supplementation with cuprizone (0.2% w/w) a copper-chelating agent, was used to induce demyelination in the central nervous system. Rod microglia (iba-1+) were evident in the somatosensory cortex after a three-week administration of cuprizone with no presence in the hippocampus. These structural elongations in microglia were paralleled by an increased mRNA expression of several inflammatory mediators (*Clec7a*, *Cd11c*, *Tnf*) and phagocytic markers (*Cd14* and *Cd68)* in the cortex and hippocampus. Rod microglia were more evident at 3-weeks as compared to a 5-week treatment. Next, mice were provided dietary supplementation with cuprizone for 5-weeks and then allowed 3-weeks of re-myelination with removal of the cuprizone supplemented diet. There was a significant decrease in the number of rod microglia after 3-weeks of re-myelination. Overall, we interpret these data to indicate that increased injury to myelin is one plausible stimulus for the formation of rod microglia with an inflammatory mRNA profile.

Disclosures: A. Davis: None. **J. Packer:** None. **L. Wangler:** None. **G.K. Matsushima:** None. **J.P. Godbout:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.05

Topic: C.10. Brain Injury and Trauma

Support: National Institutes of Health [R03-NS116301 (D.K.C.)]
National Institutes of Health [R01-NS117757 (D.K.C.)]

Title: Single mild TBI in a porcine model alters transcription patterns related to neuroinflammation, cell integrity, and neuroplasticity

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Abstract: Traumatic Brain Injury (TBI) is caused by a mechanical insult to the head and often results in prolonged or permanent brain dysfunction. Even so-called “mild” TBI - otherwise known as concussion - may induce neurophysiological deficits affecting learning, memory, and concentration that do not resolve in up to 15-20% of patients. There are currently no approved treatments to improve recovery from TBI. Previous extensive neuropathological examinations have shown that mild TBI is associated with axonal degeneration, subtle changes in synaptic loss or gain, and neuronal hypertrophy occurring concomitantly with migration and morphological alterations of microglia - the resident immune cell of the central nervous system. Here, we build on these finding by investigating the activity of neuroinflammatory and neurodegenerative related genes following mild TBI. We evaluated this relationship utilizing a pig model of closed-head rotational acceleration-induced TBI, which closely replicates human head injury biomechanics that cannot be reproduced in small animals. For this study, RNA was extracted from whole coronal brain sections of pigs that survived a single mild TBI over various timepoints out to 1 year post injury (YPI), with comparisons made to age-matched sham injured animals. Total RNA was multiplexed on an nCounter Neuropathology panel (Nanostring Technologies) that profiled 360 genes related to fundamental themes of neurodegeneration, such as neurotransmission, neuroplasticity, cell integrity, metabolism, and neuroinflammation. Pairwise differential expression analyses demonstrated 44 differentially expressed genes at 3 days post injury (DPI), 43 genes at 7 DPI, and no differentially expressed genes at 30 DPI and 1 YPI. There is notable upregulation of the interferon regulatory factor - IRF8 - at 3 and 7 DPI, downregulation of the myelin basic protein gene at 3 DPI, as well as the upregulation of several apoptosis-related genes at 3 DPI that are subsequently downregulated by 7 DPI. This work allows us to examine gene expression changes and relate these contributing molecular factors to mild TBI histopathology in a uniquely translational large animal model. Furthermore, this data set may facilitate the identification of therapeutic target pathways in animal models that may translate to potential treatment for humans. Overall, mild TBI transcriptomic characterization is a critical step in classifying degenerative and inflammatory processes that underlie the cognitive, behavioral, and motor dysfunctions that millions of Americans experience as a result of TBI.

Disclosures: M. Grovola: None. **J.E. Duda:** None. **D. Cullen:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.06

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS096369
NIH Grant NS121287
DoD Grant EP1900020
Hillblom/BARI Fellowship

Title: Spatial selectivity of thalamic inflammation following cortical injury in mice

Authors: *D. NECULA, F. S. CHO, A. HE, **J. PAZ**;
Gladstone Institutes,UCSF, San Francisco, CA

Abstract: Cortical injuries can result in long-term disabilities, including cognitive dysfunction and post-traumatic epilepsy. These consequences arise months to years after the initial injury, and are thought to be a product of secondary damage, including thalamic inflammation and neuronal death. Using mouse models of traumatic brain injury and stroke to the somatosensory, motor, visual, and prefrontal cortices, coupled with immunohistochemistry, we found that the glutamatergic relay and GABAergic reticular thalamic nuclei that exhibited the highest levels of gliotic markers Iba1 and GFAP were those that were functionally connected with the injured cortex. For example, injury to the primary visual cortex led to selective gliosis and neuronal loss in the ipsilateral visual thalamus. Further, we found that sensory (i.e. somatosensory and visual) corticothalamic regions were more vulnerable to gliosis and neuronal loss compared to non-sensory circuits (i.e. prefrontal and motor), and that first order thalamic nuclei were more vulnerable to secondary injury than higher order thalamic nuclei. Lastly, we investigated the role of C1q, the initiating protein of the classical complement cascade, in determining the intensity and spatial selectivity of thalamic damage using a mouse model of inducible microglia-specific C1q deletion. By elucidating how thalamic vulnerability depends on the site of cortical insult, we will be better poised to predict and treat long-term deficits that arise after stroke or traumatic brain injury.

Disclosures: D. Necula: None. **F.S. Cho:** None. **A. He:** None. **J. Paz:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.07

Topic: C.10. Brain Injury and Trauma

Support: Mayo Foundation
Ben-Dov Luminescence Foundation
Ed and Ethel Moore Alzheimer's Disease Research Program of Florida Department of Health
Rotary Coins for Alzheimer's Research Trust Fund
CureAlz Foundation

Goodman Family Foundation
NIH Grant NS084974

Title: Dysregulation of the inflammatory and vascular pathways in a porcine model of acute sepsis-like injury

Authors: K. C. OLNEY[1], C. DE AVILA DAL'BO[1], K. T. TODD[1], ***L. E. TALLANT**[1], J. D. BARNETT[1], K. A. GIBSON[1], P. HOTA[2], N. M. GADES[3], L. F. THOMAS[4], J. D. FRYER[1]; [1]Neurosci., [3]Epidemiology, [4]Nephrology, [2]Mayo Clin., Scottsdale, AZ

Abstract: Sepsis, the body's overwhelming response to infection, can lead to organ damage and death in affected individuals. The brain is frequently impacted by sepsis, and septic patients often experience an altered mental state (e.g. delirium). This impact can be long lasting in the form of chronic cognitive and behavioral impairments in survivors of sepsis. To profile transcriptional changes in brain and other tissues during the early stages of acute sepsis, we used a porcine model due to its large, gyrencephalic brain with abundant white matter that is more similar to humans compared to rodent models. We performed intravenous injections of lipopolysaccharide (n = 4), a component of bacterial cell walls commonly used to model inflammation due to sepsis, compared to saline controls (n = 6) in five-month-old female Yorkshire pigs (*Sus scrofa*). At approximately 5 hours following iv lipopolysaccharide, we collected blood, brain, and kidneys and performed bulk RNAseq. Our findings show massive upregulation of genes involved with the inflammatory response and cytokine storm, with a substantial number of genes and pathways conserved between brain and kidney as well as blood. Additionally, we observe many significant down-regulated genes, including down-regulation of occludin (*OCLN*) and other genes that are critical for maintenance of the blood-brain barrier. Furthermore, we profiled transcriptional changes at the isoform level and identified some specific isoform-level changes that were not detected using gene-level analysis. Our data in this porcine model reveals novel molecular pathways that could be targeted in order to better protect patients from the damage incurred in acute sepsis.

Disclosures: K.C. Olney: None. **C. de Avila Dal'Bo:** None. **K.T. Todd:** None. **L.E. Tallant:** None. **J.D. Barnett:** None. **K.A. Gibson:** None. **P. Hota:** None. **N.M. Gades:** None. **L.F. Thomas:** None. **J.D. Fryer:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.08

Topic: C.10. Brain Injury and Trauma

Support: National Institutes of Health, National Research Service Award T32 DA007097 from the National Institute on Drug Abuse
Minnesota Spinal Cord and Traumatic Brain Injury Research Grant Program

(Grant #128515 and #159891)
2019 CVM Resident & Graduate Student Research Grants

Title: Chronic morphine exposure following mild TBI induces a biphasic proinflammatory response to injury in mice

Authors: *N. L. EMMITT[1], V. D. KRISHNA[1], S. R. VAR[2], E. B. LARSON[3], G. BADGER[4], A. L. GRANDE[5], W. C. LOW[6], M. C. J. CHEERAN[4];
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Abstract: The rate of substance use disorder among those with a history of traumatic brain injury (TBI) is increased by 3-6x when compared to rates in the general population. The most vulnerable populations are adolescents in sports and deployed soldiers, who are highly likely to experience mild TBI. There is substantial evidence linking TBI to cocaine and alcohol use disorder through the inflammatory response, but the link between opiate use disorder and TBI is yet to be defined. Our lab has used controlled cortical impact TBI models to demonstrate macrophage infiltration in response to brain injury. To determine the impact of morphine on TBI-induced neuroinflammation, we utilized a mild TBI to assess temporal changes in proinflammatory immune responses with morphine exposure (5 mg/kg, s.c., bid) after injury. Mice received either sham or mild TBI injury, and then received either morphine or saline twice daily immediately following surgery up to 15 d post injury (pi). At 2, 6, and 14 dpi, they were subjected to a battery of behavioral assays to assess working memory, short term memory, and anxiety-like behavior. All injured mice increased anxiety-like behavior in the open field test at 2 dpi, however that response persisted for 14dpi in mice exposed to morphine after mild TBI. Immune cell phenotyping was performed at 1, 3, 7, and 15 dpi using flow cytometry. A biphasic infiltrating macrophage response was observed with increasing cell numbers in injured mice brains at 3 dpi, decreasing at 7 dpi, and increasing again at 15 dpi. A closer look at the cytokine and chemokine expression levels through rtPCR at 3 dpi shows increases in inflammatory markers in injured mice exposed to morphine. At 15 dpi, CD8 lymphocytes are increased in injured mice exposed to morphine, a cell population that has not previously been associated with immune response to mild TBI. Current studies are underway to investigate changes in blood brain barrier integrity, location of the inflammatory cells in the brain, and phagocytic activity of infiltrating macrophages. Overall, this present study demonstrates a biphasic proinflammatory response to mild TBI that is only present after morphine exposure. Understanding how the immune response is impacted by morphine exposure can shed light on how mild TBI is linked to increased risk of substance use disorder.

Disclosures: N.L. Emmitt: None. **V.D. Krishna:** None. **S.R. Var:** None. **E.B. Larson:** None. **G. Badger:** None. **A.L. Grande:** None. **W.C. Low:** None. **M.C.J. Cheeran:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.09

Topic: C.10. Brain Injury and Trauma

Support: Department of Defense W81XWH-19-1-0732
NINDS P30-NS045758

Title: Sleep Fragmentation Induces Time-Dependent Effects on Sleep, Behavioral, and Inflammatory Recovery from Traumatic Brain Injury

Authors: *S. HOULE[1], Z. M. TAPP[2], Z. R. ZIMOMRA[4], C. J. COTTER[5], Y. REYES[4], S. AHSAN[4], S. DOBRES[4], J. MITSCH[4], R. ROWE[6], J. LIFSHITZ[7], J. F. SHERIDAN[3], J. P. GODBOUT[8], O. KOKIKO-COCHRAN[2];
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Abstract: Traumatic brain injury (TBI) causes a prolonged inflammatory response in the CNS that can be exacerbated by subsequent stress. Sleep fragmentation (SF) is a common physiological consequence of stress, which is highly reported in TBI survivors. We hypothesize that SF stress exaggerates TBI-induced sleep/wake deficits and cognitive impairment with long-lasting neuroinflammatory effects. Here, 10 week-old, mice received either a moderate lateral fluid percussion TBI or a control sham injury. Half of the mice were exposed to automated, mechanical SF (5am-10am) and the other half were placed in control housing and left undisturbed for 14 days post-injury (DPI). At 14 DPI SF ended and all mice were allowed to recover for an additional 16 days. Primary outcome measures included the quantity and quality of sleep/wake behavior, which was constantly measured in all groups for 30 DPI, cognitive function (7, 14, 27 DPI), and cortical gene expression changes (30DPI). Contrary to what we expected, TBI did not induce chronic deficits in sleep. However, SF influenced sleep regulation regardless of injury. The length of mouse sleep bouts depends on proper regulation of sleep and arousal. Mice exposed to SF slept more than those in control housing through 7 DPI while having no difference in the length of their sleep bouts. Therefore, SF increases total sleep but does not affect the CNS' ability to regulate sleep bout length during the active SF period. Once mice are allowed to recover from SF, percent sleep was comparable between all mice 15-30 DPI. However, after two weeks of SF, increased sleep bout lengths are detected, and these changes persist even after animals are no longer exposed to SF. Post-TBI SF induced spatial learning and memory deficits in the Morris water maze (MWM) at subacute time points (14DPI) that were not otherwise observed in TBI animals. Mice that received both TBI and SF had significantly longer escape latencies. Additionally, inflammation (Spi1, Abca1, Itga7), neurodegeneration (Abca1, Atg2b), and immunometabolic (Abca1, Lpl) genes were altered by post-TBISF and remain altered even at delayed time points following a period of recovery. Canonical pathway analysis several pathways were significantly increased by the combination of TBI and SF. These included the complement cascade (C1Qa/b/c, C1s, C3AaR1, C4a/c) as well as genes involved in the production of nitric oxide and reactive oxygen species in macrophages (Akt1, Apoe, Lyz, Prkce,

Spi1). Together, these results indicate that the injured brain may be susceptible to aberrant immune activation following SF stress, which can then lead to dysregulated sleep bouts, behavioral deficits, and cellular pathology.

Disclosures: **S. Houle:** None. **Z.M. Tapp:** None. **Z.R. Zimomra:** None. **C.J. Cotter:** None. **Y. Reyes:** None. **S. Ahsan:** None. **S. Dobres:** None. **J. Mitsch:** None. **R. Rowe:** None. **J. Lifshitz:** None. **J.F. Sheridan:** None. **J.P. Godbout:** None. **O. Kokiko-Cochran:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.10

Topic: C.10. Brain Injury and Trauma

Support: MOST Grant 110-2320-B-038-055

Title: Ccl5 Protects Cortical Neuron Function by Regulating M2 Microglia Activation after Mild Traumatic Brain Injury

Authors: *S.-Y. CHOU[1], M.-H. HO[1], Y.-H. CHIANG[2], B. J. HOFFER[3];
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Abstract: Background: Cytokines and chemokines play important roles in inflammation and repairment following traumatic brain injury (TBI). After TBI, activating M1-like microglia releases proinflammatory cytokines to promote neuroinflammation, increase oxidative stress and cause neurons degeneration. M2-like microglia shows anti-inflammation function by releasing anti-inflammation molecules and activating repair system to protect neurons survival. Chemokine C-C Motif Chemokine Ligand 5 (CCL5 also called RANTES) increased after TBI shows a neuroprotective function by reducing oxidative stress. CCL5 might contribute to the balance of oxidative stress and immune response after brain injury. Herein, we like to investigate the role of CCL5 in microglia polarization after mild TBI. Methods: C57BL/6 (wildtype, WT) mouse and CCL5 knockout (CCL5-KO) mouse were induced mild TBI by weight-drop model. Neurological function as motor and sensory functions were analyzed by mNSS score, rotarod, beam walking, and adhesive removal test. The oxidative stress and neuron damage was detected by NADPH oxidase activity and immunostaining of Hypoxyloprobe and FJC. The activation of antioxidants and chemokines was analyzed by western bolt and RT-qPCR. Recombinant CCL5 was delivered into CCL5-KO mice brains through intranasal to perform rescue experiment. Microglia cell line- BV2 was treated with H2O2 and CCL5 to mimic oxidative stress and CCL5 effects. Results: The performance of motor and sensory function in both WT and CCL5-KO mice were reduced after brain injury which were recovered after 7 days post-injury (dpi) in WT group but 14 days in CCL5-KO mice group. Pro-inflammation cytokines - IL-1β, TNF-α, and IL-

6 was higher in CCL5-KO mice comparing WT mice at 4 & 14 dpi. On the contrary, M2-like microglia markers - IL-10 and Arg-1 were increased in WT mice cortical tissue at 4 dpi. An intranasal (i.n.) delivery of CCL5 reduced neuronal oxidative stress, increase IL-10 expression and rescued the motor and sensory dysfunctions in CCL5-KO after mild TBI. CCL5 treatment increased IL-10 and Agr-1 mRNA in BV2 cells.Conclusion:In summary, CCL5 has an important function in regulating M2-like microglia polarization during post-injury days 4-7 which alters immune response and protects neurons from oxidative stress.

Disclosures: S. Chou: None. **M. Ho:** None. **Y. Chiang:** None. **B.J. Hoffer:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.11

Topic: C.10. Brain Injury and Trauma

Support: Purdue University
State of Indiana

Title: Characterization of neurodegeneration, inflammation, and oxidative stress in a novel mouse blast injury model.

Authors: *Z. ZHANG[1], S. SUN[2], T. B. BEAUCLAIR[1], R. SHI[3];
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Abstract: Characterization of neurodegeneration, inflammation, and oxidative stress in a novel mouse blast injury model.Authors*Zaiyang Zhang, Siyuan Sun, Timothy Brock Beauclair, Riyi Shi; Purdue University, West Lafayette, USA**Disclosures**None.**Abstract**
Veterans and war zone civilians suffer from post-traumatic stress disorders (PTSD) and neurodegenerative diseases such as Alzheimer's diseases, Parkinson's diseases, and other related neurological disorders after repeated blast-induced traumatic brain injury (bTBI). However, little is known about the cellular and molecular mechanism leading to post-TBI chronic neurodegenerative diseases. As such, there is currently no biomarker for reliable diagnosis, prognosis, and no therapy for effective treatment. In this study, we have characterized the regional accumulation of acrolein, an established marker of oxidative stress, at the acute stage (1 day) for mice that underwent bTBIs using a novel shock-tube model. In addition, we performed multiplex cytokines immunoassay using whole brain lysates of the injured mice and noticed changes in inflammatory cytokines. Astrocytes and microglia activation at the subacute stage (7 days) were also quantified along with acrolein adducts accumulation, in regions including the cortex, hippocampus, and amygdala. We have found an elevation of oxidative stress, inflammation, glial activation, and other indicators of neurodegeneration, as well as abnormal behavior among the blast-injured mice. Our findings have provided new insights into the

mechanism of bTBI in rodent and possible interaction and synergistic effect of oxidative stress and inflammation in both neuronal and glial cells, all contributing to the progression of blast-related neurodegeneration and functional deficits.

Disclosures: Z. Zhang: None. **S. Sun:** None. **T.B. Beauclair:** None. **R. Shi:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.12

Topic: C.10. Brain Injury and Trauma

Support: NJCBIR19PIL010

Title: Mechanisms of formation of neutrophil extracellular trap in traumatic brain injury: neuroprotection using antagonistic peptides

Authors: M. R. PREETHA RANI, B. B. SAIKIA, S. BHOWMICK, ***P. M. ABDUL-MUNEER**;
Neurosci., Hackensack Meridian Hlth. JFK Univ. Med. Ctr., Edison, NJ

Abstract: Traumatic brain injury (TBI) is one of the primary causes of death and long-term disability worldwide. It causes blood-brain barrier (BBB) dysfunction and transmigration of inflammatory blood cells into the brain, an important mechanism underlying neurovascular damage and neuroinflammation. In TBI, BBB dysfunction promotes neutrophil transmigration and accumulation in the brain. Activation of neutrophils causes the release of nuclear and granular contents to form an extensive web-like structure of DNA called the neutrophil extracellular trap (NET). NETs contain double-stranded DNA, histone, and granule proteins including neutrophil elastase, cathepsin G, and myeloperoxidase (MPO). In this study, we demonstrated the mechanisms of NET formation and its role in the pathophysiology of TBI. Using peptidyl arginine deiminase type 4 (PAD4) KO mice (*PAD4*$^{-/-}$) and PAD4 deletion by CRISPR/Cas9 in hBMVECs and human neutrophil co-culture *in vitro*, we validated the role of PAD4 in the formation of NET and its role in histone citrullination, chromatin decondensation, and NET fiber expulsion. Further, we used a cohort of behavioral tests that include cognitive and sensorimotor functions, and psychological stress analyses to validate the role of NET in functional deficits following TBI. Therefore, we target a subset of events towards unraveling a larger picture of the NET formation and its impact on the pathogenesis of TBI. Thus NETs can be developed as a therapeutic target to constrain the pathophysiology of TBI for neurological remodeling and functional recovery to achieve optimal efficacy. Using a bioinformatics approach to define the conserved functional elements within the sequence of PAD4, we have designed four small peptides to block the critical activity domain of PAD4 and demonstrated that systemic treatment of one of these antagonistic peptides attenuates the formation of NET and promotes functional recovery in a mouse model of TBI. We developed a unique therapeutic strategy using

a cell-penetrating PAD4 antagonistic peptide (PAP), which will alleviate TBI-associated formation of NET, and impairment of neovascularization *in vitro* in hBMVECs and *in vivo* in a mouse model of TBI. Therefore, in this highly significant study, we will uncover novel molecular mechanisms of TBI-induced neurological deficits due to the formation of NET and develop a therapeutic strategy for TBI targeting NET formation.

Disclosures: M.R. Preetha Rani: None. **B.B. Saikia:** None. **S. Bhowmick:** None. **P.M. Abdul-Muneer:** None.

Poster

708. Brain Injury: Inflammation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 708.13

Topic: C.10. Brain Injury and Trauma

Support: R01AG068168
R56NS112207
R21NS102991

Title: Mesenchymal stem cell extracellular vesicles improve motor function, reduce inflammation and increase repair following cortical injury in the rhesus monkey

Authors: *R. P. MCCANN[1], K. M. NIST[2], Y. ZHOU[2], C. A. MOJICA[2], E. ZELDICH[2], H. XIN[3], M. MEDALLA[2], D. L. ROSENE[2], T. L. MOORE[2];
[1]Grad. Program For Neurosci., [2]Anat. & Neurobio., Boston Univ. Sch. of Med., Boston, MA; [3]Henry Ford Hlth. Syst., Detroit, MI

Abstract: In the aged population, cortical injury is a leading cause of functional disability. Due to a dearth of drug discovery, there is a critical need for interventions. Our previous work in a rhesus monkey model of cortical injury demonstrated that systemic treatment with mesenchymal stem cell extracellular vesicles (MSC-EVs) facilitated full functional motor recovery in 3-4 weeks post-injury. At 16 weeks there was a treatment-associated reduction in neuronal damage and increase in myelin repair. Temporal changes that occur with treatment are important in evaluating therapeutics, however these are largely unknown in the monkeys. Did MSC-EVs facilitate recovery through damage prevention, or through enhancing repair in chronic recovery? Considering this, we utilized a cohort with 6-week survival post-op to assess earlier recovery. We hypothesized that MSC-EVs play an immunomodulatory and regenerative role early, at the time of functional recovery. Eight middle aged female monkeys were trained to complete a fine hand motor function task. A lesion was then made in the dominant hand-representation of the primary motor cortex to produce cortical injury identical to the original study. 4 monkeys received MSC-EVs and 4 received a vehicle at 24 hours and 14 days following injury and completed post-injury testing. CSF and plasma were collected every two weeks through the post-op survival period for examination of inflammation and neuronal damage biomarkers. After 4

weeks of motor testing post-treatment to assess recovery, brain tissue was harvested. This cohort demonstrated a similar rate and pattern of recovery as the monkeys in the previous study. ELISA quantification of myelin basic protein levels as a biomarker for neuronal damage in CSF showed a peak 24 hours to 28 days post-injury, which was prolonged in vehicle treated monkeys. In preliminary experiments using Olink→ inflammation panel to assess cytokine levels in plasma, we found that EV treatment was associated with lower levels of pro-inflammatory markers such as TNF and IL-6 at 14 days following lesion. As an assessment of brain repair and plasticity, real time quantitative polymerase chain reaction (qPCR) was performed on fresh frozen brain tissue from the perilesional motor cortex to examine the expression of myelin genes. Treated monkeys had increases in myelin transcripts, suggesting a pro-myelination environment. Our current findings recapitulate the behavioral outcome of our previous study and demonstrate that MSC-EV treatment lowers levels of damage and inflammation at early points of recovery and increases markers of myelination, underscoring the potential of MSC-EVs as a cortical injury therapeutic.

Disclosures: **R.P. McCann:** None. **K.M. Nist:** None. **Y. Zhou:** None. **C.A. Mojica:** None. **E. Zeldich:** None. **H. Xin:** None. **M. Medalla:** None. **D.L. Rosene:** None. **T.L. Moore:** None.

Poster

709. Traumatic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 709.01

Topic: C.10. Brain Injury and Trauma

Support: F32 NS116205
R01-NS117757

Title: Investigating immune system dysregulation following closed-head diffuse traumatic brain injury in swine

Authors: *K. L. WOFFORD[1], K. D. BROWNE[1], D. CULLEN[2];
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Abstract: The central nervous system (CNS) regulates the peripheral immune system and maintains a homeostatic balance. Indeed, during an infection, the brain counters mounting inflammatory cascades by inducing immunodepressive or anti-inflammatory signals in the body, thereby helping the body return to a healthy homeostasis. However, following a traumatic brain injury (TBI), the brain becomes flooded with inflammatory signals, disrupting the communication and balance between the CNS and the peripheral immune system. Indeed, CNS injury-induced immunodepression (CIDS) is a leading cause of death following severe TBI. However, the specific immunological consequences of TBI have yet to be investigated in a clinically relevant model of brain injury. Here, we employed a highly translational preclinical model of diffuse closed-head brain injury in swine to characterize changes to the peripheral immune system over time. We hypothesized that following a moderate-to-severe closed-head

TBI, the immune system would exhibit hypersensitivity at acute timepoints and immunodepression at more chronic timepoints. To test this hypothesis, we collected peripheral whole blood from seven female Yucatan mini pigs prior to a sham (n=3) or a moderate-to-severe closed-head diffuse TBI (n=4). Following injury or sham procedure, whole blood was drawn 1- and 6-hours after injury as well as 1, 3-, 7-, 10-, and 14-days post injury. A Ficoll gradient was utilized to collect peripheral blood mononuclear cells (PBMCs) and plasma. Plasma protein concentration was quantified with a porcine protein multiplex array. PBMCs were stained and assessed with flow cytometry to quantify the cell population composition, reactive oxygen species production after an inflammatory challenge, and phagocytic reactivity after an inflammatory challenge. Relative to pre-injury baseline levels, the pro-inflammatory cytokine, interleukin-6, was significantly downregulated 14 days after injury. Interestingly, we observed a significant increase in the number of PBMCs collected 3 and 10 days post injury relative to pre-injury levels. We found no significant differences in reactive oxygen species production at any timepoint after TBI. Within the phagocytosis assays, we observed a significant increase in phagocytic uptake at later timepoints which was dependent upon the type of phagocytic target. Together, these data suggest that changes to the immune system are more pronounced over 3-10 days post-TBI as compared to the first 24 hours. Future studies will aim to learn how the damaged immune system contributes to neuropathology and secondary injury after TBI.

Disclosures: **K.L. Wofford:** None. **K.D. Browne:** None. **D. Cullen:** None.

Poster

709. Traumatic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 709.02

Topic: C.10. Brain Injury and Trauma

Title: Neurogenic Regions in Adult Porcine TBI Models are Differentially Affected by Injury Type and Severity: A Comparative Immunohistochemistry Study

Authors: *H. A. GAUDIO[1], R. E. DEGANI[1], S.-H. KAO[1], M. M. HEFTI[2], K. D. BROWNE[3], T. J. KILBAUGH[1];
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Abstract: Little is understood about the differential effect of traumatic brain injury on the neurogenic regions (subventricular zone and dentate gyrus) of the brain based on injury type, injury severity, and gender. Therefore, we conducted a comprehensive pathological analysis on these neurogenic regions in a rotational injury model that results in diffuse axonal injury and a controlled cortical impact (CCI) injury model that results in focal lesions and subdural hematoma. Thirty-six swine, weighing ~30kg, either received a TBI or were designated as a sham animal that received no injury. The CCI injury group contained both mild (5.5-6.5mm, 4

males, 4 females) and moderately (8-9mm, 4 males, 4 females) injured animals. The rotational injury group also contained mild (85-100rad/s, 4 males, 4 females) and moderately (100-115rad/s, 4 males, 4 females) injured animals. The sham group was comprised of 2 males and 2 females. Formalin-fixed, paraffin-embedded, 8µ thick coronal sections of brain tissue were collected from surviving animals 14 days after injury/sham procedure. Immunohistochemistry was performed on sections containing lateral ventricles and the temporal lobe to capture the neurogenic regions of interest. Protocols were designed to achieve the following goals in relation to the subventricular zone and dentate gyrus: assess proliferation and migration of doublecortin (DCX) positive cells (developing neurons), quantify beta-amyloid precursor protein (βAPP) positivity (axonal injury), classify astrogliosis through mapping of glial fibrillary acidic protein (GFAP) positive cells, assess microglial activity using ionized calcium binding adaptor molecule 1 (Iba1) in relation to the level of disturbance of the blood-brain barrier, annotated by fibrinogen staining and the vasculature. Early findings include an abundance of βAPP positive cells in the subventricular zone in animals that received a rotational injury, but minimal positive staining in the same region for both CCI injured and sham animals. Additionally, DCX positive cells migrating towards the outer layers of the subventricular zone in CCI injured animals are sparse and distributed compared with rotationally injured animals. Significant glial scarring is present at 14 days post-injury; however, astrogliosis mapping and microglial activity analysis is still ongoing. This will be the first comparative porcine study of its kind, serving as the foundation for further study into the dynamic effects of TBI on the brain's neurogenic regions.

Disclosures: H.A. Gaudio: None. **R.E. Degani:** None. **S. Kao:** None. **M.M. Hefti:** None. **K.D. Browne:** None. **T.J. Kilbaugh:** None.

Poster

709. Traumatic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 709.03

Topic: C.10. Brain Injury and Trauma

Support: the United States (U.S.) Department of Veterans Affairs Rehabilitation Research and Development Service (RR&D), Merit Review Award # 1 I01 RX003123-01A1

Title: Activated NF-kB signaling pathway, neuroinflammation, and gliosis in the vestibular nuclei following closed-head traumatic brain injury (cTBI) in rats

Authors: *S. TSUDA[1,2], J. HOU[1,2], B. W. RENGERT[1], G. M. DOOLEY[1], H. C. SHROCK[1], A. M. HEATH[1], D. PLANT[1], F. J. THOMPSON[1,3], P. BOSE[1,2,4];
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Abstract: Every year, a huge number of people suffer from TBI-induced disabilities including balance deficit. Unfortunately, the precise pathological mechanisms for this disability are not well understood. Since cTBI is known to cause neuroinflammation in the brain and vestibular neurons play major roles in maintaining the balance, one of the possible causes of TBI-induced balance disability is inflammation of vestibular neurons. However, few studies have examined the impact of cTBI on neuroinflammation in the vestibular nuclei (VN). The purpose of this study was to investigate the impact of cTBI on the major inflammatory signaling pathway and cytokine induction as well as their associations with gliosis in the rat VN. Female Sprague Dawley rats weighing 235-260g were randomly assigned into the normal and cTBI groups. For the cTBI group, a mild-to-moderate cTBI was induced using the Marmarou weight-drop model of TBI with a slight modification. Following anesthesia, a 450-g brass weight was dropped from 1.25-m height onto the dorsal surface of the skull of each animal. Eighteen weeks later, all animals were perfused with phosphate buffered saline via the left ventricle under deep anesthesia, followed by 4% paraformaldehyde in phosphate buffer. The brains of animals were sectioned coronally in 40 μm thickness and incubated with primary antibodies against neuronal nuclei, toll-like receptor 4 (TLR-4), phosphorylated inhibitor of kappa B alpha (p-IκBα), phosphorylated nuclear factor kappa B (p-NF-κB, p65 phosphorylated at serine 536 or p-p65), tumor necrosis factor alpha (TNFα), glial fibrillary acidic protein (GFAP), and integrin alpha M (IntαM). These brain sections were further immnofluorescently labelled with appropriate secondary antibodies. Then, pictures of triple immnofluorescent staining were taken by a confocal microscope (LSM 710, Carl Zeiss). Our results showed that cTBI elevated the expressions of TLR-4 and p-IκBα in the neurons of both the lateral and the spinal VN although their expressions in the neurons were undetectable in the VN of normal animals. However, the expressions of activated NF-κB (p-p65) and TNFα were higher than those of TLR-4 and p-IκBα in the VN after cTBI. Interestingly, the neurons with high expressions of TNFα were completely surrounded by GFAP-positive astrocytes and IntαM-positive microglia. These results demonstrate that cTBI promotes the activation of the TLR-4/NF-κB signaling pathway, cytokine induction, and gliosis in the vestibular neurons. These cTBI-induced detrimental neurobiological consequences in the VN might be associated with cTBI-induced balance disability.

Disclosures: S. Tsuda: None. **J. Hou:** None. **B.W. Rengert:** None. **G.M. Dooley:** None. **H.C. Shrock:** None. **A.M. Heath:** None. **D. Plant:** None. **F.J. Thompson:** None. **P. Bose:** None.

Poster

709. Traumatic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 709.04

Topic: C.10. Brain Injury and Trauma

Support: NSF EAGER

Title: Identification of novel protein biomarkers encapsulated within extracellular vesicles for the detection of moderate traumatic brain injury.

Authors: *T. TANG[1], Y. ZHAO[2], S. H. BOSSMANN[5], M. MOTAMEDI[3], B. SZCZESNY[4]; [1]Univ. Of Texas Med. Branch, Galv Neurosci. Grad. Program, Galveston, TX; [2]Intrnl. Med., [3]Ophthalmology and Visual Sci., [4]Anesthesiol., Univ. of Texas Med. Br., Galveston, TX; [5]Cancer Biol., Univ. of Kansas Med. Ctr., Kansas City, KS

Abstract: In 2019, traumatic brain injury (TBI) and its associated effects contributed to approximately 155 deaths/day in the United States. The current diagnosis of TBI via Glasgow Coma Scale and imaging tests (CT, MRI) are both time consuming and require specialized equipment that may not be available in resource-challenged environments. Thus, there is an urgent need to develop a non-specialized, accurate and cost-effective method of detecting and evaluating TBI. In this study, we propose cell-free DNA of mitochondrial origin (cf-mtDNA) and brain-specific proteins encapsulated within extracellular vesicles (EVs) in circulating blood plasma represent a novel class of biomarkers for the detection of moderate TBI. We subjected 8-10-week-old wild-type C57BL6 male mice to moderate TBI using the closed head weight drop model followed by isolation of blood plasma via cardiac puncture at 5 points post injury: 3 h, 12 h, 24 h, 3 days, and 10 days. Samples underwent differential centrifugation to remove debris and EVs were isolated by ultracentrifugation at 150,000 x g for 3 h. Western blotting analysis revealed the presence of cell-specific markers for neurons (NFL), microglia (IBA1), and astrocytes (S100β) concurrently with EVs (CD63). Furthermore, we characterized the concentration and size distribution of EVs across all time points by Nanoparticle Tracking Analysis (NTA). We discovered a significant -8x fold decrease in EV concentration at 12 h post TBI compared to sham (8.17 x 10E9 vs. 8.82 x 10E8 per mL, Student's t-test, alpha= 0.05 p= 1.81E-07); this dramatic drop in number correlated with an increase in both the average mean (85.83 vs. 133.34 nm per mL, Student's t-test, alpha= 0.05, p= 1.08E-10) and mode (74.46 vs. 103.67 nm per mL, Student's t-test, alpha= 0.05, p= 7.53E-06) size distributions of EVs at the same time point, suggesting a possible switch of EV species from exosomes to small microvesicles. Global proteomic analysis on isolated plasma EVs resulted in a number of novel protein biomarkers that are both up- and downregulated across various time points. Finally, we confirmed the presence of mitochondrial DNA (mtDNA), but not nuclear DNA (nucDNA), within EV's to be elevated in TBI samples compared to controls. Our results suggest that circulating cf-mtDNA, along with time specific post-TBI protein biomarkers could potentially serve as diagnostic targets for detecting moderate TBI. Our end goal is to translate this technology to a clinical setting with a mobile, hand-held device that can be used anywhere for rapid diagnosis of TBI.

Disclosures: T. Tang: None. **Y. Zhao:** None. **S.H. Bossmann:** None. **M. Motamedi:** None. **B. Szczesny:** None.

Poster

709. Traumatic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 709.05

Topic: C.10. Brain Injury and Trauma

Support: Biomedical Laboratory Research and Development CDA2 (5IK2BX004349)
Alzheimer's Association (NIRG-305779, NIRG-362697)
National Institute of Aging (RF1AG054156, RF1AG057768, K23AG046377, U19AG068753, AG08122, AG054076, F31NS127449)
National Institute of Neurological Disorders and Stroke (U54NS115266, U01NS086659, K23NS102399, F31NS127449)
National Institute of Aging Boston University AD Center (P30AG072978)
National Heart, Lung and Blood Institute (75N92019D00031 and HHSN2682015000011)
Department of Defense Peer Reviewed Alzheimer's Research Program (PRARP #13267017)

Title: Increased Angiogenic Mediators and Cortical Vascularity in Chronic Traumatic Encephalopathy

Authors: *D. KIRSCH[1,3,2], G. ROSEN[2,3], J. CHERRY[1,3,2], B. R. HUBER[3,2], V. E. ALVAREZ[2,3,4], A. C. MCKEE[1,2,3,4], T. D. STEIN[3,1,2,4];
[1]Dept. of Pathology and Lab. Med., [2]Chronic Traumatic Encephalopathy Ctr., Boston Univ. Sch. of Med., Boston, MA; [3]Boston VA Healthcare Syst., Boston, MA; [4]Bedford VA Healthcare Syst., Bedford, MA

Abstract: Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease linked with repetitive head impact (RHI) exposure and characterized by accumulation of hyperphosphorylated tau (p-tau) at the depths of the cortical sulci. Impact forces sustained during RHI lead to neuroinflammation and microvascular damage, which may lead to dysregulated angiogenesis. Microvascular abnormalities are frequently observed in CTE, especially in regions prone to p-tau deposition, but the mechanism underlying vascular changes is not well understood. To address this, we examined the dorsolateral frontal cortex (DLF) from postmortem brain donors, a region associated with early and progressing CTE pathology. We performed quantitative immunoassay for vascular endothelial growth factor (VEGF) A, C, and D, fibroblast growth factor (FGF), placental growth factor (PIGF), VEGF receptor-1 (Flt1), and angiopoietin-1 receptor (Tie2) with DLF tissue from participants with CTE (Low stage, n = 22, High stage n = 46) and RHI-exposed (n = 28) and -naïve controls (n = 38), all without comorbid neuropathological or vascular disease. Immunohistochemistry and histological area quantification with HALO software was used to assess vascular (CD105), microglial (Iba1 and CD68), and p-tau (AT8) staining density. Significant between-group differences were determined by analysis of covariance and associations were determined by multiple linear regression, both adjusting for age. CTE and RHI-exposed groups had increased levels of VEGF-C, VEGF-D, FGF, Tie2, Flt1, and PIGF compared to RHI-naïve controls. Vascular density in the DLF sulcus was increased in High CTE compared to Low CTE and controls and increased in Low CTE and RHI-exposed controls compared to -naïve controls. RHI exposure duration was positively associated with Tie2, Flt1, and PIGF levels and negatively with VEGF-C and FGF levels. Microglial density positively correlated to VEGF-D, Tie2, Flt1, and PIGF levels and negatively correlated to VEGF-A levels. Flt1 levels were associated with increased p-tau staining in the DLF sulcus. Taken together, these results suggest that neoangiogenic processes begin before development of p-tau pathology in CTE and are related to RHI exposure. Chronically elevated angiogenic factors may further neuroinflammation and increased vascularity, which

may promote formation of CTE p-tau pathology. CTE currently lacks validated treatments, but neoangiogenesis and increased vascularity may be potential diagnostic biomarkers and therapeutic targets.

Disclosures: D. Kirsch: None. **G. Rosen:** None. **J. Cherry:** None. **B.R. Huber:** None. **V.E. Alvarez:** None. **A.C. McKee:** None. **T.D. Stein:** None.

Poster

709. Traumatic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 709.06

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R01NS100793
Valley Research Partnership VRP2256030
Arizona Biomedical Research Commission ADHS14-00003606
Phoenix Children's Hospital Mission Support

Title: Traumatic Brain Injury Induces Regional Hypothalamic-Pituitary-Adrenal Axis Dysregulation in Rats

Authors: *C. HAIR[1,2,3], A. SATINSKY[1], E. MIAN[1,2], G. KRISHNA[1,2], P. ADELSON[1,2], T. THOMAS[1,2,3,4];
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Abstract: Each year, 2.8 million traumatic brain injuries (TBI) are reported in the United States, of which over 75% are mild TBIs associated with diffuse axonal injury (DAI). TBI is associated with increases in circulating glucocorticoid levels released from the HPA axis, which, along with DAI, is responsible for feedback dysregulation and post-injury affective symptoms. Post-injury affective symptoms in both sexes typically evolve beyond 2 weeks post-injury, however, few preclinical studies, have evaluated the etiology underlying late-onset affective symptoms after mild TBI, and none included females. Our previous studies showed 60% less baseline corticosterone at 56 days post injury (DPI) with no evidence of neuropathology in the hypothalamus at 7- and 28DPI in male rats, demonstrating neuronal degeneration is likely not the cause. We hypothesized that axonal damage in feedback relays of the HPA axis and changes in glucocorticoid receptors (GR) help mediate glial-driven neuroinflammation in rats subjected to midline fluid percussion brain injury. To test the hypothesis, DAI was induced in young adult male and naturally cycling female Sprague Dawley rats using midline fluid percussion injury (5-10 per sex/timepoint). GR protein levels and gliosis were evaluated in the hippocampus, hypothalamus, and amygdala at 7 and 56DPI. In the paraventricular nucleus of the hypothalamus microglial response at 7DPI indicated mild neuroinflammation in males compared to sex-

matched shams, but not females. Robust microglia activation in the dentate gyrus (DG) was found in both sexes compared with shams, with a significant interaction between sex and injury regarding microglial cell count. GFAP intensity and astrocyte numbers also increased as a function of injury indicative of astrocytosis at 7DPI. Along with robust gliosis in the DG, GR protein were elevated in females by 30%, but not in males. In the amygdala, microglia processes increased at 7DPI in males. When sexes were consolidated, processes significantly increased in sham rodents from 7 to 56DPI. There was a 35% decrease in GR protein in males at 7DPI and GR levels in male shams were 27% greater than GR levels in female shams in the amygdala. Taken together, these data indicate neuroinflammation and GR protein is still disrupted sub-acutely and GR could serve as a biomarker for feedback regulation progression within the HPA axis.

Disclosures: C. Hair: None. **A. Satinsky:** None. **E. Mian:** None. **G. Krishna:** None. **P. Adelson:** None. **T. Thomas:** None.

Poster

709. Traumatic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 709.07

Topic: C.10. Brain Injury and Trauma

Support: CIHR FDN 143337

Title: A lateral head impact model for mouse studies on hypothalamic dysfunction associated with traumatic brain injury

Authors: *J. O'REILLY, N. J. SIMPSON, Z. S. THIROUIN, P. A. BASTONE, C. W. BOURQUE;
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Abstract: Objective: The development of central autonomic and endocrine dysfunction after traumatic brain injury (TBI) is believed to involve the hypothalamus, but the underlying mechanisms are unknown. We developed a model of lateral head injury to study TBI-related dysautonomias in mice. Methods: C57Bl/6 male mice aged 2 to 4 months were lightly anesthetized with isoflurane and subjected to TBI using a Gothenburg Impactor (Collision Analysis Inc). This instrument was used to deliver a reproducible, calibrated blow to the side of the helmeted head of mice via a 50 g projectile launched at predetermined velocities (v). Mice treated the same way, but without the head impact served as controls (shams). Results: TBI caused increased righting times proportional to impact velocity, from 38 ± 11 s at v = 5 m/s (n = 3) to 358 ± 100 s at v = 11 m/s (n = 3). At v = 9 m/s, no mortality, skull fracture or external bleeding was observed and grimace scale score assessed 3 hours following TBI was 0 (n = 19). During the 7 days that followed TBI at v = 9 m/s, mice displayed a decrease in body weight of 10.7 ± 3.9% (n = 4). We examined c-Fos expression by immunohistochemistry in the

paraventricular nucleus (PVN), a key structure involved in diverse functions including osmoregulation, autonomic control, energy metabolism and thermoregulation. Our analysis revealed a significantly higher c-Fos nucleus density in the PVN of TBI mice (1.41 ± 1.14 nuclei/mm2, n = 6) compared to sham mice (0.57 ± 0.08 nuclei/mm2, n = 6, t(10) = -5.16, p = 0.0004). After TBI, c-Fos expression was significantly elevated in PVN oxytocin neurons (TBI: 18.69 ± 0.95% vs sham: 6.75 ± 0.87%; Mann-Whitney U = 0.00, p = 0.002) as well as in vasopressin neurons (TBI: 8.46 ± 0.71% vs sham: 3.82 ± 0.41% ; t(10) = -5.68, p = 0.0002). Conclusion: This model may be useful for studies on hypothalamic dysfunction associated with TBI.

Disclosures: J. O'Reilly: None. **N.J. Simpson:** None. **Z.S. Thirouin:** None. **P.A. Bastone:** None. **C.W. Bourque:** None.

Poster

709. Traumatic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 709.08

Topic: C.10. Brain Injury and Trauma

Support: NINDS/NIA Grant U54NS115266

Title: Multiplex immunofluorescent characterization of reactive astrocytes in repetitive head impacts and chronic traumatic encephalopathy

Authors: *K. BABCOCK[1], M. BUTLER[1], B. ABDOLMOHAMMADI[1], J. D. CHERRY[2], A. C. MCKEE[3], B. R. HUBER[4];
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Abstract: A history of repetitive head impacts (RHI), such as that which occurs in American football and military blast exposure, increases the risk for neurobehavioral and cognitive issues, and the neurodegenerative disease chronic traumatic encephalopathy (CTE). The biological mechanisms leading to the pathogenesis of CTE from RHI exposure are unknown, and no diagnostic or therapeutic strategies are currently available. Astrocytes are important mediators of post-traumatic injury processes and following trauma, undergo structural and functional changes in a process known as reactive astrogliosis. In the current study, we investigated reactive astrogliosis in the context of RHI and CTE. We analyzed postmortem brain tissue from former American football players and military veterans with and without CTE, and controls without head trauma exposure or a CTE diagnosis. Multiplex immunofluorescence was performed using different astrocyte reactivity markers such as GFAP, ALDH1L1, YKL-40, and AQP4, and quantified in distinct cortical compartments associated with concentration of mechanical forces upon head injury, including the grey-white matter interface, subpial surface, and perivascular region. Within the dorsolateral frontal cortex, astrogliosis was higher at the grey-white matter

interface, with mixed effects at the subpial surface and underlying cortex, in RHI donors with and without CTE compared to controls. These findings suggest that astrocytes become activated in regions of increased mechanical force following RHI which persists in CTE, and that regional heterogeneity is a feature of the reactive astrocytic response in repetitive, mild head trauma.

Disclosures: K. Babcock: None. **M. Butler:** None. **B. Abdolmohammadi:** None. **J.D. Cherry:** None. **A.C. McKee:** None. **B.R. Huber:** None.

Poster

709. Traumatic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 709.09

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS120628

Title: Involvement of Lateral Habenula Dysfunction in Repetitive Mild Traumatic Brain Injury-Induced Motivational Deficits

Authors: *W. FLERLAGE[1], L. LANGLOIS[2], M. RUSNAK[3], S. C. SIMMONS[3], S. GOUTY[2], R. ARMSTRONG[2], B. COX[2], A. J. SYMES[3], M. C. TSUDA[2], F. S. NUGENT[2];
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Abstract: Affective disorders including depression (characterized by reduced motivation, social withdrawal and anhedonia), anxiety and irritability are frequently reported as long-term consequences of mild traumatic brain injury (mTBI) in addition to cognitive deficits, suggesting a possible dysregulation within mood/motivational neural circuits. One of the important brain regions that control motivation and mood is the lateral habenula (LHb) whose hyperactivity is associated with depression. Here we used a repetitive closed head injury mTBI model that is associated with social deficits in adult male mice and explored the possible long-term alterations in LHb activity and motivated behavior 10-18 days post-injury. We found that mTBI increased the proportion of spontaneous tonically active LHb neurons yet decreased the proportion of LHb neurons displaying bursting activity. Additionally, mTBI diminished spontaneous glutamatergic and GABAergic synaptic activity onto LHb neurons, while synaptic excitation and inhibition (E/I) balance was shifted toward excitation through a greater suppression of GABAergic transmission. Behaviorally, mTBI increased the latency in grooming behavior in the sucrose splash test suggesting reduced self-care motivated behavior following mTBI. To show whether limiting LHb hyperactivity could restore motivational deficits in grooming behavior, we then tested the effects of Gi (hM4Di)-DREADD-mediated inhibition of LHb activity in the sucrose splash test. We found that chemogenetic inhibition of LHb glutamatergic neurons was sufficient to reverse mTBI-induced delays in grooming behavior. Overall, our study provides the first

evidence for persistent LHb neuronal dysfunction due to an altered synaptic integration as causal neural correlates of dysregulated motivational states by mTBI.

Disclosures: **W. Flerlage:** None. **L. Langlois:** None. **M. Rusnak:** None. **S.C. Simmons:** None. **S. Gouty:** None. **R. Armstrong:** None. **B. Cox:** None. **A.J. Symes:** None. **M.C. Tsuda:** None. **F.S. Nugent:** None.

Poster

709. Traumatic Injury

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 709.10

Topic: C.10. Brain Injury and Trauma

Support: NIH/CTSI # UL1TR002529

Title: Biomechanical and mechanistic investigations utilizing TBI-on-a-chip: connecting physical impacts to neurodegeneration

Authors: *E. A. ROGERS[1], T. B. BEAUCLAIR[1], T. DIORIO[1], J. MARTINEZ[2], S. J. MUFTI[1], J. CRODIAN[3], D. KIM[1], V. RAYZ[1], R. SHI[3];
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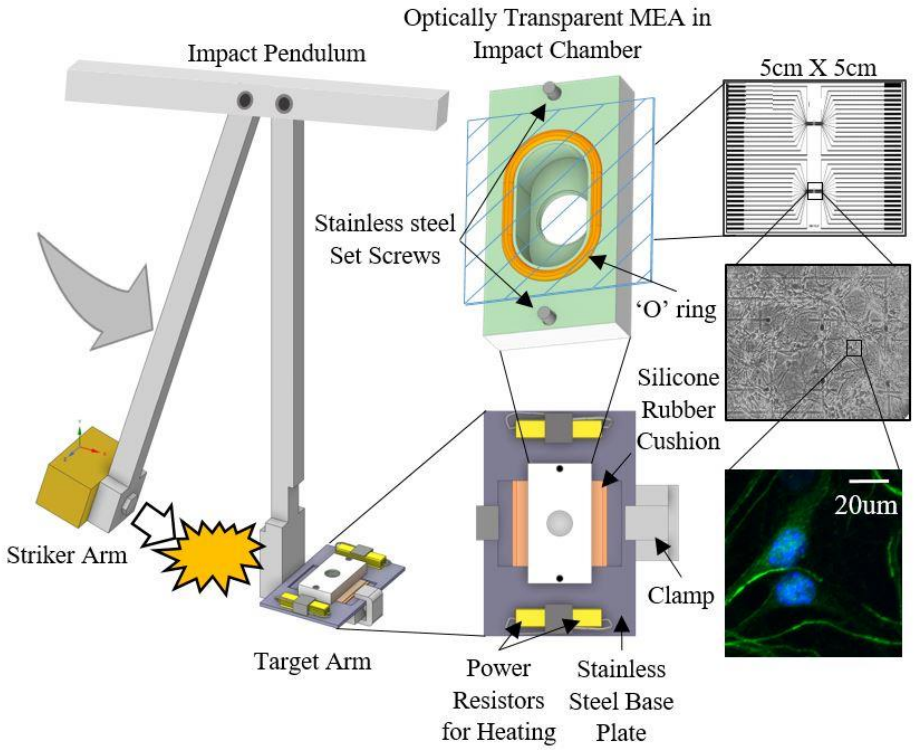
Abstract: The rapidly increasing prevalence of post-traumatic brain injury (TBI) long-term neurological sequelae is an alarming trend with profound societal consequences. Unfortunately, the associated underlying mechanisms remain elusive, hindering our ability to develop treatments and identify novel biomarkers for improved diagnosis. This is partly due to technological and physiological constraints: real-time access to the native cells of interest during a traumatic experience has not been feasible. In response, we have developed an in vitro model of trauma, capable of monitoring neuronal networks experiencing rapid acceleration injury, providing unprecedented electrophysiological and sub-cellular access for force induced injury investigations (Fig. 1). Utilizing acrolein, a clinically established biomarker of trauma and oxidative stress, we demonstrate the system's ability to separate mechanical (primary) and biochemical (secondary) injuries, while simultaneously evaluating comorbidities. In addition, through a series of exciting preliminary experiments we observe impact-induced inflammation and protein aggregation, further indicating the versatility of the system while providing a unique opportunity to investigate trauma-induced neurodegeneration in a controlled environment. Furthermore, we explore the biomechanics of the TBI-on-a-chip system utilizing a finite element model to describe shear stresses acting upon cells during impact-injury. By decomposing macroscale stress analyses into single-neuron resolution, we are able to better resolve the relationship between physical-stress and changes in aggregation, inflammation, and oxidative stress. Ultimately, it is our hope that this technology will improve our mechanistic understanding of both trauma and neurodegeneration, solo and in concert, while providing a semi high-throughput platform to investigate potential pharmaceutical interventions/treatments.



Disclosures: **E.A. Rogers:** None. **T.B. Beauclair:** None. **T. Diorio:** None. **J. Martinez:** None. **S.J. Mufti:** None. **J. Crodian:** None. **D. Kim:** None. **V. Rayz:** None. **R. Shi:** None.

Poster

710. Human Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 710.01

Topic: D.02. Somatosensation – Pain

Support: 1R21NS087472-01A1
1R01NS095937-01A1
1R01NS094306-01A1
W81XWH-14–1-0543

Title: The impact of COVID-19 pandemic-related disruptions on neuroinflammation in chronic pain patients

Authors: ***L. BRUSAFERRI**[1], P. C. KNIGHT[3], Z. ALSHELH[2], E. J. MORRISSEY[3], M. KIM[3], Y. ZHANG[3], D. S. ALBRECHT[4], A. TORRADO-CARAVAJAL[3], O. AKEJU[5], R. R. EDWARDS[6], V. NAPADOW[3], M. L. LOGGIA[7];

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Abstract: Background And Aims: Recently, we showed that, compared to subjects tested in pre-COVID-19 times, healthy volunteers examined after the onset of the pandemic exhibit higher levels of multiple (neuro)inflammation markers: IL-16 and MCP-1 (in the blood) and myo-Inositol (mIns) and TSPO PET signal (in the brain) (Brusaferri et al, Brain Behav. 2022). The latter was positively associated with physical/mental fatigue and mood alteration measures, demonstrating a possible link between pandemic-related stress and neuroimmune response. Here, we extend our investigation to patients with chronic low back pain (cLBP), a condition we have previously linked to neuroinflammation even pre-COVID (Loggia et al, Brain 2015). We assess the hypothesis that elevations in neuroinflammatory signals might be a mechanism underlying the exacerbation of symptom severity, which has been documented in chronic pain patients since the onset of the pandemic (e.g. Leite et al, Front Cell Neurosci, 2021).
Methods: 27 Pre-Pandemic cLBP patients [48.4 ± 15.4 years old (mean ± SD)] and 27 Pandemic patients (43.8 ± 16.1 years old), underwent PET/MRI imaging with the TSPO ligand ^{11}C-PBR28. Ala147Thr polymorphism, which predicts binding affinity (Owen et al, Clinical and Translational Imaging, 2015), was modeled as a covariate. Pandemic patients underwent COVID-19 antibody testing, and subjects resulting positive (n=3) were excluded in subanalyses, to ensure that neuroimmune responses to the virus wouldn't drive/confound our results. [^{11}C]PBR28 signal was compared across groups in voxel-wise analyses (FSL FEAT, cluster-forming threshold Z = 3.1; cluster size significance threshold P = 0.05). Groups were also compared in terms of pain (Brief Pain Inventory) and depression (Beck Depression Inventory) using a GLM (Statistica v.10).
Results:
The two groups did not statistically differ in terms of pain or depression (p=0.35). However, the Pandemic group showed increased [^{11}C]PBR28 within a cluster encompassing precentral/dorsolateral prefrontal cortex, and underlying white matter, overlapping a subset of the region demonstrating elevated TSPO signal in (Brusaferri et al, Brain Behav. 2022). Exclusion of patients with a history of COVID-19 exposure did not alter our results. No correlations were found between imaging and the clinical variables examined.
Conclusion:
Here, we replicated our observations linking pandemic-onset to neuroimmune activation in a different group, further supporting the solidity of the initial observation (Brusaferri et al, Brain Behav. 2022). Future investigations will be needed to understand the clinical implication of these observations.

Disclosures: L. Brusaferri: None. **P.C. Knight:** None. **Z. Alshelh:** None. **E.J. Morrissey:** None. **M. Kim:** None. **Y. Zhang:** None. **D.S. Albrecht:** None. **A. Torrado-Caravajal:** None. **O. Akeju:** None. **R.R. Edwards:** None. **V. Napadow:** None. **M.L. Loggia:** None.

Poster

710. Human Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 710.02

Topic: D.02. Somatosensation – Pain

Support: NIH R01-EB026439
NIH U24-NS109103
NIH U01-NS108916
NIH P41-EB018783
NIH R01-NS101013
NIH R01-CA203861
NIH R01-NS104500

Title: Brain-computer interface mediated reinforcement of frontal theta power leads to a reduction in perceived pain in chronic pain patients: a pilot study

Authors: *P. DEMAREST[1,2], N. RUSTAMOV[1,3], J. R. SWIFT[1,3], T. XIE[1,3], M. ADAMEK[1,3], H. CHO[1,3], E. WILSON[1,4], P. BRUNNER[1,3], S. HAROUTOUNIAN[1,4], E. C. LEUTHARDT[1,3]; [1]Div. of Neurotechnology, [2]McKelvey Sch. of Engin., [3]Dept. of Neurosurg., [4]Dept. of Anesthesiol., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: About 20% of the global population experience chronic pain, a physio-psychological disease that causes physical discomfort even in the absence of noxious stimuli. Despite considerable efforts, current pharmacological interventions often fail to achieve long-term relief from pain, creating a need for alternative approaches. Neuromodulation-based approaches for treating chronic pain present an attractive alternative to medication as they enable non-pharmacological modulation of central nervous system (CNS) electrophysiology. Neuromodulation in this context involves training participants to develop control over their CNS to decrease their pain perception. Recent evidence has demonstrated that frontal theta power (4-7 Hz) is modulated by pain perception, creating a compelling target for neuromodulation. Further studies have suggested that vibrotactile stimulation leads to decreased pain perception in experimental and clinical models and improves electrophysiological correlates of chronic pain. Building on these results, we propose a novel surface EEG-based vibrotactile brain-computer interface (BCI) system to treat chronic pain symptoms. In this pilot study, we have designed a BCI using visual and vibrotactile feedback to reinforce relative increases in frontal theta power. Here, we present the clinically relevant results of using this novel BCI system on five chronic pain patients. Patients received three 45-minute BCI training sessions weekly for five to six weeks. A real time signal-processing filter was used to compare frontal theta power to baseline values. Neurofeedback was provided when theta power at the F3 electrode was greater than average theta power at the same location during baseline recordings. In patients with high BCI performance, we observe consistent modulation of frontal theta power. We also observe a statistically significant negative correlation between BCI performance and self-reported pain within these subjects (Spearman's Rho -0.33, $p < 0.01$). Furthermore, we observe decreases in patient reported pain severity and pain interference over the course of the study. These results indicate that frontal theta is related to pain perception and enhancing this activity pattern through

BCI-mediated neuromodulation may be a viable treatment option for chronic pain. In order to elucidate the acting mechanism of pain modulation in chronic pain patients, we will study plastic changes in the anterior cingulate and left dorsal lateral pre-frontal cortex using functional MRI and stereotactic EEG studies.

Disclosures: P. Demarest: None. **N. Rustamov:** None. **J.R. Swift:** None. **T. Xie:** None. **M. Adamek:** None. **H. Cho:** None. **E. Wilson:** None. **P. Brunner:** None. **S. Haroutounian:** None. **E.C. Leuthardt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Equity in Neurolutions, Equity in Sora Neuroscience, Equity in Inner Cosmos.

Poster

710. Human Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 710.03

Topic: D.02. Somatosensation – Pain

Title: Acetylated alpha-tubulin and neurofilament light chain as clinical plasma biomarkers in charcot-marie-tooth disease

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Abstract: Charcot-Marie-Tooth disease (CMT) is a progressive peripheral neuropathy affecting 2.6 million people worldwide with limited treatment options available. It can be divided into demyelinating (Type 1) and axonal damaging forms (Type 2), along with other more complex forms. CMT diagnosis is dependent on neurophysiological and neurological examination of the patient, with no fluid-based biomarkers available. This creates a challenge for drug discovery in CMT as there is no validated biomarker to track disease progression or any potential benefits derived from a novel therapy. Thus, we investigated whether two markers of neuronal health are suitable to track CMT severity and progression, either on their own or as a composite. Plasma was collected from CMT patients (n=13) with a mutation in either *PMP22* (duplication; CMT1A; n=10) or *MFN2* (CMT2A; n=3). Comparisons were made with hereditary neuropathy with liability to pressure palsies (HNPP) patients, caused by PMP22 deletion (n=5), and healthy volunteers (n=16). All work was performed following ethical approval from Tallaght University Hospital, Dublin. Neurofilament light chain (NfL), a marker of axonal damage, has been associated with CMT and alterations in acetylated alpha-tubulin (Acet-Tub), a marker of microtubule dynamics, have been identified in preclinical CMT models. Acet-Tub was measured using infra-red Western blot and a significant decrease in the Acet-Tub/total Tub ratio was found in CMT ($p<0.05$) and HNPP patients ($p<0.001$). Genotype comparisons revealed that this

decrease was found in both CMT1A (p<0.05) and HNPP patients (p<0.001), with a non-significant tendency towards a decrease in CMT2A patients compared to healthy volunteers. NfL was measured using an R-Plex Mesoscale assay system. This revealed a significant increase in CMT (p<0.01) and HNPP patients (p<0.05) compared to healthy volunteers. Specifically, NfL levels were significantly higher in CMT2A (p<0.001) and HNPP patients (p<0.01), with a non-significant tendency towards an increase in CMT1A patients compared to healthy volunteers. Analysis of CMT1A and CMT2A severity using the CMT Examination Score (CMTES) showed non-significant tendencies towards a negative correlation with Acet-Tub/total Tub ratio (r= -0.4546; p=0.1376), and a positive correlation with NfL (r= 0.4551; p =0.1371). This study suggests that plasma-based biomarkers may be of benefit to the drug discovery process in CMT and related neuropathies, with demyelinating CMT1A showing alterations in microtubule proteins and axonal CMT2A showing alterations in NfL. In comparison, HNPP patients showed simultaneous changes in both biomarkers.

Disclosures: **A. Freeburn:** None. **J. Kealy:** None. **D. Disha:** None. **T. Onishi:** None. **K. Otake:** None. **M. Tanaka:** None. **H. Iwashita:** None. **A. Suzuki:** None. **Z. Togher:** None. **S. Murphy:** None. **M. Bianchi:** None.

Poster

710. Human Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 710.04

Topic: D.02. Somatosensation – Pain

Support: NIH Grant 1R01DA046064-01

Title: Structural equation modeling of shared genetic variance for resting-state connectivity and pain conditions from the UK Biobank

Authors: *C. BANGO[1], K. ZORINA-LICHTENWALTER[2], M. CEKO[3], N. FRIEDMAN[2], T. WAGER[1];
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Abstract: Pain states have been linked to neural patterns in neuro-imaging studies (e.g., [1]) and genetic risk profiles in large-scale genomic studies.[2, 3] However, shared genetic predispositions (i.e., genetic correlations) between functional brain networks and chronic pain conditions have yet to be characterized. Here, we used summary statistics from genome-wide association studies (GWAS) to evaluate shared genetic variance for brain imaging-derived phenotypes of fMRI resting-state connectivity data and pain conditions from the UK Biobank. We obtained GWAS summary statistics from the Oxford BIG dataset for 27 imaging-derived phenotypes (IDPs) for 33,000 participants from the UK Biobank. The IDPs consisted of 21 Independent Component Analysis (ICA) components, which represent patterns of temporally synchronized activity

between brain regions during rest (i.e., functional networks), and six ICA summary features derived by Smith et al. 2021representing linear combinations of all functional connectivity components.[4] We incorporated the brain IDP summary statistics into a 2-factor structural equation model (SEM) of 24 persistent, heritable pain conditions from the UK Biobank previously derived by our group using GenomicSEM. This model shows that all 24 pain conditions have a shared genetic component (factor 1), with 11 musculoskeletal conditions sharing an additional genetic component (factor 2). We ran linkage disequilibrium score regression (LDSC) to estimate heritability for and genetic correlations between brain IDPs and chronic pain conditions and then used confirmatory factor analysis in GenomicSEM to model the structure of their genetic overlap. For each IDP, we ran a separate model to estimate its correlations with the individual pain conditions and with the two pain factors (54 models total). Our results showed 62 significant ($p < .05$) genetic correlations (ranging from -.4 to .39) between individual pain conditions or multi-condition pain factors and the 27 IDPs. However, only four significant genetic correlations survived FDR correction ($q < .05$). Of these, neck pain was correlated with ICA #17, characterized by auditory cortex activity. Both the general pain factor and stomach pain were correlated with the ICA derived feature #5, whereas the musculoskeletal factor was correlated with ICA derived feature #4. Taken together, our results suggest that the shared genetic variance for chronic pain conditions and functional connectivity is small and widely distributed. These findings pave the way for future investigations of genetic and phenotypic associations and predictive validity between chronic pain and functional connectivity states.

Disclosures: C. Bango: None. **K. Zorina-Lichtenwalter:** None. **M. Ceko:** None. **N. Friedman:** None. **T. Wager:** None.

Poster

710. Human Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 710.05

Topic: D.02. Somatosensation – Pain

Support: NIH Grant 1P50DA044121-01A1
NSF Grant DGE-1324585

Title: Morphometric similarity networks discriminate patients with lumbar disc herniation from healthy controls and predict pain intensity

Authors: *L. HUANG[1], L. YANG[2], A. VIGOTSKY[3], B. WU[2], B. SHEN[2], Z. YAN[2], A. V. APKARIAN[1];
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Abstract: We used a recently advanced technique, morphometric similarity (MS), in a large sample of lumbar disc herniation patients with chronic pain (LDH-CP) to examine morphometric features derived from multimodal MRI data. To do so, we evenly allocated 136 LDH-CPs to exploratory and validation groups with matched healthy controls (HC), randomly chosen from the pool of 157 HCs. We developed three MS-based models to discriminate LDH-CPs from HCs and to predict the pain intensity of LDH-CPs. In addition, we created analogous models using resting state functional connectivity (FC) to perform the above discrimination and prediction of pain, in addition to comparing the performance of FC- and MS-based models and investigating if an ensemble model, combining MS and FC, could improve performance. We conclude that (1) MS-based models were able to discriminate LDH-CPs from HCs and the MS networks (MSN) model performed best; (2) MSN was able to predict the pain intensity of LDH-CPs; (3) FC networks constructed were able to discriminate LDH-CPs from HCs, but they could not predict pain intensity; and (4) the ensemble model neither improved discrimination nor pain prediction performance. Generally, MSN is sensitive enough to uncover brain morphology alterations associated with chronic pain and provides novel insights regarding the neuropathology of chronic pain.

Disclosures: L. Huang: None. **L. Yang:** None. **A. Vigotsky:** None. **B. Wu:** None. **B. Shen:** None. **Z. Yan:** None. **A.V. Apkarian:** None.

Poster

710. Human Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 710.06

Topic: D.02. Somatosensation – Pain

Title: Definition and clinical validation of Pain Patient States from high-dimensional mobile data: application to a chronic pain cohort

Authors: *J. M. REINEN[1], C. AGURTO[1], G. A. CECCHI[2], J. L. ROGERS[3], D. HUYNH[4], K. LECHLEITER[5], B. HERSHEY[4], R. WOON[4], M. MCDONALD[4], A. NAVITAS & ENVISION STUDIES PHYSICIANS AUTHOR GROUP[5];
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Abstract: Chronic pain is a heterogeneous condition impacting not only pain magnitude but also mood, sleep, medication use, and mobility. Most current practice evaluates outcomes based on pain magnitude, though the technical capacity to monitor a multitude of symptoms with a mobile device has drastically expanded. However, the data produced from this approach are often difficult to interpret. We present a solution to produce a meaningful representation of patient status not only from pain alone but from large, complex data streams, leveraging both a data-driven approach, and use clinical knowledge to validate results. Data were collected from a clinical trial enrolling chronic pain patients, and included questionnaires, voice recordings,

actigraphy, and standard health assessments. Mobility and voice data were processed and decomposed. Next, all data were combined and reduced using a k-means clustering analysis. Optimal k was determined using multiple methods, including consensus clustering. In an initial exploratory analysis with only questionnaire data, we found up to 3 stable cluster solutions that grouped symptoms on a positive to negative spectrum. Objective features (actigraphy, speech) expanded the cluster solution granularity. Using a 5 state solution with questionnaire and actigraphy data, we found significant correlations between cluster properties (centroid distances) and assessments of disability and quality-of-life. The correlation coefficient values showed an ordinal distinction, confirming the cluster ranking on a negative to positive spectrum. This suggests we captured novel, distinct Pain Patient States with this approach, even when multiple clusters were equated on pain magnitude. The stable solutions that emerged from this method suggest the discovery of distinct clinical states with non-obvious properties that may serve as new knowledge that informs biological mechanisms and clinical care. This improves upon the approach of only using pain magnitude as an outcome by considering a more comprehensive picture of patient experience. Relative to using complex time courses of many variables, Pain Patient States holds promise as an interpretable, useful, and actionable metric for a clinician or caregiver to simplify and provide timely delivery of care.

Disclosures: **J.M. Reinen:** A. Employment/Salary (full or part-time):; IBM Research. **C. Agurto:** A. Employment/Salary (full or part-time):; IBM Research. **G.A. Cecchi:** A. Employment/Salary (full or part-time):; IBM Research. **J.L. Rogers:** A. Employment/Salary (full or part-time):; IBM Research. **D. Huynh:** A. Employment/Salary (full or part-time):; Boston Scientific. **K. Lechleiter:** A. Employment/Salary (full or part-time):; Boston Scientific. **B. Hershey:** A. Employment/Salary (full or part-time):; Boston Scientific. **R. Woon:** A. Employment/Salary (full or part-time):; Boston Scientific. **M. McDonald:** A. Employment/Salary (full or part-time):; Boston Scientific. **A. NAVITAS & ENVISION Studies Physicians Author Group:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boston Scientific.

Poster

710. Human Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 710.07

Topic: D.02. Somatosensation – Pain

Support: NINDS R25 NS070680
NIH BRAIN Initiative UH3 NS109556
DARPA-BAA-14-09

Title: Characterizing brain networks of analgesia in humans undergoing deep brain stimulation for chronic pain

Authors: *J. C. MOTZKIN[1], J. PROSKY[2], I. JOSEPH[2], A. SHAUGHNESSY[2], P. A. STARR[2], E. F. CHANG[2], M. D'ESPOSITO[4], P. SHIRVALKAR[3];
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Abstract: Chronic pain is a highly prevalent, poorly understood, and disabling condition that is notoriously refractory to treatment. Trials of deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS) for refractory chronic pain have targeted individual brain regions implicated in pain perception (e.g., thalamus, anterior cingulate cortex) and modulation (e.g., periaqueductal gray, primary motor cortex) with promising initial results, but with variable and short-lived reductions in pain that may not be clinically significant in the long term. Complex, multidimensional experiences like pain can be conceptualized as emergent properties of parallel, distributed processing in large-scale neural networks. Accordingly, functional MRI (fMRI) activity across a distributed 'pain network', but not individual regions, can accurately predict fluctuations in both acute and chronic pain. We therefore hypothesized that deriving a 'relief network' in patients undergoing analgesic brain stimulation may facilitate the identification of personalized intervention targets for patients with refractory pain. To explore network level correlates of stimulation-induced analgesia, we collected resting state functional MRI (rs-fMRI) data in four patients undergoing a trial of multi-site DBS for chronic neuropathic pain. After the MRI session, patients completed a rigorous inpatient DBS trial period during which temporary sEEG electrodes containing hundreds of electrical contacts were surgically implanted in key brain regions informed by prior population level imaging studies. Contacts were systematically stimulated in a sham-controlled fashion and scores of pain intensity, pain unpleasantness, and pain relief were recorded. Maps of whole brain resting state functional connectivity (rsFC) were calculated between regions of interest (ROIs) corresponding with each stimulation contact and the rest of the brain, such that each contact was associated with one z-scored rsFC map and one pain rating. Regressing pain scores on correlation maps generated a network map for each patient consisting of regions where rsFC predicts relief ('relief network'). Specific 'relief networks' were variable between patients but contained notable overlap with previously identified pain relevant regions, including thalamus, dorsolateral prefrontal cortex, and periaqueductal gray. In ongoing work, we are quantifying the importance of specific nodes to relief, evaluating whether global network features like modularity are more predictive than network topology, and generating predictive models to derive optimal stimulation targets for future studies.

Disclosures: J.C. Motzkin: None. **J. Prosky:** None. **I. Joseph:** None. **A. Shaughnessy:** None. **P.A. Starr:** None. **E.F. Chang:** None. **M. D'Esposito:** None. **P. Shirvalkar:** None.

Poster

710. Human Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 710.08

Topic: D.02. Somatosensation – Pain

Support: NIH Grant T32

Title: Chronic pain dynamically modulates theta and gamma power and cross-frequency coupling

Authors: *J. RYU, A. BARI;
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Abstract: Chronic pain is one of the most common reasons to seek medical care, and it impacts approximately 50 million adults in the United States. Despite its wide prevalence, little is known about the brain dynamics that lead to the experience of chronic pain. Electrophysiological studies in patients with chronic pain have thus far revealed oscillatory dynamics mainly at the cortical level using EEG, with converging evidence towards theta and alpha band power increase as a biomarker for chronic pain and gamma band power increase for acute pain. Nevertheless, systematic understanding of pain modulation is grossly lacking and neuronal recordings from deeper brain structures in the context of pain are limited. In this study, we aimed to characterize the spontaneous pain states at bilateral subgenual cingulate cortex (SCC) and prefrontal cortex, with a data-driven approach to identify the oscillatory band and local cross-frequency coupling that maximally differentiate varying levels of pain.
In this study, one chronic low back pain patient underwent an awake deep brain stimulation (DBS) surgery, targeting the SCC for treatment of chronic low back pain as part of a clinical trial. During the surgery, the patient was asked to continuously rate the pain level on a visual analog scale (VAS) for 8 minutes. The patient's leg was raised passively at varying angles to simulate an acute low back pain. Electrophysiological signals were recorded from the bilateral SCC and the prefrontal cortex, spanning from the orbitofrontal cortex (OFC) to dorsolateral prefrontal cortex (DLPFC). During the task, the patient registered an increase in VAS rating from 6 to 7. When we compared these two states (6 vs. 7), higher pain level exhibited an increase in alpha and theta band power in the left SCC and OFC, with a reversal at the DLPFC area, and an increase in gamma band power for all regions. Furthermore, higher pain levels were associated with an increased phase-amplitude coupling at the theta-gamma band in the right SCC, and theta-beta band at OFC.
Our results demonstrate a first in human simultaneous intracranial recordings from the SCC and the prefrontal cortex that reflect the spontaneous changes in pain level. To that end, they reveal the self-organizing dynamics of the brain that naturally unfolds in the context of pain, and suggest the theta/alpha and gamma band as a band range of interest for further analyses. These studies will help to identify pain biomarkers for future closed-loop brain stimulation approaches.

Disclosures: J. Ryu: None. **A. Bari:** F. Consulting Fees (e.g., advisory boards); Medtronic.

Poster

710. Human Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 710.09

Topic: D.02. Somatosensation – Pain

Title: Decoding subjective pain experience from multi-day intracranial electroencephalography in humans

Authors: *T. V. PHAM[1], S. H. SUN[1], K. E. WEAVER[2], J. A. HERRON[3,4], A. L. KO[3], J. G. OJEMANN[3], R. P. N. RAO[5,6,4];
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Abstract: While pain processing has been linked to several structures and circuits in the brain, the underlying neural electrophysiology of pain is not well understood. The possibility of identifying electrophysiology-based biomarkers may allow for real-time pain state classification. Here, we present a decoding model that classifies patient-reported low and high pain states from neural activity. We used intracranial electroencephalography (iEEG) to collect multi-day neural activity from epilepsy patients (n=4) undergoing seizure monitoring. Neural activity was time-synchronized to patient-reported, clinically-acquired visual analog scale (VAS) pain intensities. Pain intensities were binarized to low (VAS < 3) vs. high (VAS $\geq$ 3) pain states. Power estimates from canonical frequency bands were used as feature input to our model. Our subject-specific logistic regression decoder achieved near perfect accuracy in classifying between low and high pain states. In one patient, the decoder had a 99% classification accuracy using beta power from the middle frontal gyrus (MFG). Additionally, the delta band had the highest mean accuracy across all contacts at 75.4% ($\pm$ 16.7), with highest performance from the anterior cingulate cortex (ACC) at 81.4% ($\pm$ 14.6). Our data suggest that beta power in the MFG and delta power in the ACC may dissociate binarized, acute pain states, results consistent with activation patterns within the prefrontal cortex and ACC during pain processing (Bushnell et al., 2013). This provides initial evidence suggesting that acute pain states can be decoded from intracranial human neural electrophysiology and provides the groundwork for electrophysiology-based pain evaluation methods.

Disclosures: **T.V. Pham:** None. **S.H. Sun:** None. **K.E. Weaver:** None. **J.A. Herron:** None. **A.L. Ko:** None. **J.G. Ojemann:** None. **R.P.N. Rao:** None.

Poster

710. Human Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 710.10

Topic: D.02. Somatosensation – Pain

Support: Medical Research Council Career Development Award (MR/T010614/1)
Wellcome Trust grants
Fonds de la Recherche Scientifique - FNRS

Title: Confidence-weighted nociceptive learning: behavioral evidences and EEG correlates

Authors: *D. MULDERS[1,2], B. SEYMOUR[3], A. MOURAUX[1], F. MANCINI[4];
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Abstract: Pain perception is a warning signal enabling animals to preserve their body integrity. When pain persists over time, the brain needs to learn to predict its temporal evolution in order to minimize harm. Whereas several studies have already shown the effects of experience and expectations on responses to isolated nociceptive stimuli using axiomatic approaches, it remains largely unknown how individuals can learn to predict a stream of nociceptive events and how these processes are implemented in the brain. To clarify these aspects, we exposed healthy human participants (n = 31) to probabilistic sequences of contact thermal stimuli of two clearly distinct intensities while recording their brain activity with electroencephalography (EEG). Each sequence was generated using two Markovian transition probabilities (TPs) and participants were instructed to try predicting the probability of forthcoming intensities. Participants were occasionally asked to report their probability estimates and confidence in these predictions on numerical scales. First, we found that the probability and confidence reports were well approximated by a Bayesian model learning the sequence TPs. At the opposite of non-Bayesian models, this suggests that participants employed a confidence-weighted learning strategy: when confidence gets higher, the effect of newly received stimulus intensities is reduced. Then, we observed a negative correlation between the model confidence and the amplitude of the Vertex Potential (VP): the higher the confidence in the TP estimates, the smaller the VP. Overall, these findings confirm key predictions of a Bayesian learning model for nociception and suggest that the VP is modulated by inferential confidence when participants learn the structure of sequences of nociceptive stimuli.

Disclosures: D. Mulders: None. **B. Seymour:** None. **A. Mouraux:** None. **F. Mancini:** None.

Poster

710. Human Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 710.11

Topic: D.02. Somatosensation – Pain

Support: NIH Grant R21-AT010352
NIH Grant R01AT009693

Title: Mindfulness meditation directly reduces acutely exacerbated chronic back pain through non-opioidergic mechanisms

Authors: *L. KHATIB[1], J. G. DEAN[1], N. E. GONZALEZ[1], V. OLIVA[1], G. RIEGNER[1], J. BIRENBAUM[2], J. ROSS[1], G. CRUANES[1], M. REYES[1], N. HOLLENBECK[1], Z. NAZIR[1], C. LOPEZ[1], A. ALLEN[1], N. JAMPANA[1], R. FUENTES[1], T. DANG[1], H.-C. KIM[1], M. PATTERSON[1], J. MILLER[1], M. WALLACE[1], K. CHAKRAVARTHY[1], F. ZEIDAN[1]; [1]Anesthesiol., UCSD, San Diego, CA; [2]Univ. of California, Irvine, Irvine, CA

Abstract: Chronic pain is a highly prevalent and cost-debilitating disorder. There are no known therapies that directly reduce movement-evoked chronic pain. Mindfulness meditation, a technique premised on sustaining nonreactive attention to somatic sensations, reliably reduces pain. Cognitive-based pain modulatory techniques reduce pain via periaqueductal gray matter (PAG) mediated descending inhibition. In contrast, mindfulness-based analgesia is associated with 1) PAG deactivation and 2) non-opioidergic processing in healthy volunteers. Yet, it is unknown if meditation directly reduces evoked chronic low back pain (cLBP) and if said analgesia is mediated through endogenous opioids. The proposed 7-session clinical trial (NCT04034004) employed a double-blinded, cross-over, randomized, and placebo-controlled design to determine if mindfulness or non-mindfulness meditation reduces evoked cLBP through non-opioidergic processes. The straight leg raise test (SLR) was used to evoke radicular lower back pain in 59 cLBP patients (M age = 46 years; 30 females). Visual analog scale ratings (0 = no pain; 10 = worst pain imaginable) were collected before and after each SLR (SLR 1 vs. 2). In session 1, we administered SLR 1 and SLR 2, respectively. Each SLR was divided by 13 minutes. Patients were then randomized to a mindfulness (n = 30) or non-mindfulness (n = 29; slow-breathing-based) meditation regimen (four, 20-min sessions). In sessions 6 and 7, patients were instructed to rest after SLR 1 and to meditate after SLR 2. During SLR 2, naloxone (0.15 mg/kg) or saline was intravenously administered. In session 7, patients received the drug not administered in session 6. A 2 (group) x 2 (rest vs. meditation) x 3 (baseline; naloxone; saline) ANOVA examined if cLBP relief varied by group and/or session. Planned paired samples t-tests (Bonferroni corrected) tested study hypotheses. The session x meditation interaction (p = .005, η^2_p= .09) was associated with significant cLBP reductions in both groups after training. Mindfulness significantly reduced evoked cLBP during saline and naloxone infusion ($ps \leq .002$). In contrast, non-mindfulness meditation reduced cLBP during saline (p = .002) but not naloxone (p = .21). The present study provides novel evidence that mindfulness and non-mindfulness meditation directly reduces one's cLBP. We found that mindfulness-based cLBP relief was not opioidergically mediated. Yet, non-mindfulness-induced cLBP relief was reversed by opioidergic antagonism. These findings could optimize pain therapies to target multiple analgesic mechanisms.

Disclosures: L. Khatib: None. **J.G. Dean:** None. **N.E. Gonzalez:** None. **V. Oliva:** None. **G. Riegner:** None. **J. Birenbaum:** None. **J. Ross:** None. **G. Cruanes:** None. **M. Reyes:** None. **N. Hollenbeck:** None. **Z. Nazir:** None. **C. Lopez:** None. **A. Allen:** None. **N. Jampana:** None. **R. Fuentes:** None. **T. Dang:** None. **H. Kim:** None. **M. Patterson:** None. **J. Miller:** None. **M. Wallace:** None. **K. Chakravarthy:** None. **F. Zeidan:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.01

Topic: D.02. Somatosensation – Pain

Support: NIG Grant R21 DA051636

Title: Novel mechanisms of peripheral opioid tolerance: involvement of keratinocytes and PDGFR-ß singling

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Abstract: Many aspects of the current opioid epidemic relate to the necessity of escalating opioid doses to maintain analgesia in patients as tolerance develops. Peripheral opioid delivery is an attractive alternative as it provides effective local analgesia with limited central side-effects. However, tolerance also occurs peripherally, via mechanisms that remain unknown. Centrally, activation of the mu-opioid receptor (MOR) by opioids induces spinal release of platelet-derived growth factor-B (PDGF-B), and inhibition of platelet-derived growth factor receptor beta (PDGFRβ) by imatinib prevents opioid tolerance. In the periphery, MOR and PDGF-B are expressed in keratinocytes, and PDGFRß is expressed in peripheral sensory neurons (PSNs), which are known to convey tolerance. Previous studies, showed that, acute optogenetic stimulation of keratinocytes in mice that selectively expressed ChR2 under the control of the Krt14 promoter (Krt14-ChR2), modulated peripheral sensory neurons (PSNs) activity. Importantly, ChR2-evoked response seemed to be mediated via release of keratinocytes-derived factors. Thus, we hypothesized that mechanisms of peripheral opioid tolerance (POT) could involve PDGFR-ß signaling on PSNs, recruited via release of PDGF-B from MOR-activated keratinocytes by opioids. Using a pharmacological approach in mice, we found that intraplantar (i.pl.) co-administration of morphine with imatinib (PDGFR-ß inhibitor), or with PDGFRß-Fc (PDGF-B scavenger), prevented POT. In parallel, using Krt-14-ChR2 mice, we discovered that repeated optogenetic activation of keratinocytes in the absence of opioids, induced POT which could be reversed with imatinib. Repeated i.pl. administration of PDGF-B was also sufficient to induce POT in opioid naïve mice. Finally, *in situ* hybridization showed that MOR and PDGF-B are co-expressed in keratinocytes, suggesting that PDGF-B could be released from opioid-MOR activated keratinocytes. Together, these data show that keratinocytes activation is sufficient to induce tolerance, via activation of PDGFR-ß signaling, possibly via release of PDGF-B. Ongoing studies are determining whether POT could affect expression of PDGF-B in keratinocytes, and whether keratinocytes could, in fact be releasing PDGF-B upon opioid peripheral stimulation. PDGFRβ inhibitors are FDA approved and could be repurposed to prevent peripheral tolerance and reduce opioid side-effects and the risk of addiction, overdose and death.

Disclosures: L. Posa: None. **P. Joseph:** None. **S. Miracle:** None. **A. McDonald:** None. **Z. Freyberg:** None. **K. Albers:** None. **R. Logan:** None. **S. Puig:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.02

Topic: D.02. Somatosensation – Pain

Support: NIH 1P50DA044121
NIH F31NS126012
NSF DGE-1324585

Title: Behavioral and brain consequences of opioid exposure for more than three months in chronic back pain patients

Authors: *G. RACHED[1], R. JABAKHANJI[5], A. VIGOTSKY[2], P. BRANCO[3], L. HUANG[2], T. J. SCHNITZER[2], A. V. APKARIAN[6], M. N. BALIKI[4];
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Abstract: Chronic pain management is intimately linked with opioid abuse, despite unclear evidence of long-term opioid use for treating chronic pain. Conversely, long-term opioid therapy leads to several complications, ranging from opioid dependence to death. To understand the effects of opioids in chronic pain populations, we compared differences in pain, clinical properties, and brain activity between chronic back pain patients on long-term opioids and chronic back pain patients with no opioids. We also investigated the relationship between opioid doses and drug-related behavior. We recruited 40 patients with chronic low back pain for at least six months and on opioid therapy for at least three months (CBP-op), and 40 controls not taking opioids matched for age, sex, pain intensity, and pain duration (CBP-nop). All patients completed questionnaires to assess personal health history, physical function, emotion, and pain characteristics, and underwent anatomical and function brain scans. We used amplitude of low-frequency fluctuation (ALFF) to compare resting state brain activity between the two groups. For CBP-op, we measured opioid use from daily prescriptions converted into morphine milligram equivalent (MME). We also collected blood samples from participants either before or after brain scans to quantify systemic opioids concentrations which we converted to a relative opiate equivalent (ROE). Finally, we evaluated the risk of opioid misuse with the Current Opioid Misuse Measure (COMM) and the intensity of opioid withdrawal using the Subjective Opioid Withdrawal Scale (SOWS). Principal component analysis revealed that clinical parameters grouped into functional, emotional, and pain components. Compared to, CBP-op patients had higher emotional and functional disabilities and greater ALFF activity in several mesocorticolimbic regions. In addition, pain, emotion, and physical function disability mapped to ALFF in different regions in the brain. In the CBP-op group, the COMM and the SOWS were not associated with opioid prescription or opioid blood levels, but rather with emotional disability, while opioid blood levels were associated with functional disability. Most patients' COMM scores were below the clinical threshold for opioid misuse. These results indicate that chronic opioid use in chronic back pain patients leads to increased brain activity, especially in

the mesolimbic system, and increased functional and emotional disability. Therefore, long term opioid exposure in chronic back pain has both brain and behavioral negative consequences.

Disclosures: G. Rached: None. **R. Jabakhanji:** None. **A. Vigotsky:** None. **P. Branco:** None. **L. Huang:** None. **T.J. Schnitzer:** None. **A.V. Apkarian:** None. **M.N. Baliki:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.03

Topic: D.02. Somatosensation – Pain

Support: Arizona Biomedical Research Commission New Investigator Award #ADHS18-198875
R01DA052340

Title: Investigating the role of phospholipase C in enhancing opioid pain relief during Hsp90 inhibition

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Abstract: Opioids are very effective in the treatment of moderate to severe pain and may be the only adequate treatment available for some patients. However, clinical use of opioids is limited by side effects that contribute to alarming numbers of hospitalizations and deaths. Strategies to lessen opioid doses and reduce side effects, while still providing acceptable levels of pain relief, are urgently needed to confront this growing health crisis. We have shown that intrathecal delivery of the heat shock protein 90 (Hsp90) inhibitor 17-(Allylamino)-17-demethoxygeldanamycin (17-AAG) in mice enhances the anti-nociceptive potency of morphine by 2-4 fold while significantly reducing side effects, suggesting Hsp90 inhibition as a promising opioid dose reduction approach. To identify mechanistic details of the pathway driving opioid-enhancing effects, proteomic analysis of murine spinal cords (n=3/group) comparing vehicle-treated to 17-AAG-treated (0.5 nmol, i.t.) CD-1 female mice was performed. We identified an upregulation of Phospholipase C (PLC) in 17-AAG treated mice ($p = 0.00138$, fold change 1.52). PLC cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) into diacyl glycerol (DAG) and inositol 1,4,5-trisphosphate (IP3), critical second messengers in many signal transduction pathways. Several studies have shown PLC may alter delta-opioid-receptor-mediated anti-nociception in the spinal cord and play a role in neuropathic pain, suggesting its potential involvement in the mu opioid receptor/Hsp90 signaling pathway investigated here. To test this hypothesis, adult female CD1 mice (n=5/group) were treated with either 17-AAG (0.5 nmol, i.t.) or vehicle, followed 24 hours later by treatment with U-73122, a small molecule aminosteroid PLC inhibitor (10 nmol, i.t.) or vehicle. Anti-nociceptive behavior was measured with a tail flick

assay following a 3.2 mg/kg subcutaneous morphine dose. Our findings indicate that spinal cord inhibition of PLC alone does not alter anti-nociceptive behavior measured by thermal latency. However, inhibition of PLC with concurrent inhibition of Hsp90 fully reversed the anti-nociceptive enhancement conferred by Hsp90 inhibition, demonstrating a key mechanistic link for PLC signaling and the anti-nociception conferred by Hsp90 inhibition in the spinal cord. Our data suggests that PLC is directly activated by 17-AAG treatment to enhance pain relief and may be a critical component of this evolving opioid reduction strategy. We further report our efforts to measure PLC activity directly in 17-AAG treated spinal cords, along with immunohistochemistry studies to identify the location and cell type in which PLC is upregulated.

Disclosures: B.D.K. Gratreak: None. **J.M. Streicher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teleport Pharmaceuticals, LLC, Botanical Results, LLC.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.04

Topic: D.02. Somatosensation – Pain

Support: NIDA Grant DA25267
NIDA Grant DA48353

Title: The kratom alkaloid mitragynine reverses paclitaxel chemotherapy-induced peripheral neuropathy via opioid and adrenergic receptor involvement and, when combined with cannabidiol, has additive pharmacological interactions

Authors: *Y. T. ORTIZ[1], M. MOTTINELLI[2], C. R. MCCURDY[2], L. R. MCMAHON[3], J. L. WILKERSON[3];
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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is a problematic side effect in patients receiving chemotherapeutic cancer treatments. Clinical use of approved analgesic drugs often does not adequately control CIPN pathological pain. *Mitragyna speciosa* (kratom) contains the alkaloid mitragynine (MTG), which in various preclinical pain models exhibits analgesic properties. However, the underlying pharmacological mechanisms of mitragynine and its possible side effects are not well understood in relation to its use as a potential CIPN pain treatment. Furthermore, anecdotal reports of cannabidiol (CBD) consumption with kratom suggests enhanced chronic pain relief effects. Male and female C57BL/6 mice received intraperitoneal (i.p.) injections of paclitaxel every other day over the course of 7 days for a cumulative dose of 32 mg/kg to induce mechanical allodynia. The von Frey assay was utilized to

assess CIPN-induced mechanical allodynia. In separate paclitaxel-naïve food-restricted mouse cohorts, schedule-controlled responding for food was conducted under a fixed ratio (FR)-10, and hot plate antinociceptive testing was also examined. MTG i.p. (ED_{50} 112.83 (105.78 – 120.35) mg/kg) and morphine i.p. (ED_{50} 6.65 (6.14 – 7.20) mg/kg) dose-relatedly reversed CIPN-induced mechanical allodynia. Pretreatment with the opioid antagonist naltrexone (0.032 mg/kg, i.p.) produced a 4.2- and 1.9-fold rightward shift in both morphine and MTG dose-response curves, respectively. The α_2-adrenergic agonist clonidine attenuated mechanical allodynia (ED_{50} 0.12 (0.10 – 0.15) mg/kg). The α_2-adrenergic antagonist yohimbine (3.2 mg/kg, i.p.) administered prior to clonidine and MTG produced a 6.84- and 1.756-fold rightward shift in dose responses, respectively. MTG reduced schedule-controlled responding (ED_{50} 46.04 (38.99 – 54.34) mg/kg) and produced acute antinociception (ED_{50} 68.83 (53.14 – 89.15) mg/kg), without attenuation from naltrexone or yohimbine pretreatment. CBD alone attenuated mechanical allodynia (ED_{50} of 85.14 (67.65 – 107.16) mg/kg) and did not decrease schedule-controlled response rates or increase hotplate latencies. Isobolographic analysis revealed MTG + CBD had an additive effect in mechanical allodynia attenuation at 1:1 and 3:1 mixture ratios. MTG + CBD also decreased schedule-controlled responding and increased hot plate latencies. We report that MTG reversed mechanical allodynia associated with paclitaxel CIPN in a manner likely mediated through opioid and adrenergic receptor activity and the combination of MTG with CBD may be a promising analgesic treatment option for patients experiencing painful CIPN.

Disclosures: **Y.T. Ortiz:** None. **M. Mottinelli:** None. **C.R. McCurdy:** None. **L.R. McMahon:** None. **J.L. Wilkerson:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.05

Topic: D.02. Somatosensation – Pain

Support: National Institutes of Health grant R01DA044481
The New York Stem Cell Foundation
UNC-Chapel Hill SMART research program
UNC-Chapel Hill Summer Undergraduate Research Experience in Biological Mechanisms SURE-REU
G.S. is a New York Stem Cell Foundation

Title: Elucidating the function of mu opioid receptors in distinct populations of spinal neurons

Authors: *A. TASSOU[1,2,3], K. HUANG[1,2,3], V. MORALES[1,2,3], J. SAJU[1,2,3], S. GARRISON[1,2,3], G. SCHERRER[1,2,3,4];
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Abstract: Mu opioid receptors (MOPr) mediate the effects of both clinically used and abused opioids, including analgesia, opioid-induced hyperalgesia (OIH), tolerance, withdrawal, and muscle rigidity. However, MOPr is broadly distributed in the nervous system, and which populations of neurons underlie these different effects has yet to be determined. In the spinal cord, we previously showed that MOPr is expressed not only by nociceptive neurons of the dorsal horn, but also, unexpectedly, by neurons in ventral horn motor circuits. Here, we generated three different conditional knockout (cKO) mouse lines to eliminate MOPr expression specifically in dorsal horn, V1 or V2a ventral horn neurons (*Lbx1*^{Cre};*Oprm1*^{flox}, *En1*^{Cre};*Oprm1*^{flox} or *Chx10*^{Cre};*Oprm1*^{flox}, respectively) and evaluated the consequences on morphine effects. We found that Lbx1 cKO mice displayed decreased morphine antinociception against mechanical and heat pain, establishing the contribution of MOPr-positive dorsal horn neurons to morphine analgesia. In contrast, Chx10 cKO mice showed intact morphine antinociception. Remarkably, however, we found that morphine-induced hyperlocomotion and straub tail were absent in Chx10 cKO mice, suggesting that Chx10-positive neurons serve a critical function in the motor effects of opioids. Consistent with this phenotype, EMG recordings of the sacro-coccygeus dorsalis muscle revealed that morphine increases muscle activity in control littermates, but not in Chx10 cKO mice. Strikingly, deletion of MOPr in En1-positive neurons did not affect morphine-induced antinociception or straub tail, but completely abolished morphine-induced hyperlocomotion and instead produced a morphine-induced immobility phenotype. Collectively, these results begin to elucidate and dissociate the cell type and circuit mechanisms by which MOPr alter pain perception and movement.

Disclosures: A. Tassou: None. **K. Huang:** None. **V. Morales:** None. **J. Saju:** None. **S. Garrison:** None. **G. Scherrer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cofounder of Epiodyne, a drug discovery company, and inventor on a US patent application (#20210220489) related to imaging of neural dynamics to discover analgesics. F. Consulting Fees (e.g., advisory boards); Member of the National Institutes of Health Preclinical Screening Platform for Pain (PSPP) External Consulting Board.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.06

Topic: D.02. Somatosensation – Pain

Support: NIH Grant DA042902
NIH Grant DA051876
NIH Grant UL1TR000114

Title: Loss of SUR1 subunits in astrocytes decreases hypersensitivity in neuropathic pain and opioid tolerance models in mice

Authors: K. JOHNSON, S. HULKE, S. MUJTEBA, A. BRESKE, ***A. H. KLEIN**;
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Abstract: K_{ATP} channels are octamers composed of four potassium subunits (Kir6.1 or Kir6.2) and four sulfonylurea subunits (SUR1 and SUR2). SUR1-containing K_{ATP} channels are expressed in the peripheral and central nervous system on both neurons and astrocytes. Previous data indicate pharmacological stimulation of K_{ATP} channels can promote antinociception, while loss of SUR1 subunits in neurons decreases opioid analgesia. Recent data indicate that SUR1 expression on astrocytes may be coupled to TRPM4 signaling, increasing cation channel activity after nerve injury. Using genetic approaches, we tested whether the activity of SUR1 in neurons or astrocytes confers antinociception or pronociception in mouse models of neuropathic pain (spinal nerve ligation, SNL), inflammatory pain (Complete Freund's Adjuvant, CFA), or morphine tolerance. We found that intrathecal injection of AAV9-GFAP-Cre in SUR1 flox mice did not impact acute morphine antinociception, but did decrease morphine tolerance in naïve mice. After SNL, the baseline mechanical thresholds were slightly elevated in AAV9-GFAP-Cre mice, and morphine induced antinociception and morphine-induced hypersensitivity were decreased compared to AAV9-HSyn-Cre inoculated mice. Intrathecal administration of AAV9-GFAP-Cre did not appear to improve hypersensitivity or morphine tolerance after intraplantar CFA treatment. From this data we hypothesize that it is possible that following nerve injury, inhibiting SUR1 by acting on SUR1-TRPM4 on astrocytes would decrease neuropathic pain and improve opioid efficacy. Conversely, stimulating SUR1 expressed in neurons could dampen sensory signaling by acting via K_{ATP} channels thereby ameliorating neuropathic pain. Future directions will include the investigation of post-translational modifications/trafficking of SUR1 in neurons vs glia and how each are involved in antinociceptive vs pronociceptive neurotransmission.

Disclosures: K. Johnson: None. **S. Hulke:** None. **S. Mujteba:** None. **A. Breske:** None. **A.H. Klein:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.07

Topic: D.02. Somatosensation – Pain

Support: Department of Physiology, ECU

Title: Adjuvant application of a dopamine D3 receptor agonist to an ineffective morphine dose provides analgesia in a model of chronic pain

Authors: M. K. SCHAUB, K. L. BREWER, ***S. CLEMENS**;
East Carolina Univ., Greenville, NC

Abstract: Chronic neuropathic pain (CNP) typically results from injury to CNS or PNS and has a prevalence of 12-15% in the U.S. population. Current treatments are not highly efficacious in maintaining long-term analgesia and expose patients to an increased risk for opioid overdose.We have previously shown that adjuvant administration of a dopamine (DA) D3 receptor agonist with low-dose morphine achieved analgesia in a centrally induced model of CNP, and the opioid dose in the adjuvant was lower than that needed when using opioid alone. Here, we tested if this novel drug regimen was also as effective in a more prevalent disease of peripherally induced CNP (sciatic nerve ligation, SNL).

Male C57BL/6 mice (n=35) underwent a unilateral SNL, and thermal pain withdrawal reflex latencies (TPWRLs) were measured on injured and uninjured sides under control and drug treatment conditions. TPWRLs were tested 10 days after injury under naïve conditions, and then again under the following drug conditions: morphine at 1 mg/kg, morphine at 2 mg/kg, pramipexole (PPX) at 0.5 mg/kg, morphine 1 mg/kg + PPX 0.5 mg/kg (adjuvant 1), morphine 2 mg/kg + PPX 0.5 mg/kg (adjuvant 2), and saline (0.9% NaCl). Drug effects on TPWRLs were tested 1) 2-3 times per week in an acute treatment protocol, or 2) daily for 4 weeks in a repeated exposure protocol. Following behavioral studies, sciatic nerves (injured and control) were harvested from each animal to measure compound action potentials (CAPs).

We found that SNL induced a long-lasting decrease in TPWRLs (> 4 weeks) that was restored only after administration of either adjuvant, but not after application of any of the drugs alone. Furthermore, animals exposed to the adjuvant showed no signs of tolerance. CAPs of the injured sciatic nerves were strongly decreased compared to the non-injury controls, and neither long-term treatment with morphine or PPX alone changed this phenotype. In contrast, long-term application with the PPX/opioid adjuvant at the low dose (1 mg/kg) induced a clear trend towards a recovery of CAP function.

Together, these data suggest that adjuvant treatment of a D3 receptor agonist with morphine at a low and ineffective dose can achieve and maintain analgesia in a peripherally induced CNP model over time, and that this effect may be mediated in part by restoration of function in the injured sciatic nerves.

We posit that these findings may lead to the development of a novel pain relief therapeutic that reduces negative side effects associated with high dose opioids, thereby reducing the opioid epidemic.

Disclosures: **M.K. Schaub:** None. **K.L. Brewer:** None. **S. Clemens:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.08

Topic: D.02. Somatosensation – Pain

Support: NIH Grant P30-033934
NIH Grant T32-DA007024

Title: Selectivity and efficacy of novel C9-substituted 5-phenylmorphans to bind and activate mu opioid receptors

Authors: *N. NASSEHI[1], S. S. NEGUS[1], D. LUO[2], T. E. PRISINZANO[2], E. BOW[3], E. S. GUTMAN[3], J. A. LUTZ[3], A. SULIMA[3], A. JACOBSON[3], K. C. RICE[3], D. E. SELLEY[1]; [1]Dept. of Pharmacol. & Toxicology, Virginia Commonwealth Univ., Richmond, VA; [2]Col. of Pharmacy, Univ. of Kentucky, Lexington, KY; [3]Natl. Inst. on Drug Abuse and the Natl. Inst. on Alcohol Abuse and Alcoholism, Natl. Inst. of Health, Dept. of Hlth. and Human Services, Bethesda, MD

Abstract: Introduction: The prevalence of opioid use disorder (OUD) in the U.S.A. has prompted efforts to develop therapeutics that avoid the side effects caused by currently available OUD treatments. Recent attention has shifted towards developing low efficacy mu opioid receptor (MOR)-selective drugs to mitigate adverse effects such as dependence and respiratory depression. Likewise, there has been growing interest in biased ligands that preferentially activate G protein signaling over β-arrestin signaling, which aim to enhance analgesic benefits while minimizing tolerance and adverse effects. The purpose of this study was to characterize a series of compounds designed to be selective, low efficacy MOR agonists for potential therapeutic applications.
Methods: Four C9-substituted phenylmorphan analogs (labeled here as Compounds 1, 2, 3, and 4), previously found to have minimal to no efficacy to recruit β-arrestin2 to MOR, were screened for their binding affinities, potencies, and efficacies for G-protein activation at MOR. MOR affinities were determined by competitive binding assays. Potencies and efficacies at MOR were determined by receptor-stimulated guanosine-5'-O-[γ-^{35}S]-triphosphate binding assays. In vitro efficacy was calculated as a percentage of maximal stimulation by [D-Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO), a MOR-selective full agonist. Both assays were performed using membranes from mouse MOR-expressing Chinese hamster ovary cells. In vivo efficacy was determined by stimulation of locomotor activity in mice, calculated as a percentage of maximal activation by the high-efficacy MOR agonist methadone.
Results: All four compounds displayed high affinity for MOR: Compounds 1, 2, 3, and 4 have MOR K_i values of 0.83 nM, 0.39 nM, 0.76 nM, and 4.23 nM, respectively, with >10-fold selectivity vs. KOR and DOR. All four compounds have EC_{50} values < 25 nM at MOR, indicating greater potency than morphine (123 nM) and similar potency to nalbuphine (17.3 nM). Compound 1 has the highest E_{max} value at 20.8% DAMGO stimulation, while Compound 4 produced 0% stimulation. Compounds 1 and 2 both stimulated locomotor activity, comparable to morphine and buprenorphine, while Compounds 3 and 4 did not stimulate locomotor activity.
Discussion: These data show that these novel compounds have high MOR affinity, greater MOR selectivity than buprenorphine, nalbuphine or naltrexone, and a range of low MOR efficacies below buprenorphine. As such, these compounds may have desirable pharmacodynamic characteristics to serve as therapeutics against OUD or moderate pain.

Disclosures: N. Nassehi: None. **S.S. Negus:** None. **D. Luo:** None. **T.E. Prisinzano:** None. **E. Bow:** None. **E.S. Gutman:** None. **J.A. Lutz:** None. **A. Sulima:** None. **A. Jacobson:** None. **K.C. Rice:** None. **D.E. Selley:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.09

Topic: D.02. Somatosensation – Pain

Title: Bitopic engagement of the orthosteric and allosteric sodium binding sites on the mu and delta opioid receptors produces low efficacy agonists with reduced liabilities of use.

Authors: *J. P. MCLAUGHLIN[1], T. CHE[2], V. KATRITCH[3], B. R. VARGA[2], S. M. BERNHARD[2], S. O. EANS[1], G. SKINIOTIS[4], B. KOBILKA[5], S. MAJUMDAR[2]; [1]Pharmacodynamics, Univ. of Florida, Gainesville, FL; [2]Ctr. for Clin. Pharmacol., Univ. of Hlth. Sci. & Pharm. and Washington Univ. Sch. of Med., Saint Louis, MO; [3]Dept. Quantitative & Computat. Biol. & Chem. and Michelson Ctr. for Convergent Biosci., USC, Los Angeles, CA; [4]Dept. of Mol. and Cell. Physiol. and Dept. of Structural Biol., [5]Dept. of Mol. and Cell. Physiol., Stanford Univ., Stanford, CA

Abstract: Whereas agonists activate GPCR signaling by interacting with conventional orthosteric binding sites, ligands interacting at putative allosteric binding sites modulate the activity of agonists. For instance, sodium acts as a negative allosteric modulator at opioid receptors. High-resolution crystal structures of several inactive-state Family A GPCRs reveal a sodium binding pocket interacting with the highly conserved $D^{2.50}$ residue of the second transmembrane domain. Guided by insights obtained by structured aided design we designed and explored the functional selectivity of a series of bitopic ligands simultaneously targeting the classical orthosteric and Na^+ site at the mu opioid receptor (MOR) and delta opioid receptor (DOR). Optimal interactions with both sites were validated by cryo-electron microscopy for MOR-selective C6-guano and DOR-selective C6-quino. In cellular *in vitro* testing, both bitopic ligands displayed potent G-protein partial agonism with reduced arrestin signaling and a distinct Gα-subtype profiling compared to orthosteric site binders. As hypothesized, control compounds (C5-guano for MOR and C5-quino for DOR, respectively) predicted incapable of dual site engagement instead displayed potent activation of both G-protein signaling and arrestin recruitment, validating the bitopic design. When tested *in vivo* in mice, C6-guano and C6-quino demonstrated dose-dependent but non-maximal antinociception in the 55^{o}C warm-water tail-withdrawal assay, with ED_{50} (and 95% confidence interval) values of 18.8 (5.49-55.5) nmol, i.c.v. and 12.0 (9.14-16.4) mg/kg s.c. mediated by the MOR and DOR, respectively. Both compounds further demonstrated dose-dependent anti-allodynia in the chronic constriction injury (CCI) assay of neuropathic pain. Importantly, neither compound demonstrated respiratory depression and minimal locomotor effect, and lacked conditioned place preference characteristic of clinically used opioids such as morphine. Additionally, whereas the conventional DOR agonist SNC80 produced robust seizures, the DOR-selective bitopic ligand C6-quino showed no seizure activity. Taken together, the approach of engaging an allosteric sodium site with bitopic ligands leads to a differential and unique G-protein and arrestin recruitment profile compared to known agonists binding only the orthosteric site on opioid receptors, with the lead ligands C6-guano and C6-quino displaying *in vivo* antinociceptive efficacy without typical opioid CNS adverse effects.

Disclosures: **J.P. McLaughlin:** None. **T. Che:** None. **V. Katritch:** None. **B.R. Varga:** None. **S.M. Bernhard:** None. **S.O. Eans:** None. **G. Skiniotis:** None. **B. Kobilka:** None. **S. Majumdar:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.10

Topic: D.02. Somatosensation – Pain

Support: NIH P50 Grant DA044121

Title: Decreased interhemispheric and corticolimbic white matter fractional anisotropy in chronic back pain patients with long-term opioid usage

Authors: *O. CONG[1], G. RACHED[2], R. JABAKHANJI[3], L. HUANG[6], M. N. BALIKI[7], P. BRANCO[8], T. J. SCHNITZER[4], A. V. APKARIAN[5];
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Abstract: Opiates are more and more commonly prescribed to treat chronic back pain (CBP), the most prevalent chronic pain condition in the United States, resulting in an opioid epidemic with escalating adverse effects. Despite millions of patients regularly using opioids and known risks of dependence, addiction, hyperalgesia, and cognitive impairment, little is elucidated about the long-term impact of opioids on the brain. We sought to determine the effects of opioid usage on structural brain properties in CBP patients.
A total of 58 CBP patients with long-term opioid usage underwent an MRI brain scan and completed various cognitive, emotional, pain, and opioid-related questionnaires. These patients were matched based on age, gender, pain intensity, and pain duration with 58 CBP patients with no history of or current usage of opioids. We studied diffusion tensor imaging to characterize possible alterations in anatomical connectivity caused by long-term opioid usage. To do so, we used tract-based spatial statistics (TBSS) to measure the anisotropic diffusion of water in white matter tracts by examining fractional anisotropy (FA) in a voxel-wise statistical analysis.
In group-level TBSS results, CBP patients with opioid usage had significantly decreased anisotropy in two clusters- one involved in the inferior fronto-occipital fasciculus, anterior thalamic radiation, and uncinate fasciculus axonal tracts and one in the body of the corpus callosum. The first cluster involves overlapping tracts that have previously been found to be implicated in white matter changes caused by long-term opioid use. We searched for correlates in the opioid usage group between anisotropy values and three opioid-related measures- opioid misuse, morphine milligram equivalent, and subjective withdrawal symptoms- but did not find significant associations between these parameters.
These findings suggest that long-term opioid usage is associated with changes in structural

connectivity between brain regions in the dopaminergic mesocorticolimbic circuitry, which are implicated in pain, reward, and drug addiction processes, and in tracts connecting the left and right frontal lobes through the corpus callosum. More generally, these findings align with current evidence showing analogous compromised mesolimbic white matter integrity in brains of substance-abuse patients.

Disclosures: O. Cong: None. **G. Rached:** None. **R. Jabakhanji:** None. **L. Huang:** None. **M.N. Baliki:** None. **P. Branco:** None. **T.J. Schnitzer:** None. **A.V. Apkarian:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.11

Topic: D.02. Somatosensation – Pain

Support: NIH/NIDA R01 DA038645
Dr. Maharaj Ticku Professorship Fund

Title: Kappa opioid receptors in keratinocytes are essential for peripherally-restricted, kappa agonist-mediated antinociception

Authors: E. K. DEBNER, M. M. PANDO, W. P. CLARKE, *K. A. BERG;
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Abstract: Peripherally expressed kappa opioid receptors (KOR) are a promising target to treat inflammatory pain without producing adverse central nervous system effects. In an inflammatory model of pain, we have found that local injection of the KOR agonist, U50488, into the hindpaw produces a profound antinociceptive behavioral response mediated by activation of G protein-coupled inwardly-rectifying potassium (GIRK) channels in both male and female rats. Both KOR and GIRK channels are expressed on intraepidermal nerve fibers (IENF) that innervate the hindpaw and propagate nociceptive signals from the periphery to the spinal cord. Recent studies suggest that keratinocytes, which are the major cell type in the epidermis, play an active role in pain and sensory processing. Here, we have found that keratinocytes in the rat hindpaw express both KOR and GIRK1/2 channels. Knockdown of GIRK2 channels in keratinocytes with intraplantar injection of shRNA, prevented antinociceptive effects of the GIRK channel activator, ML297 and U50488. Additionally, knockdown of KOR in keratinocytes with intraplantar shRNA also prevented antinociception by U50488. Knockdown of GIRK and KOR in rat hindpaws was verified using RT-qPCR, RNAscope and immunohistochemistry. Collectively, these data suggest that the KOR signaling via GIRK channels in keratinocytes is required for peripheral KOR-mediated antinociceptive signaling in the rat hindpaw.

Disclosures: E.K. Debner: None. **M.M. Pando:** None. **W.P. Clarke:** None. **K.A. Berg:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.12

Topic: D.02. Somatosensation – Pain

Support: NIH, NINDS Grant NS055159-12
NIH, NINDS Grant F31NS125940

Title: The Role of TRPM3 Ion Channels in Opioid-Induced Pruritus

Authors: *N. KIM, Y. YUDIN, S. SU, T. ROHACS;
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Abstract: Morphine, a powerful opioid, is standard treatment for the management of severe pain. The desired analgesic effect of the neuraxial administration of morphine has the distressing side effect of pruritus. Opioid antagonists are the first line of treatment, which can counteract the analgesia from the initial opioid therapy. Antihistamine treatments are also ineffective against morphine-induced pruritus. Therefore, a more target-specific treatment for morphine-induced pruritus is needed. Pruritus from morphine is caused by the inhibition of inhibitory neurons, while the analgesia is caused by inhibition of excitatory neurons in the spinal cord. Morphine acts on opioid receptors which couple to heterotrimeric Gαi-proteins exerting acute effects on downstream ion channel targets to inhibit neuronal activity. However, the ion channel responsible for morphine-induced pruritus is unknown. This project aims to investigate if the transient receptor potential melastatin 3 (TRPM3) ion channels are involved in opioid-induced pruritus. TRPM3 is a non-selective, heat-sensitive cation channel expressed in neurons that is inhibited upon opioid receptor activation. This inhibition is mediated by direct binding of Gβγ to a 10-amino acid binding site in the channel, encoded by an alternatively spliced exon. We created a genetically mutated mouse line ($TRPM3^{DEx17}$) in which TRPM3 channels lack this exon, thus the channels are not inhibited by opioid receptor activation. Upon intrathecal injection of morphine, the $TRPM3^{DEx17}$ mice experienced significantly less scratch bouts compared to wild-type (WT) mice, while histaminergic itch was conserved in the mutant mice. Exogenously activating TRPM3 with intrathecal co-injection of pregnenolone sulfate (PS) along with morphine significantly decreased scratching. Intrathecal injection of the TRPM3 antagonist, primidone, caused spontaneous itch in WT mice. As TRPM3 shows higher level of co-expression with the μ-opioid receptors in the inhibitory neurons responsible for the pruritic pathway compared to the excitatory neurons for the analgesic pathway, the results are consistent with the claim that the activation of TRPM3 can decrease morphine-induced itch without significant side effects. This study outlines the first distinct phenotype found in the novel mouse model $TRPM3^{DEx17}$ and provides evidence for a potential new therapy to relieve morphine-induced pruritus by targeting TRPM3.

Disclosures: **N. Kim:** None. **Y. Yudin:** None. **S. Su:** None. **T. Rohacs:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.13

Topic: D.02. Somatosensation – Pain

Support: Canadian Institutes of Health Research (FDN-148413)

Title: Analgesic effectiveness of biased opioid-neurotensin bifunctional ligands

Authors: É. BREAULT[1], J. DE NEVE[2], S. PREVITI[2], E. VANGELOVEN[2], R. BROUILLETTE[1], M. CHARTIER[1], B. HOLLERAN[1], É. EISELT[1], *J.-M. LONGPRÉ[1], L. GENDRON[1], S. BALLET[2], P. SARRET[1];
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Abstract: The clinical management of various types of pain relies on the use of opioid analgesics. Paradoxically, long-term use and increasing doses of opioids are accompanied by diverse adverse effects, which are primarily mediated by mu-opioid receptor (MOR) activation, including constipation and respiratory depression. In the search for safer analgesics, G protein *versus* β-arrestin biased agonism at the MOR has been proposed as an opportunity to produce antinociception with reduced adverse effects. Furthermore, the design of multifunctional ligands co-targeting opioid and non-opioid receptors offers a promising strategy for the treatment of pain. As one of the non-opioid pharmacophores, neurotensin (NT) receptor agonists can be considered in the rational design of such chimeric compounds. Since activation of the NT receptor type 1 (NTS1) induces hypotension and hypothermia, selective targeting of NTS2 is a preferred approach for pain relief. Here, we fused the NTS2-selective NT(8-13) analog Arg-Arg-Pro-(6-OH)Tic-Tle-Leu-OH via a classical peptide bond to the *C*-terminal residue of a series of tetrapeptide opioid agonists derived from a dual MOR/DOR analog H-Dmt-D-Arg-Aba-β-Ala-NH_2 to improve the analgesic/adverse effect ratio. Modifications were introduced within the opioid tetrapeptide, in particular, substitutions of Aba^3 by $1\text{-}Ana^3$ and/or βAla^4 by Gly^4 or $GABA^4$ to investigate the influence on the linker between the two pharmacophores and the hydrophobicity on the opioid part. As a single modification on the NT part, a β^3-homo-Arg residue was also inserted in position 8 of NT(8-13). These new opioid-NT hybrids were then characterized *in vitro* for their affinity and selectivity towards MOR, DOR, NTS1 and NTS2 receptors and their ability to modulate the $G_{\alpha i}$ and β-arrestin-2 signaling pathways at the opioid receptors. All opioid-NT hybrid peptides exhibited high affinity for NTS2 (1 to 5 nM), good selectivity over NTS1 (Ki > 1800 nM), and MOR affinity values in the subnanomolar range (< 1 nM). In addition, the replacement of βAla by Gly or GABA slightly improved DOR binding. BRET-based biosensors were then used to measure the potency and efficacy of the bifunctional peptides in recruiting β-arrestin-2 and $G_{\alpha i}$ activation to MOR and DOR. Interestingly, these chemical modifications result in chimeric peptides with either partial agonist activity or biased signaling profiles at the opioid receptors. Finally, their analgesic efficacy, assessed using the rat acute tail-flick pain model, revealed a strong analgesic effect after intrathecal administration. Hence, these opioid-NT hybrids represent a promising avenue towards the development of safer analgesics.

Disclosures: **É. Breault:** None. **J. De Neve:** None. **S. Previti:** None. **E. Vangeloven:** None. **R. Brouillette:** None. **M. Chartier:** None. **B. Holleran:** None. **É. Eiselt:** None. **J. Longpré:** None. **L. Gendron:** None. **S. Ballet:** None. **P. Sarret:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.14

Topic: D.02. Somatosensation – Pain

Support: Noble Family Innovation Fund Seed Program
Schiebel Scholarship - UCLA
UCLA I2URP

Title: Abuse deterrent opioid prodrugs with low addiction potentials

Authors: *A. TANZILLO, K. SETH, B. TREACY, H. MAYNARD, C. M. CAHILL; UCLA, UCLA, Los Angeles, CA

Abstract: Prescription opioids contribute to thousands of deaths each year. Pharmaceutical companies have developed abuse-deterrent formulas (ADFs) with chemical safeguards intended to decrease abuse of prescription opioids, but methods to circumvent these safeguards can be found easily online. This project aims to develop and assess a novel oxycodone prodrug ADF (Compound X or “X") that contains an unprecedented number of safeguards. In this study, we aim to demonstrate that X will produce antinociception following only oral, but not other parental administration. We subjected adult male and female C57Bl/6 mice (8-10 weeks of age) to acute phasic (hot plate test, 55^{o}C), tonic inflammatory (formalin test, 10mL/kg of 2.5% formalin) and postoperative pain models (Hargreaves test following intraplantar incision). Mice were treated with oral gavage vehicle (water 0.1mL/10g, p.o.), oxycodone (3 mg/kg, p.o.) or X (3/10/30 mg/kg p.o., for the surgical models, formalin test and hot plate test, respectively) prior to nociceptive testing. Mice were habituated to the testing environment and apparatus for three days prior to all experimentation. The hot plate test elucidated the time course of action of X. Oxycodone (n=6) and X (n=7) produced peak antinociceptive effects 30 and 40 minutes after administration and thermal withdrawal thresholds returned to baseline at 50 and 70 minutes, respectively. To test the effects of X in an inflammatory pain model, mice received water (n=11) or oxycodone (n=10) 10 minutes prior to formalin injection. X (n=10) was given 60 minutes prior to formalin. Mice treated with water showed a typical bi-phasic nocifensive response characterized by licking and flinching of the hind paw. Oxycodone reduced only the first phase of formalin-induced behavior. X significantly reduced both the first and second phases. Intraperitoneal injection of X in both the hot plate (n=4) and formalin tests (n=2) confirmed lack of antinociceptive effects via this route of administration. We used a postoperative pain model where the flexor digitorum brevis was then incised. Post-surgical thermal withdrawal thresholds were assessed 24 to 72 hours after surgery prior to oral administration of water, oxycodone, or X.

Both X and oxycodone returned postoperative withdrawal thresholds back to pre-surgical levels. No sex differences were observed in any of the data sets. These data indicate that X produces antinociception following oral administration in various nociceptive modality tests. X will ideally replace current opioid analgesics used in clinical practice.

Disclosures: **A. Tanzillo:** None. **K. Seth:** None. **B. Treacy:** None. **H. Maynard:** 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.; Noble Foundation. **C.M. Cahill:** 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.; Noble Foundation.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.15

Topic: D.02. Somatosensation – Pain

Support: PhRMA Foundation Research Starter Grant
NIH Grant R03TR003667

Title: Evaluation of Antinociceptive Effects of a GPR171 Agonist and Morphine in Mice

Authors: C. PORTER, M. MATTOON, *E. BOBECK;
Utah State Univ., Logan, UT

Abstract: Pain is one of the most common motives for seeking medical attention. Opioid pharmaceuticals are among the most effective for treating pain, yet are limited due to adverse side effects, addiction, dependance, and tolerance. Recently, a novel G protein-coupled receptor, GPR171, and a GPR171 agonist, MS15203, have been identified as a potential pain target. Activation of GPR171 via MS15203 in combination with morphine has been shown to enhance morphine antinociception in acute pain. This increase in antinociception by MS15203 shows the potential to decrease morphine dosages while achieving the same analgesic effect as a higher dosage of morphine. With the addition of MS15203 and lessening the amount of morphine, this would provide that same pain relief for an individual and reduce opioid adverse side effects. To further elucidate the GPR171 agonist's antinociceptive properties, in the current study combinations of MS15203 and morphine were used to determine if a lower dosage of morphine with the addition of MS15203 would provide a similar antinociceptive effect as a higher dosage of morphine. Two combinations of morphine and MS15203 were used. The first consisting of 0.10mg/kg morphine plus 50mg/kg MS15203 and the second being 1.0 mg/kg morphine with 25 mg/kg MS15203. Each dose of morphine and MS15203 were also tested independently. Mice were injected once with a randomly assigned treatment and tested on the hot plate and tail flick

tests at five time intervals (0, 15, 30, 60, 90, and 120 minutes). Current data indicates treatment of MS15203 does not enhance antinociception with lower morphine dosages. However, minimal antinociception following injection was achieved in subjects treated with the combination and MS15203 alone. In addition, analysis of neurological cell death using an *in situ* cell death fluorescent detection kit in subjects treated with MS15203 was conducted. Results show the agonist does not produce neurological apoptosis. Future studies utilizing various behavior and fluorescent staining methods will further assess MS15203's antinociceptive properties in chronic pain and determine the agonist's side effect profile.

Disclosures: C. Porter: None. **M. Mattoon:** None. **E. Bobeck:** 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.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.16

Topic: D.02. Somatosensation – Pain

Support: NIH-NIDA P50DA044121

Title: Smore: smart opioid reduction, an algorithm for personalized dynamic opioid reduction

Authors: *R. JABAKHANJI[1,2,3], A. VIGOTSKY[4,2,3], G. RACHED[1,2,3], B. WU[10], L. HUANG[1,2,3], J. W. GRIFFITH[5,2,3], T. J. SCHNITZER[6,7,8,2,3], A. APKARIAN[1,3,7,9,2]; [1]Neurosci., [2]Ctr. for Translational Pain Res., [3]Ctr. of Excellence for Chronic Pain and Drug Abuse, [4]Biomed. Engin., [5]Med. Social Sci., [6]Physical Med. and Rehabil., [7]Anesthesia, [8]Rheumatology, [9]Pain Med. and Rehabil., Northwestern Univ., Chicago, IL; [10]The Second Affiliated Hosp. and Yuying Children's Hospital, Wenzhou Med. Univ., Wenzhou, China

Abstract: Opioids are among the most widely used drugs for treating chronic pain. Long-term opioid regiments are associated with dependence, hyperalgesia, respiratory depression, and death, and a large societal and economic burden. Approximately one in five long term users will misuse prescribed opioids. According to the CDC, around 70,000 overdose deaths involved an opioid in 2020. In 2017, opioid misuse and dependence economic burden related to health care, criminal justice, and lost productivity amounted to 127 billion dollars. Despite a national call, and effort to taper opioid dosage and decrease prescriptions, mortality is still rising. Current methods to taper and discontinue opioids are associated with increased risk of suicide, transition to street drugs and overdose. More research is needed to develop patient centric methods for reducing opioid consumption safely.We conducted a survey to understand the attitudes, concerns, and priorities of patients with chronic pain on long-term opioids with regards to dose tapering. All respondents indicated that they are interested in participating in a study seeking to

reduce opioid consumption, with 75% very or extremely interested. 94% indicated that controlling pain is very or extremely important, and 66% indicated that controlling drug cravings is very or extremely important.We implemented a personalized, data driven approach for dynamically dosing and reducing opioid intake in chronic pain patients while managing pain and cravings. In contrast with current constant dose prescription schemes, our approach uses a reinforcement learning (RL) algorithm that uses pain and craving levels provided by the patient via a mobile friendly website, prior to taking their meds, to recommend an optimal dose. The RL agent also places a value on lowering opioid doses and will tend to reduce opioid intake over time. An initial one-week phase where doses are chosen at random is used by the RL to learn the dose response of the patient and which dose is best for some pain/craving state. Initial simulation results are very promising. We ran two scenarios: 1) reduce the does while taking into account pain level only, 2) taking into account pain and craving levels. In scenario 1, we observed an average of 50% dose reduction within the first two weeks with an initial increase in pain of 2.5/10 that was down to zero by end of week 2. In scenario 2, stable dose reduction was 35% by the end of week 2 with final pain and craving of 0/10 and 2/10 respectively. Currently we are conducting a two-month pilot study with chronic pain patients on long term opioid regiment recruited from a pain management clinic.

Disclosures: **R. Jabakhanji:** None. **A. Vigotsky:** None. **G. Rached:** None. **B. Wu:** None. **L. Huang:** None. **J.W. Griffith:** None. **T.J. Schnitzer:** None. **A. Apkarian:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.17

Topic: D.02. Somatosensation – Pain

Support: Margo Cleveland Fund

Title: G alpha subunits selectively modulate mu opioid receptor pharmacology

Authors: M. E. BARNETT, B. I. KNAPP, ***J. M. BIDLACK**;
Pharmacol. and Physiol., Univ. of Rochester Sch. of Med. and Dent., Rochester, NY

Abstract: The μ opioid receptor (MOR) is a G protein coupled receptor that couples to the Gαi/o class of proteins. The diversity within this class is often downplayed. Gαz is an often-overlooked member of this class, yet its prevalent expression in similar regions of the brain as opioid receptors suggests it may serve a distinct role in MOR signaling. Using a bioluminescence resonance energy transfer (BRET) sensor, we investigated the potential of Gαz and its regulator of G protein signaling counterpart, RGSZ, as a means to control both efficacy and potency of MOR agonists. To avoid hindering the MOR•Gαz interaction, Gα signaling was correlated to the interaction of Venus-tagged Gβγ with a non-functional, C-terminal fragment of its effector, G protein-coupled receptor kinase 3 (GRK3ct). Agonist binding to MOR resulted in an increase in

BRET due to G-protein dissociation. The full agonists [D-Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO), β-endorphin, endomorphin-1, methadone, etorphine and fentanyl were more potent when MOR signaled through Gαz compared to other Gαi/o subunits. For example, the EC_{50} value of fentanyl increased 3-fold when the MOR signaled through Gαi1 compared to Gαz. Fentanyl was equally efficacious with similar E_{max} values with both Gα subunits. Additionally, partial agonists, such as morphine, (-)pentazocine, metazocine, and ethylketocyclazocine, were more potent and more efficacious when the MOR signaled through Gαz compared to the other Gαi/o subunits. In the case of (-)pentazocine, when MOR signaled through Gαz, the EC_{50} value was 2-fold lower compared to when MOR signaled through Gαi1. The E_{max} value was also 2-fold higher when the MOR signaled through Gαz compared to Gαi1. When RGSZ was present in the system, the concentration-response curves of DAMGO and morphine had a significant rightward shift. Increased activation and deactivation rates were correspondingly observed in the presence of RGSZ. Gαz has a slow rate of GTP hydrolysis in comparison to other Gαi/o proteins. To mimic the biochemical properties of Gαz, two different mutations were made in GαoA. GαoA G183S was RGS-insensitive and GαoA 41TSN43 had a slower intrinsic rate of GTP hydrolysis. Both mutants resulted in decreased rates of activation and deactivation for DAMGO and morphine. When the MOR signaled through either mutant, the concentration-response curves of DAMGO and morphine both had a significant leftward shift. Taken together, signaling through mutant GαoA can mimic the ability of Gαz to enhance opioid potency and efficacy downstream of receptor binding. Enhanced potency and efficacy observed the MOR signaling through Gαz may be the result of slower GTP hydrolysis.

Disclosures: **M.E. Barnett:** None. **B.I. Knapp:** None. **J.M. Bidlack:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.18

Topic: D.02. Somatosensation – Pain

Support: Arizona Biomedical Research Commission New Investigator Award #ADHS18-198875

Title: Systemic Isoform-Selective Heat Shock Protein 90 Inhibitors Improve the Therapeutic Index of Morphine

Authors: *K. CHOU[1], C. S. CAMPBELL[3], P. BEJARANO[2], D. I. DURON[2], J. M. STREICHER[1];
[1]Univ. of Arizona, [2]Pharmacol., Univ. of Arizona, Tucson, AZ; [3]The Univ. of Arizona, The Univ. of Arizona, Tucson, AZ

Abstract: Opioids like morphine are the benchmark for treating severe acute pain; however, severe side effects including respiratory depression and addiction limit their viability. One

approach to improve opioid therapy focuses on a dose-reduction strategy by amplifying opioid analgesia without boosting side effects, so less opioids are needed. To this end, we've focused on Heat shock protein 90 (Hsp90), a central protein regulator in the cell; ongoing studies from our lab have shown that inhibition of Hsp90 in the spinal cord improves morphine antinociceptive potency by 2-4 fold in acute and chronic pain while reducing tolerance, rescuing established tolerance, and not changing reward and constipation. However, our results also showed that non-selective Hsp90 inhibitors given systemically (intravenous) have the opposite effect, blocking opioid pain relief. Seeking a means to surmount this roadblock, we determined which Hsp90 isoforms regulate opioid pain relief in brain and spinal cord in mice using selective small molecule inhibitors and CRISPR/Cas9 gene editing. We found that Hsp90α alone regulated opioid signaling and pain relief in the brain. However, in the spinal cord, we found that the isoforms Hsp90α, Hsp90β, and Grp94 all regulates opioid signaling and pain relief. This led to our hypothesis that targeting spinal cord Hsp90 with isoform-selective inhibitors given IV could boost opioid pain relief without altering side effects, enabling a dose-reduction strategy. We tested this hypothesis with the novel Grp94-selective inhibitor KUNG65 and the novel Hsp90β-selective inhibitor KUNB106, given at a 1mg/kg dose IV in male and female CD-1 mice, followed by a 24hr treatment time, then analysis of opioid antinociception and side effects. We found that systemic (IV) KUNG65 treatment resulted in a 1.9 fold increase in morphine potency to relieve tail flick pain and 3.3 fold increase for KUNB106, consistent with our earlier studies injecting inhibitors directly into the spinal cord. We also found that both KUNG65 and KUNB106 boosted morphine potency in paw incision pain. Additionally, both inhibitors could rescue established morphine tolerance in the tail flick assay, again as found for direct spinal cord injection. These results support our hypothesis that isoform-selective Hsp90 inhibitors can selectively engage Hsp90 in the spinal cord when given systemically, resulting in improved opioid antinociception and side effects and strongly suggest that they can be a powerful new tool to improve opioid therapy through a dose-reduction strategy, and further show that this effect can be achieved through a translationally relevant dosing route.

Disclosures: K. Chou: None. **C.S. Campbell:** None. **P. Bejarano:** None. **D.I. Duron:** None. **J.M. Streicher:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.19

Topic: D.02. Somatosensation – Pain

Support: NIH Grant R01DA052340

Title: Investigation of the Role of Wnt/Delta-Catenin Signaling in Regulating Opioid Pain Relief After Heat Shock Protein 90 Inhibition

Authors: *C. MAHRER, J. STREICHER;
Univ. of Arizona, Tucson, AZ

Abstract: Opioid receptors are important regulators of pain, and opioid drugs like morphine are used in a wide variety of clinical settings throughout the world. In spite of their clear utility and efficacy concerning the treatment of pain, the addictive nature of opioids limits their use as an option for the treatment of chronic pain. This illustrates the great medical and social need to improve opioid therapy, both enhancing analgesia and reducing side effects like addiction. More recently, we showed that Heat shock protein 90 (HSP90), a molecular chaperone that participates in a vast array of critical molecular processes in the cell, has been implicated as an important modulator of opioid-induced pain relief within the spinal cord. We found that inhibition of HSP90 improved the therapeutic index of opioids, boosting pain relief and reducing side effects. In an effort to elucidate the molecular pathways responsible for these benefits, we performed proteomic analysis of spinal cord tissue from male and female CD-1 mice treated with intrathecal Vehicle or 17-AAG (0.5 nmol, 24 hrs), an HSP90 inhibitor. We found that the signaling molecule delta-catenin2 was reduced by 27.6% by 17-AAG treatment in spinal tissue. Since delta-catenin2 stabilizes and enables Wnt signaling, this suggests that Wnt signaling is also reduced by HSP90 inhibition. As Wnt has been shown to promote pain, this fits with our model that suppressed Wnt/Catenin signaling could enhance opioid pain relief after HSP90 inhibition. We thus report here our efforts to test this hypothesis by using a Wnt activator (AMBMP) and Wnt inhibitor (JW74) combined with 17-AAG and morphine in a mouse tail flick pain model; we also report our efforts to confirm molecular Wnt signaling changes in spinal cord by Western Blot and qPCR for Wnt itself along with established Wnt signaling targets VEGF-A and LEF1. Together these studies will establish a new mechanistic node linking HSP90 to the regulation of opioid pain relief in the spinal cord. This will enhance our basic science understanding of this system and could lead to novel therapeutic targets.

Disclosures: C. Mahrer: None. **J. Streicher:** 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 is funded by R01DA052340 to JMS.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); JMS has an equity stake in Botanical Results, LLC and is a co-founder and equity holder in Teleport Pharmaceuticals, LLC.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.20

Topic: D.02. Somatosensation – Pain

Title: Stress Exposure induces Morphine Sensitization: Involvement of the Dopaminergic System in the Nucleus Accumbens

Authors: *S. MOHAMMADI, A. HAGHPARAST;
Neurosci. Res. Ctr., Shahid Beheshti Univ. of Med. Sci., Tehran, Iran, Islamic Republic of

Abstract: Dopamine is a neurotransmitter that is increased in the nucleus accumbens (NAc) by administration of morphine as a sedative, and repeated exposure to morphine accompanied by stress leads to enhancement of dopamine overflow in the NAc. This study aimed to evaluate the cross-sensitization of stress and morphine, focusing on the role of dopaminergic receptors in the NAc. Two stainless steel guide cannulae were implanted 1mm above the NAc of the adult male Wistar rats weighing 220-250g via stereotaxic surgery. Various doses of SCH23390 as a D1-like dopamine receptor antagonist (0.125,0.25,1 and 4 μg/0.5μl/NAc) and Sulpiride as a D2-like dopamine receptor antagonist (0.25,1 and 4μg/0.5μl/NAc) were microinjected into the NAc. Five minutes after microinjection, three hours of restraint stress (RS) as psychological stress, or six min forced swim stress (FSS) was applied as physical stress. Ten minutes after exposure to stress, an ineffective dose of morphine (1mg/kg) was injected subcutaneously. The procedure was repeated for three consecutive days as a sensitization period followed by a 5-day drug and/or stress-free period. On the ninth day, morphine sensitization was verified by evaluating the antinociceptive response of an ineffective dose of morphine to the tail-flick test. The results revealed that although co-administration of morphine (1mg/kg) and stress in three consecutive days led to morphine sensitization, intra-accumbal microinjection of SCH23390 and Sulpiride disrupted morphine cross-sensitization with stress, either RS or FSS. Our findings suggest an undeniable role for dopamine receptors within the NAc, in morphine sensitization induced by morphine-stress co-administration.

Disclosures: S. Mohammadi: None. **A. Haghparast:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.21

Topic: D.02. Somatosensation – Pain

Support: NIH 1RF1NS113840-01

Title: Diroximel fumarate protects against opioid-induced hyperalgesia and tolerance in mice

Authors: *M. RASHEED, F. R. CHERRY, M. V. CHAVEZ, P. M. GRACE;
Labs. of Neuroimmunology, Dept. of Symptom Research,MD Anderson Pain Res. Consortium, The Univ. of Texas MD Anderson Cancer Ctr., Houston, TX

Abstract: Long term administration of opioids results in development of tolerance and opioid-induced hyperalgesia (OIH). It is believed that tolerance and OIH are caused in part by oxidative stress. We hypothesized that activating the antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) will alleviate morphine tolerance and OIH. For the OIH experiment, male and female mice were implanted with subcutaneous osmotic minipumps to

infuse morphine for 7 days (10 mg/kg/day) or saline. Diroximel fumarate (DRF), an FDA approved drug, was used to activate Nrf2. Oral DRF (100 mg/kg/day) or equivolume vehicle was administered the day before minipump implantation, and then daily for the 7-day morphine infusion. Mechanical allodynia and thermal hyperalgesia were measured using von Frey and hot plate test respectively, daily after DRF dosing. For the tolerance experiment, male and female mice were administered morphine (5 mg/kg/twice daily, subcutaneous) or equivolume saline along with oral DRF (100 mg/kg/day) or vehicle for 5 days. On day 5, cumulative doses of morphine (1.8, 3.2, 5.6, 10.0 and 18.0 mg/kg) were injected after every 20 min. Withdrawal thresholds to heat and mechanical stimuli were assessed using hot plate and von Frey tests respectively. Lipid peroxidation was assessed using MDA quantification through thiobarbituric acid reactive substance assay and gene expression analysis of antioxidant genes was conducted using quantitative real-time PCR in the dorsal horn of mice. Mice treated with morphine alone had decreased withdrawal thresholds to heat and mechanical stimuli by day 7, indicating development of OIH. However, DRF co-treatment blunted development of OIH. Mice treated with DRF alone did not show any change in withdrawal thresholds. Similarly, cumulative doses of morphine on day 5 caused a rightward shift in the dose response curve of morphine treated mice when compared to saline, showing development of tolerance. DRF co-treatment partially prevented development of tolerance. DRF upregulated the expression of antioxidant genes and attenuated the increase in MDA level in the dorsal horn of morphine treated mice. Therefore, our study shows that DRF has the potential to partially prevent the development of OIH and tolerance, thereby suggesting that DRF has opioid-sparing properties. Future studies will investigate the effects of DRF on other adverse effects of opioids.

Disclosures: **M. Rasheed:** None. **F.R. Cherry:** None. **M.V. Chavez:** None. **P.M. Grace:** 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.; Biogen.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.22

Topic: D.02. Somatosensation – Pain

Support: T32DA007097
R21NS118499
R36DA054455

Title: Role of astrocytes and CD38 in Spinal Opioid Antinociception

Authors: *R. QUINTANA, A. GUEDES;
Univ. Of Minnesota, Minneapolis, MN

Abstract: Chronic opioid therapy for pain management is associated with the development of opioid tolerance and dependance, which are risk factors for opioid misuse. Better understanding of the mechanisms that modulate opioid antinociception and tolerance could lead to the development of better pain treatment alternatives with reduced abuse potential. The transmembrane glycoprotein CD38, which is important for intracellular calcium homeostasis, has been linked to supraspinal opioid antinociception and tolerance, but its role in spinal antinociception and tolerance remain unknown. There is also a lack of information regarding cellular expression of CD38 at the spinal level, a site relevant for opioid actions. Our study aims to understand the role of CD38 in opioid antinociception in chronic neuropathic pain and to explore the cellular expression of CD38 in the spinal cord. To investigate the role of CD38 in neuropathic pain, we used the spared nerve injury (SNI) model in male and female, 2-6 month old wild type (WT) and CD38 knockout (CD38KO) mice. We determined mechanical withdrawal thresholds using von Frey filaments using the up-and-down method. We found that both mice developed similar magnitudes and significant mechanical hypersensitivity as determined using the von Frey test during a 12-week test period. To determine the role of spinal CD38 in opioid antinociception in the SNI model, CD38KO and WT animals received cumulative doses of the mu-opioid receptor agonist morphine (0, 0.125, 0.25, 0.5, 1 and 2 μmol/5μl, I.T.). We found the anti-nociceptive effect of morphine to be significantly decreased in CD38KO compared to WT mice. Together, these results suggest that CD38 is not involved in the development and maintenance of mechanical hypersensitivity due to peripheral nerve injury, but its presence in the spinal cord is required for the pain-relieving action of mu-opioid receptor agonists. To further understand how CD38 might mediate opioid-induced anti-nociception, we performed in-situ hybridization and immunohistochemistry in spinal cord tissues from WT mice and found that CD38 is localized exclusively in astrocytes. The canonical opioid anti-nociceptive mechanisms have been thought to be exclusively neuronal, but our results suggest that CD38-expressing astrocytes are important for effective opioid anti-nociception in the SNI model of neuropathic pain. Further exploration of astrocytic mechanisms in opioid signaling at the spinal level could reveal novel anti-nociceptive targets for neuropathic pain.

Disclosures: R. Quintana: None. **A. Guedes:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.23

Topic: D.02. Somatosensation – Pain

Support: CIHR grant PJT-162103
NSERC grant RGPIN-2018-06100
CIHR fellowship to CB

Title: Distribution of delta and mu opioid receptor mRNA in primary afferents

Authors: *C. BEAULIEU[1], B. QUIRION[1], L. CÔTÉ[3], N. J. PIMENTA[2], J.-L. PARENT[3], L. GENDRON[1];
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Abstract: Opioids are commonly used to alleviate moderate to severe pain. Clinically used opioids act via mu opioid receptors (MOP), also responsible for the numerous undesired effects such as respiratory depression, nausea and addiction. There are two other receptors belonging to the opioid receptors family, namely delta (DOP) and kappa opioid receptors (KOP). Our lab investigates the potential role of the DOP in nociception. Activation of DOP was shown to produce analgesia in various animal pain models, without inducing the unwanted effects commonly associated with MOP. In this study, we sought to determine and compare the distribution of both DOP and MOP in dorsal root ganglia (DRG) and trigeminal ganglia (TG) neurons of rodents, nonhuman primates, and human. The distribution of DOP and MOP mRNA in primary afferents was studied using the RNAscope™ *in situ* hybridization approach. The identity of the neurons expressing these receptors was determined using antibodies (NF200, IB4) and RNAscope™ probes (P2X3, TAC1) against neuronal markers commonly used for myelinated, non peptidergic and peptidergic neurons. We found that DOP and MOP mRNA are located in all type of neurons in both DRGs and TGs. Our results further revealed that DOP mRNA is mainly expressed in NF200-positive, myelinated neurons in rats while it is preferentially expressed in P2X3-positive, small non peptidergic neurons in mice and monkeys. The MOP mRNA was rather found in small peptidergic (Tac-1 positive) and non peptidergic neurons in rats (IB4-positive) and mice (P2X3-positive). In monkeys, MOP mRNA was mostly seen in small peptidergic, Tac-1 positive neurons. In all species, the coexpression of DOP and MOP preferentially takes place in myelinated fibers. Therefore, we conclude that despite interspecies differences, both DOP and MOP are expressed in all DRG and TG neuronal types, where they likely participate in regulating nociception.

Disclosures: C. Beaulieu: None. **B. Quirion:** None. **L. Côté:** None. **N.J. Pimenta:** None. **J. Parent:** None. **L. Gendron:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.24

Topic: D.02. Somatosensation – Pain

Support: NIH NIDA grant DA042888
NIH NIDA grant DA007242
NIH R35HG010719

Title: Promoting morphine tolerance and reward through an exon 7-associated severn transmembrane C-terminal variant, mMOR-1O, of the mouse mu opioid receptor gene, Oprm1, in a new gene targeting mouse model

Authors: *Y. PAN[1], S. LIU[1], J. XU[1], A. F. MALIK[1], R. CHIEN[1], R. QUADROS[2], C. B. GURUMURTHY[2];
[1]Anesthesiol., Rutgers New Jersey Med. Sch., Newark, NJ; [2]Pharmacol. and Exptl. Neurosci., Univ. of Nebraska, Omaha, NE

Abstract: The single-copy mu opioid receptor gene, *OPRM1*, undergoes extensive alternative pre-mRNA splicing, generating multiple mu opioid receptor splice variants conserved from rodent to human. One variant type includes seven-transmembrane (7TM) C-terminal variants that are identical except for the tip of the intracellular C-terminal tail. Our previous studies using C-terminal truncation mouse models have revealed distinct pharmacological functions of these C-terminal variants, particularly exon 7 (E7)-associated variants. Truncating E7 in mE7M-B6 mice diminished morphine tolerance and reduced morphine CPP. Although E7 C-terminal truncation involves both 7TM and 6TM variants, it is most likely that E7-associated 7TM variants are responsible. However, the role of individual E7-associated 7TM C-terminal variant remains unknown. To further explore *in vivo* functions of individual E7-associated 7TM variants, we generated a new mouse model, mMOR-1O$^{Ina/Ina}$ (^{Ina}: inactive), using an *Easi*-CRISPR approach. In this model, we knocked out E1, which eliminates all 7TM variants and in its place, we knocked in an inverted loxP-floxed mMOR-1O, an E7-associated 7TM variant that is most conserved and abundant. Neither [^{3}H]-DAMGO binding nor mu opioid analgesia was observed in mM1O$^{Ina/Ina}$ mice, indicating loss of all 7TM variants and no function of the knock-in mMOR-1O cassette. We then bred the mMOR-1O$^{Ina/Ina}$ mouse with an EIIa-Cre mouse to flip the inverted mMOR-1O cassette, generating mMOR-1O$^{Act/Act}$ (^{Act}: active) in which only mMOR-1O is expressed under the control of the endogenous exon 1 promoter. Distribution and expression of mMOR-1O mRNA in mMOR-1O$^{Act/Act}$ mice determined by a modified BaseScope assay with a mMOR-1O-specific probe were similar to those in WT mice. Opioid receptor binding using [^{3}H]-DAMGO revealed high affinity toward [^{3}H]-DAMGO and mu selectivity for the knock-in mMOR-1O. Mu opioid-induced G protein coupling profiles measured by [^{35}S]-GTPγS autoradiography and [^{35}S]-GTPγS binding using isolated membranes from various brain regions in mMOR-1O$^{Act/Act}$ mice were comparable with those seen in WT mice. Morphine analgesia in mM1O$^{act/act}$ mice was normal. However, mM1O$^{Act/Act}$ mice developed morphine tolerance faster and more robust than WT mice and showed a significant increase of morphine CPP compared to WT mice, suggesting that mMOR-1O promotes morphine tolerance and enhances morphine reward, complementing the results from mE7M-B6 mice. This new mouse model provides an invaluable tool to further decipher *in vivo* mechanisms and functions of mMOR-1O and potentially identify novel targets that contribute to morphine tolerance and reward.

Disclosures: **Y. Pan:** Other; I am a scientific co-founder of Sparian Biosciences.. **S. Liu:** None. **J. Xu:** None. **A.F. Malik:** None. **R. Chien:** None. **R. Quadros:** None. **C.B. Gurumurthy:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.25

Topic: D.02. Somatosensation – Pain

Support: NIH Grant R01DA044481
New York Stem Cell Foundation

Title: The functional organization of the opioid system in dorsal root ganglion neurons

Authors: *M. GERON[1,2,3], A. TASSOU[1,2,3], A. SHUSTER[4], G. SCHERRER[1,2,3,5];
[1]Dept. of Cell Biol. and Physiol., [2]UNC Neurosci. Ctr., [3]Dept. of Pharmacol., The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Neurobio., Harvard Med. Sch., Boston, MA; [5]New York Stem Cell Fndn. – Robertson Investigator, Chapel Hill, NC

Abstract: Targeting specific opioid receptor types in distinct sensory neurons could lead to safer and more effective treatments for pain and itch. However, the extent to which different DRG neurons that express opioid receptors (MOP, DOP, KOP, NOP) and/or peptides (endorphins, enkephalins, dynorphins, nociceptin) innervate distinct organs and what particular sensory modalities they encode represent long-standing questions in the field. To determine the functional organization of the opioid system in DRG neurons, we utilized novel (*Oprd1*^{Cre}, *Oprm1*$^{Flp,\ or\ CreERT2\ or\ Dre}$) and published knock-in mouse lines expressing DNA recombinases in opioid receptor–or peptide–positive cells. We injected these mice intrathecally with viruses encoding recombinase-dependent tdTomato and analyzed the labeling of somata in DRG and axon terminals in peripheral tissues using immunostaining and tissue clearing protocols. In the DRG of *Oprm1*^{Cre} *and Oprk1*^{Cre} mice, tdTomato was primarily expressed in peptidergic CGRP+ small-diameter neurons. In contrast, in *Oprd1*^{Cre} mice, the majority of tdTomato+ DRG neurons were large-diameter myelinated neurons, confirming our previous finding that DOP is expressed in mechano-sensitive DRG neurons. We next crossed these Cre mice with Cre-dependent reporter mice such as CAG-Sun1/sfGFP mice to compare developmental (sfGFP) versus adult (tdTomato) expression patterns for each opioid receptor. For MOP, DOP, and KOP, DRG neurons expressing tdTomato comprised 30%-60% of the expression fate map. Analysis of tdTomato expression in *Penk*^{Cre}, *Pdyn*^{Cre}, *and Pnoc*^{Cre} mice suggests that opioid peptides are sparsely expressed in DRG neurons. In hairy skin of *Oprm1*^{Cre} *and Oprd1*^{Cre} mice, tdTomato labeled free nerve endings as well as circumferential nerve endings around hair follicles. However, DOP+ circumferential endings were also NFH+ whereas MOP+ ones were not, suggesting that MOP is expressed by high-threshold mechanoreceptors responding to hair pull, whereas DOP is expressed by low-threshold mechanoreceptors (LTMRs) activated by stroking of the skin. Innervation of hairy skin by opioid peptide–expressing neurons is scarce, with sporadic lanceolate nerve endings. Overall, our findings confirm that DOP+ DRG neurons are primarily LTMRs, whereas MOP is predominantly expressed by peptidergic C and A nociceptors. The new Cre and Flp mouse lines, used independently or in combination, enable the labeling and manipulating of discrete neurons expressing (or coexpressing) opioid receptors and peptides, to determine their molecular identity, connectivity, and function via single-cell RNA sequencing, circuit tracing, and behavioral experiments.

Disclosures: **M. Geron:** None. **A. Tassou:** None. **A. Shuster:** None. **G. Scherrer:** F. Consulting Fees (e.g., advisory boards); Cofounder of Epiodyne, a drug discovery company, an inventor on a US patent application (#20210220489) related to imaging of neural dynamics to discover analgesics. Other; Member of the National Institutes of Health Preclinical Screening Platform for Pain (PSPP) External Consulting Board..

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.26

Topic: D.02. Somatosensation – Pain

Support: INPFRM grant NC12165994.0

Title: The antinociceptive effect of the weak opiate tramadol is boosted by the D2-like receptor agonist quinpirole by systemic administration.

Authors: *A. ALMANZA-GUTIERREZ[1], J. I. MERCADO REYES[2], P. SEGURA-CHAMA[3], A. ROSARIO-MUJICA[4], F. PELLICER[5], F. MERCADO[6];
[1]Inst. Nacional De Psiquiatria RFM, México DF, Mexico; [2]Fisiologia Celular, Inst. Nacional De Psiquiatria Ramon de la Fuen, Ciudad DE Mexico, Mexico; [3]Inst. Nacional de Psiquiatria RFM, Ciudad de Mexico, Mexico; [4]Inst. Nacional de Psiquiatria RFM, Ciudad de México, Mexico; [5]Inst. Nacional De Psiquatria RFM, Huipulco, Mexico; [6]Dirección de Investigaciones en Neurociencias, Inst. Nacional de Psiquiatría Ramón de la Fuente Muñiz, Ciudad de Mexico, Mexico

Abstract: Pain is a morbidity or comorbidity with high incidence and great impact in the well-being of the patients. In this work we evaluate the antinociceptive effect of tramadol (weak MOR agonist) plus quinpirole (D2-like receptor agonist) by a systemic route administration. The work was done in naïve rats and rats with induced inflammatory and neuropathic pain. For the measurement of antinociceptive effect of the drugs thermonociceptive and mechanonociceptive stimuli were used, as well the evaluation of emotional aspects of pain with conditional place preference (CPP) experiments.
We found that tramadol plus quinpirole administration produced a complete reversion of the allodynia and hyperalgesia induced by the inflammatory and neuropathic insult, which was not alleviated by quinpirole or tramadol by themselves. The CPP experiments revelated that systemic quinpirole plus tramadol treatment was effective to relief from ongoing and/or spontaneous pain under only the inflammatory pain model.
In conclusion, D2-like agonists are effective adjuvants for the treatment of painful conditions in combination with a MOR agonist, these results could lead to investigate if this drug combination could reduce the opioid dose meanwhile is possible to obtain high analgesic effect, expecting reduce opioid associated side-effects.

Disclosures: **A. Almanza-Gutierrez:** None. **J.I. Mercado Reyes:** None. **P. Segura-Chama:** None. **A. Rosario-Mujica:** None. **F. Pellicer:** None. **F. Mercado:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.27

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH P50 DA044121

Title: Social isolation and chronic pain alter opioid-induced tactile allodynia and opioid motivation

Authors: *J. M. COX[1], M. V. CENTENO[1], S. CERMAK[1], A. VIGOTSKY[2], R. JABAKHANJI[3], A. BRINK[1], A. V. APKARIAN[3];
[1]Neurosci., [2]Northwestern Univ., Chicago, IL; [3]Neurosci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: The United States is in the midst of an opioid addiction and overdose epidemic. Although rates of opioid prescriptions have decreased, millions of chronic pain patients still use opioids, and these patients may be at increased risk of opioid use disorder (OUD). Additionally, chronic pain is often associated with periods of social isolation. How social isolation affects opioid self-administration is unclear, however. Moreover, it is unknown how chronic pain may affect relevant neural circuits to increase susceptibility to OUD. To address these questions, it is necessary to develop robust mouse models of OUD with and without chronic pain because of the many tools available for the precise recording and manipulation of specific populations of neurons in mice. Thus, we used a fentanyl vapor self-administration paradigm to evaluate how chronic pain, social isolation and their combination affects opioid self-administration, opioid motivation and opioid-induced tactile allodynia. We trained 4 groups of mice to self-administer fentanyl vapor. We used spared nerve injury (SNI) to induce chronic pain (n=16) to compare with control mice that received sham surgery (n=16). Additionally, half of SNI and sham mice were socially isolated starting 1 month prior to opioid self-administration training. Mice were trained on fixed ratio (FR) 1, 5 and 10 schedules for a total of 21 days, and drug seeking was assessed after different durations of abstinence. Drug seeking was tested by putting the mice in the fentanyl vaping chamber, but when they entered the active nose poke, only the drug-associated visual cue was presented without delivery of the drug. Following 8 days of FR1 training and 7 days of abstinence all groups showed increases in active nose poking during the drug seeking test without differences between the groups. Mice then underwent additional training and were tested for drug motivation after 2 and 9 days of abstinence. Again, all groups showed robust increases in active nose poking during the drug seeking test after 2 days of abstinence. Following 9 days of abstinence, the rate of active nose poking increased in SNI mice but decreased in sham mice. This suggests that after extended self-administration training, SNI

mice show increased motivation to seek opioids with longer periods of abstinence while sham mice do not. Additionally, social isolation increased opioid-induced allodynia in sham mice. Together, these results suggest that chronic pain and social isolation affect opioid craving and withdrawal-induced pain, and demonstrate that fentanyl vapor self-administration provides a powerful context to study the neural mechanisms underlying opioid misuse.

Disclosures: **J.M. Cox:** None. **M.V. Centeno:** None. **S. Cermak:** None. **A. Vigotsky:** None. **R. Jabakhanji:** None. **A. Brink:** None. **A.V. Apkarian:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.28

Topic: G.09. Drugs of Abuse and Addiction

Support: P50 DA044121

Title: Evaluating the Effects of Fentanyl Exposure on Brain Circuitry in Mice with Chronic Pain

Authors: *S. CERMAK[1], M. V. CENTENO[2], P. BRANCO[3], J. M. COX[4], R. JABAKHANJI[5], A. BRINK[3], D. PROCISSI[7], N. BERTOLINO[8], A. V. APKARIAN[6];
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Abstract: In recent years, overdose deaths have increased, especially given the prevalence of synthetic opioids such as fentanyl. In the case of chronic pain, opioid addiction is comorbid, but its mechanisms are poorly understood. As such, one would expect different activity during initial and prolonged exposure of fentanyl, as well as withdrawal. However, it is conceivable that chronic pain and sham animals have different brain activity across these time points. Given the lack of knowledge on fentanyl addiction in rodents, we aimed to understand how fentanyl exposure impacts brain circuitry in animals with and without spared-nerve injury.As a part of a larger experiment concurrently investigating the longitudinal effects of opioid self-administration in mice, we carried out a task-based fMRI study, in which mice were administered fentanyl in the scanner. In our opioid self-administration experiment, we placed mice in vapor self-administration chambers, in which mice learned to nosepoke for 5mg/kg on a fixed-ratio(FR) 1 and 5 schedule. Structural functional, and task-based fentanyl scans were conducted at baseline, FR1, FR5, and abstinence.We scanned sedated mice who underwent either spared-nerve injury (SNI) or sham procedures (8 male +8 female SNI; 7 male + 7 female sham). We used a novel method of administering fentanyl vapor in the scanner to understand the biological correlates of fentanyl use in rodents. Animals were anesthetized with isoflurane briefly followed by sedation with 0.3 mg/kg medetomidine. Fentanyl was presented in a block design consisting of 5 sec on followed by 55 sec off, for a total of ten minutes. We modeled the fentanyl stimulus to study the

time course of fentanyl using different durations of 1.5, 5, 10, 20, and 30 seconds in the brain. We fit a general linear model to estimate group averages and contrast conditions. We found that the hemodynamic response function was best modeled using a 5-second time course, indicating a short-lasting effect. Specifically, we observed increased brain activation in olfactory and subcortical regions, including the dorsal and ventral striatum, olfactory areas, and amygdala in all animals during initial exposure, but no differences between sham and SNI survived correction. Differences across time points are yet to be determined. We conclude that we can detect the effects of fentanyl in the brain in real-time. Future studies will investigate different anesthetics and fentanyl dosages to better understand opioid addiction and chronic pain.

Disclosures: S. Cermak: None. **M.V. Centeno:** None. **P. Branco:** None. **J.M. Cox:** None. **R. Jabakhanji:** None. **A. Brink:** None. **D. Procissi:** None. **N. Bertolino:** None. **A.V. Apkarian:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.29

Topic: G.09. Drugs of Abuse and Addiction

Support: U.S. Department of Defense Grant W81XWH-16-1-0522
NIDA Grant R01DA042033
NIDA Grant R01DA048094
NIDA Grant R01DA051420
NIDA Grant R01DA049733

Title: Psychophysiological and Self-Report Prediction of Opioid Choice Behavior in Chronic Pain Patients: Double Dissociation

Authors: *P. DHAYAGUDE[1], S. J. MOELLER[1], J. HUDAK[2], E. L. GARLAND[2];
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Abstract: Misuse of prescription opioids is a key factor driving the growing number of opioid use disorder (OUD) diagnoses and overdose deaths (>80,000 in 2021). In OUD, opioids assume heightened salience over pleasant rewards, which become devalued. This hedonic imbalance can be objectively measured with the late positive potential (LPP), which indexes sustained attention to arousing stimuli. Here, we tested the hypothesis that chronic pain patients with OUD, and especially more severe OUD, would have greater reward blunting (reduced LPPs elicited by pleasant images) that would correlate with increased opioid-seeking behavior (separate choice task to view images of opioid pills). Data were acquired from 47 patients prescribed opioids for chronic pain (18 OUD, 29 non-OUD). First, participants passively viewed pleasant and neutral images while LPPs were recorded (400-2000 ms window after image onset); self-report ratings

of image pleasantness were acquired in parallel. Second, participants completed a validated picture-choice task, selecting pleasant, unpleasant, neutral, and opioid pill images for extended viewing. Pleasant LPPs, self-report ratings, OUD severity, and their interaction(s) were entered into general linear models (GLMs) to predict opioid choice. Four GLMs were tested, each predicting opioid picture choice with a corrected significance of $p<0.0125$. Predictors were: pleasant LPPs x OUD diagnosis (GLM 1), pleasant LPPs x OUD severity (GLM 2), self-report ratings x OUD diagnosis (GLM 3), and self-report ratings x OUD severity (GLM 4). All 4 models revealed the expected main effects where OUD diagnosis and more OUD severity correlated with choosing more opioid images (all $p<0.006$). More importantly, an LPP x OUD Symptom interaction in GLM 2 ($p=0.001$) revealed an increasingly strong negative correlation between LPPs and choice with increasing OUD severity. A Self-Report Rating x OUD Diagnosis interaction in GLM 3 ($p=0.010$), showed a negative correlation between pleasant self-reports and opioid choice in non-OUD patients only. We found that objectively-measured reward blunting (low LPPs to pleasant stimuli) predicted higher opioid choice especially in more severe OUD phenotypes, consistent with a hedonic reward imbalance in these patients that is biased toward opioid reinforcement. In contrast, self-reported reward blunting predicted opioid choice in non-OUD. This double dissociation, pointing toward using LPPs for the most severely impaired and self-reports for the non-impaired, may be clinically impactful, by suggesting a strategy for efficient allocation of treatment resources in a chronic pain population at high risk for opioid misuse.

Disclosures: **P. Dhayagude:** None. **S.J. Moeller:** None. **J. Hudak:** None. **E.L. Garland:** None.

Poster

711. Opioids and Pain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 711.30

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA T32 DA007281
NIH R01 DA042779

Title: Exposure to SNC-80 or Persistent Pain Alters Delta Opioid Receptor Signaling in Anterior Cingulate Cortex Parvalbumin Neurons

Authors: *M. WALICKI[1], A. L. PEREZ-MEDINA[1], W. BIRDSONG[2];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Pharmacol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: The anterior cingulate cortex (ACC) plays a role in the neural circuitry of pain and its output influences downstream neural circuits. ACC activity is regulated by endogenous opioids like enkephalins, which can act at both mu and delta opioid receptors to alter cortical function.

The delta opioid receptor (DOR) is expressed in a majority of parvalbumin (PV) interneurons within the ACC and DOR activation on these interneurons inhibits GABA release, disinhibiting nearby pyramidal cells. DOR activation has multiple cellular effects activating a potassium conductance at PV cell soma and inhibiting neurotransmitter release from presynaptic axon terminals. DOR signaling in some brain regions can be dynamic, changing in response to repeated drug exposure or persistent pain. Within PV cells in the cortex, it is not known whether DOR signaling adapts to drug exposure or pain and whether DOR signaling in soma and presynaptic terminals is differentially regulated. The aim of this study was to understand DOR signaling adaptations in soma and presynaptic terminals in response to repeated drug exposure and pain. We used patch clamp electrophysiology, optogenetics and pharmacology in brain slices to measure somatic and presynaptic DOR signaling following repeated exposure of mice to the selective DOR agonist SNC-80. SNC-80 treatment induced cross tolerance to Met-enkephalin in both somatic and presynaptic effector pathways, however tolerance at the soma developed more rapidly. Additionally, exposure to SNC-80 altered DOR regulation of feed-forward inhibition in the ACC. Like SNC-80 treatment, persistent pain resulted in tolerance to Met-enkephalin at the presynaptic effector pathway. These data suggest that development of cellular tolerance in ACC PV neurons is heterogenous based on subcellular receptor location and that SNC-80 treatment and pain can disrupt endogenous opioid signaling.

Disclosures: **M. Walicki:** None. **A.L. Perez-Medina:** None. **W. Birdsong:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.01

Topic: D.05. Auditory & Vestibular Systems

Support: NIH (NIDCD) R01 DC017532

Title: Can vision modulate the ear? Recordings in human ear canals during observation of silent visual stimuli

Authors: *J. HERCHE, C. D. KING, S. N. LOVICH, J. M. GROH;
Duke Univ., Durham, NC

Abstract: BACKGROUND: How does what we see change what we hear? Sensory integration involves two principles in tension. The brain: 1) builds its perceptions from a synthesis of sensory afferents and 2) controls its own inputs through sensory efferents. Where along ascending pathways do efferents act and how do signals from one sensory modality alter another? In the auditory system, visual information biases sound responses across numerous CNS regions, from the brainstem to the primary auditory cortex. Where does audio-visual sensory interaction begin?RATIONALE: Here, we tested whether visual stimuli exert measurable effects on the auditory periphery. Auditory efferent pathways control sensitivity and

responsiveness to incoming sound (e.g. middle ear reflexes, otoacoustic emissions). Our group's recent work identified an efferent process activated with eye movements. We postulated visual content may also influence the auditory efferent system and tested the hypothesis with a silent visual known to produce auditory illusions in at least some participants - the so-called 'jumping pylons' stimulus.METHODS: Microphone recordings captured ear-canal-air-pressure changes in 14 human participants viewing jumping pylon and freeze frame control stimuli in alternating blocks. We evaluated (a) non-specific modulation of ear-canal noise across a wide frequency spectrum to identify global efferent signal and (b) specific changes in ear canal noise at the periodicity of pylon jumping.RESULTS: We found broadband changes in 7 subjects (50%), suggesting a global influence of visual stimuli on auditory gain. To date, we have not observed a specific periodic signal elicited by the jumping pylons, even in the 4 subjects that experienced the illusion (29%).CONCLUSION: We hypothesize that, in some subjects, primary hearing structures modulate sound transduction based on inferences from the visual system. Future work should clarify the timing and variability of response phenotypes across subjects to assess the role of visually gated auditory efferents in shaping sound processing.

Disclosures: J. Herche: None. **C.D. King:** None. **S.N. Lovich:** None. **J.M. Groh:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.02

Topic: D.05. Auditory & Vestibular Systems

Support: CRC 889

Title: A mutation in ATP11A causes autosomal dominant auditory neuropathy type 2

Authors: *S. CHEPURWAR, N. STRENZKE;
Univ. of Göttingen Med. Ctr., Göttingen, Germany

Abstract: Auditory neuropathy/auditory synaptopathy (AN/AS) is characterized by disrupted encoding of sound in the auditory nerve and inner hair cells, respectively, despite preserved active cochlear amplification by the outer hair cells. AN/AS can be caused by genetic or environmental factors. Human non-syndromic autosomal dominant auditory neuropathy type 2 (AUNA2) has previously been mapped to chromosomal bands 12q24 or 13q34. AUNA2 patients show an age-dependent increase in hearing thresholds associated with poor auditory brainstem responses and relatively well-preserved otoacoustic emissions. Speech perception is impaired but not as poor as in other AN/AS cases. We now show that AUNA2 is caused by a deletion of 5500bp in ATP11A located in 13q34. ATP11a is a P-4 ATPase which flips phospholipids from the exoplasmic to cytoplasmic leaflet of the plasma membranes. The mutation in the AUNA2 family leads to a loss of flippase activity in vitro. Immunohistochemistry and confocal microscopy demonstrate high ATP11A expression in auditory nerve fibers and in the cochlear

nucleus. We generated conditional Atp11a knockout mice under the control of the Parvalbumin-Cre promoter. Atp11a cKO mice show an age- dependent progressive loss of auditory brainstem responses despite preserved DPOAE, recapitulating the age-progressive auditory neuropathy phenotype in affected humans. We hypothesize that the loss of flippase activity leads to the degeneration of a fraction of auditory nerve fibers.

Disclosures: S. Chepurwar: None. **N. Strenzke:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.03

Topic: D.05. Auditory & Vestibular Systems

Support: NIDCD/NIH R01DC014658 to GIF
Hearing Health Foundation 2018 ERG to ACV
UK CCTS pilot grant to ACV through NIH (NCRR and NCATS) UL1TR001998

Title: Trpa1 is required for proper innervation of the organ of Corti

Authors: D. Y. CALDERON-BRICENO, S. TORRES-GALLEGO, R. STEPANYAN, R. S. LARSON, G. I. FROLENKOV, ***A. C. VELEZ-ORTEGA**;
Dept. of Physiol., Univ. of Kentucky, Lexington, KY

Abstract: TRPA1 channels are expressed in somatosensory nociceptive neurons where they are essential for nociceptive responses and inflammatory pain. These channels are also expressed in the cochlea where their function remains unknown given that mice lacking TRPA1 channels (*Trpa1*$^{-/-}$) exhibit normal hearing thresholds, vestibular function, and hair cell mechanotransduction. Here, we analyzed waveforms of the auditory brainstem responses (ABR) to supra-threshold click stimuli and found that *Trpa1*$^{-/-}$ mice have larger wave I (coming from the auditory nerve activity) and smaller wave V (generated by the brainstem circuitry) amplitudes compared to wild type littermates. These data indicate potential developmental abnormalities of cochlear afferent pathways in *Trpa1*$^{-/-}$ mice.
Proper wiring of the auditory nerve pathways depends on ATP-driven calcium waves that occur spontaneously in the cochlear epithelium before the onset of hearing. Our patch clamp recordings in heterologous cells transfected with mouse *Trpa1* showed that TRPA1 channels can be activated by extracellular ATP via endogenous P2Y receptors. In addition, ratiometric calcium imaging of early postnatal cochlear explants shows long-lasting calcium responses to the local delivery of TRPA1 agonists that often propagate and trigger the self-propagating ATP-dependent calcium waves. Thus, the absence of TRPA1 channels could lead to deficits in cochlear innervation that could explain the differences we found in the ABR waveforms. Therefore, we evaluated the innervation pattern of the adult cochlea with immunolabeling against (*i*) CtBP2/RIBEYE to quantify hair cell afferent synapses and (*ii*) neurofilament heavy polypeptide

(NF-H) to label neuronal projections. Our results demonstrated no differences between *Trpa1*$^{-/-}$ mice and wild type controls in the number of synaptic ribbons in inner hair cells. However, *Trpa1*$^{-/-}$ mice exhibited an abnormal pattern of thin long fibers that travel along the outer hair cell rows and innervate large tissue segments (thus presumed to be the type II spiral ganglion neurons). Additional immunolabeling against parvalbumin (to differentiate afferent from efferent fibers) is currently underway to verify the identity of these neurons.
We concluded that TRPA1 channels may play a role in the early development and/or refinement of cochlear innervation, particularly of type II afferent fibers.

Disclosures: D.Y. Calderon-Briceno: None. **S. Torres-Gallego:** None. **R. Stepanyan:** None. **R.S. Larson:** None. **G.I. Frolenkov:** None. **A.C. Velez-Ortega:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.04

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant DC017147
NIH Grant DC018785
RNID Discovery Research Grant

Title: Reducing Taperin Expression Restores Hearing in Grxcr2 Mutant Mice

Authors: *B. ZHAO;
Indiana Univ. school of medicine, INDIANAPOLIS, IN

Abstract: Recessive mutations in GRXCR2 cause deafness in both humans and mice. In *Grxcr2* null hair cells, the sensory receptors for sound in the inner ear, stereocilia are disorganized. Reducing the expression of taperin, a protein that interacts with GRXCR2 at the base of stereocilia, corrects the morphological defects of stereocilia and restores hearing in *Grxcr2* null mice. To further validate this finding, recently we generated two novel *taperin* mutant mouse lines that exhibit progressive hearing loss. Then *Grxcr2* null mice were crossed with one of these *taperin* mutant mice. The following morphological analysis revealed that reducing taperin expression indeed corrected stereocilia morphological abnormalities in *Grxcr2* null mice. Functional analysis further confirmed that reducing taperin expression partially restored hearing in *Grxcr2* null mice. Additionally, the *Grxcr2* and *taperin* double mutant mice exhibited profound hearing loss, although *taperin* single mutant mice retained some hearing, indicating that GRXCR2 has additional functions besides regulating taperin.

Disclosures: B. Zhao: None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.05

Topic: D.05. Auditory & Vestibular Systems

Support: NIH R01 DC015271

Title: In-silico electrophysiology of experimentally supported AlphaFold 2 TMC models of the vertebrate inner-ear mechanotransduction channel

Authors: W.-H. WENG[1], J. S. MONTGOMERY[1], S. WALUJKAR[1], J. M. LOTTHAMMER[1], C. R. NISLER[1], A. P. J. GIESE[2], Z. M. AHMED[2], M. P. FOSTER[1], ***M. SOTOMAYOR**[1]; [1]Ohio State Univ., Columbus, OH; [2]Univ. of Maryland, Baltimore, MD

Abstract: At the foundation of vertebrate hearing and balance is the process of mechanotransduction, in which forces from sound and head movements are transduced into electrochemical signals in the inner ear. Mechanotransduction takes place in inner-ear hair cells and involves tip-link filaments that pull on ion channels to trigger sensory perception. Each tip link is made of cadherin-23 (CDH23) and protocadherin-15 (PCDH15) proteins, while the pore forming subunits of the transduction ion channel are formed by transmembrane channel-like proteins (TMCs) 1 and 2, likely coupled to accessory units formed by calcium- and integrin-binding proteins (CIBs) 2 and 3, the transmembrane inner-ear expressed protein TMIE, and the tetraspan membrane protein of hair-cell stereocilia TMHS (also known as LHFPL5). Here we present structural, biochemical, and computational studies aimed at elucidating the molecular mechanisms underlying function of the hair-cell transduction apparatus components. We used AlphaFold 2 models and nuclear magnetic resonance data to build TMC protein models in complex with CIBs suggesting a ‘clamp-like’ architecture involving TMC cytosolic domains. These models are supported by and consistent with prior structural and biochemical data and were used in molecular dynamics simulations that predict cation conduction at rates that match the conductance of the native inner-ear mechanotransduction channel. Additional simulations of TMHS coupled to PCDH15 provide insights into possible mechanisms underlying the role of membrane tension in TMC gating. These data and models, obtained from a combination of experimental and computational approaches, are providing a rigorous molecular view of mechanotransduction in normal and impaired hearing and balance.

Disclosures: W. Weng: None. **J.S. Montgomery:** None. **S. Walujkar:** None. **J.M. Lotthammer:** None. **C.R. Nisler:** None. **A.P.J. Giese:** None. **Z.M. Ahmed:** None. **M.P. Foster:** None. **M. Sotomayor:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.06

Topic: D.05. Auditory & Vestibular Systems

Support: NIDCD RO1 DC013798
NIDCD RO1 DC008846
CTSI (Pilot Award), Wallace H. Coulter Foundation

Title: Sound-evoked vestibular myogenic potentials in rattus norvegicus

Authors: *F. RACITI[1], Y. MORALES[2], H. SNAPP[1], S. RAJGURU[3];
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Abstract: Over the years, vestibular evoked myogenic potentials (VEMPs) have become an essentialcomponent in the neuro-otology test battery as they represent an objective measure of theintegrity of the vestibulothalamic pathway. VEMPs are small vestibular-dependent reflexeselicited via air-conducted sound stimuli (ACS) or bone-conducted vibration (BCV) from tonicallycontracted cervical muscles (cVEMPs) and extraocular muscles (oVEMPs). The anatomicalprojections of otolith afferents to neck and eye muscles make these techniques a valid diagnostictool for primarily assessing saccular and utricular function. Moreover, recent neurophysiologicalstudies have also proposed a semicircular canal response to high-intensity acoustic stimuli. Given the increased popularity of VEMPs in the clinical domain, it is crucial to further examine the neuralbasis of the responses and validate their relevant features for future interpretation and use. Thisstudy presents an extensive dataset looking at cVEMPs at several intensities and frequencies innaïve Brown Norway (BN) rats. Smart EP evoked potentials system (Intelligent Hearing Systems,USA) was used to record sound-evoked VEMPs from the neck extensor muscle in anesthetizedfemale and male adult BN rats. To maintain muscle tension the head was turned to one side at a90° angle and held in place via a custom-made band. Pure tone bursts from 1 to 16 kHz (50-100dB SPL) were delivered via the ER3A earphone inserted into the external auditory canal. Themyogenic signals were amplified by 100k and band-passed between 30 and 1000 Hz. Eachrecording consisted of 1024 sweeps at a rate of 5/s with an alternating phase and sampling rateof 200µs. Within the cohort, no changes in vestibular thresholds were observed across all thefrequencies tested (50 dB). A cubic fit was performed on cVEMPs' wave I (P1) amplitudes(R^2=0.97), and latencies (R^2=0.93) at 90 dB SPL across frequencies (1-16 kHz). The respectivelocal maximum and minimum values were identified at 6-8 kHz: the myogenic potentials evokedby stimuli within this frequency range showed significantly larger (8.2±0.76 µV) and faster(3.4±0.07 ms) responses than the ones observed at low (1-4 kHz) and high (10-16 kHz)frequencies. P1 amplitudes averaged 7±0.54 and 6.8±0.51 µV for low and high frequenciesrespectively. P1 latency values at 1-4 kHz averaged 3.7±0.06 ms whereas 10-16 kHz averaged3.6±0.05 ms ($p<0.01$). This work details new characteristics of ACS-evoked myogenic potentialsin a pre-clinical rat model. The important clues provided by this study will help developing optimalcVEMP test protocols to further elucidate physiological characteristics of vestibular dysfunction.

Disclosures: F. Raciti: None. **Y. Morales:** None. **H. Snapp:** None. **S. Rajguru:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.07

Topic: D.05. Auditory & Vestibular Systems

Support: NIH R01 DC014685

Title: Basilar membrane is a mechanical reference for outer hair cell motility

Authors: W.-C. LIN, ***J.-H. NAM**;
Univ. of Rochester, Rochester, NY

Abstract: The mechanical gradient of the basilar membrane (BM) and the tectorial membrane shapes the traveling wavesof the mammalian cochlea. The outer hair cells (OHCs) are cellular actuators that modulate the traveling waves.The shape of cochlear traveling waves represents hearing sensitivity and selectivity. While longitudinal vibratingpatterns (traveling waves) of the BM have been researched extensively, little is known about its radial vibratingpatterns. We measured the radial vibrating patterns of the BM in excised gerbil cochleae at the resolution fineenough to distinguish the displacement of individual cells. A 3-D finite element model of fully deformable organof Coti was exploited to analyze the measured data in detail. While pressure-driven vibrations resulted inprimary-mode vibrations, OHC motility generated higher-mode vibrations of the BM. Our results indicate thatthe BM acts as if a mechanical reference for OHC motility.

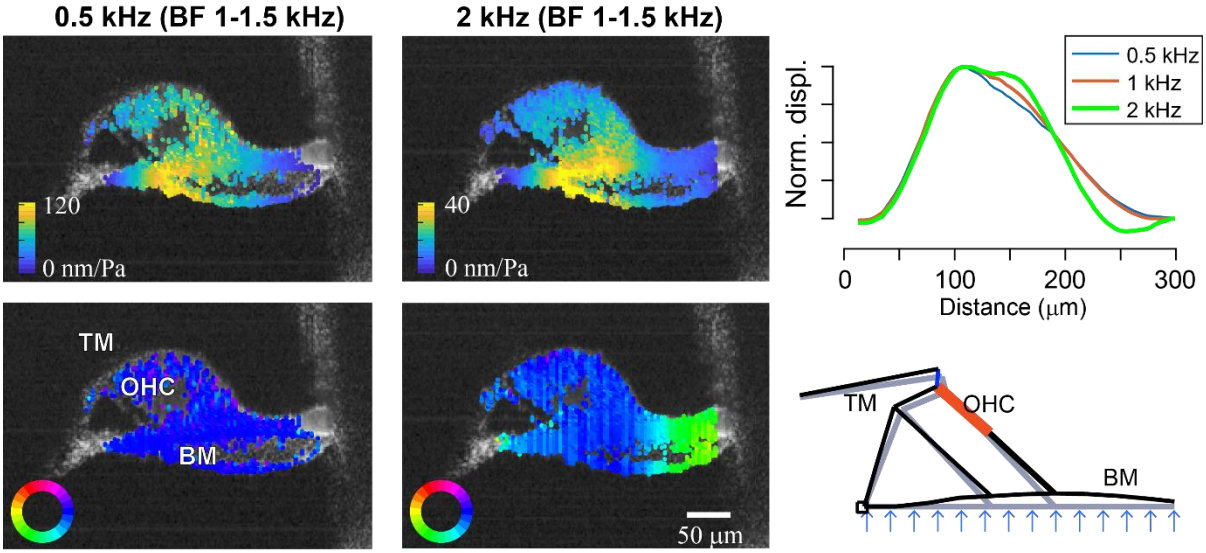

Figure 1. Passive vibrations due to fluid pressures. Left) Below BF. Mid) Above BF. Right top) Vibrations patterns.Right bottom) Model simulation.

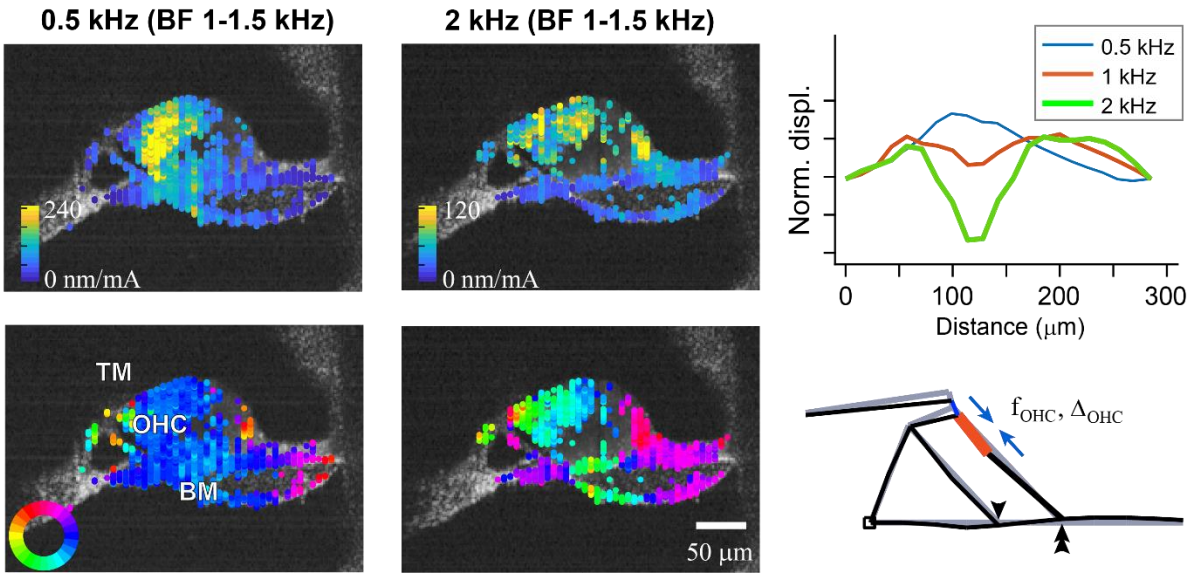

Figure 2. Active vibrations due to OHC motility. Left) Below BF. Mid) Above BF. Right top) Vibrations patterns.Right bottom) Model simulation. active.

Disclosures: W. Lin: None. **J. Nam:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.08

Topic: D.05. Auditory & Vestibular Systems

Support: Funded by department of Anatomy, AIIMS, New Delhi

Title: Stereological estimation of volume of human stria vascularis and length of the capillaries in the stria vascularis

Authors: *S. AGARWAL[1], T. G. JACOB[1], C. KAUR[3], P. KUMAR[1], T. S. ROY[4], D. N. BHARDWAJ[2];
[1]Anat., [2]Forensic Med. and Toxicology, All India Inst. of Med. Sci., New Delhi, India; [3]Dept. of Otolaryngology – Head and Neck Surgery, Massachusetts Eye and Ear, Boston, MA; [4]Anat., North DMC Med. Col. and Hindu Rao Hosp., New Delhi, India

Abstract: Stria vascularis (SV) is a specialized vascular epithelium on the peripheral wall of cochlea that secretes endolymph. It maintains the ionic composition of endolymph, which is essential for the activity of receptor hair-cells in the organ of Corti. Metabolic presbycusis occurs due to age-related strial changes like atrophy and reduced length of capillaries, but there are very few human studies. Here, we estimated the strial volume and the length of strial capillaries using

unbiased stereology, in human cochleae. Ten human cochleae, from deceased persons aged 13 to 74 years were fixed, decalcified, dehydrated and embedded in celloidin. Then sections of 50µm thickness were cut on a sliding microtome and every 10^{th} section was stained with hematoxylin and eosin. These were used for unbiased stereological estimation of volume of SV by the point-counting probe and of the length of capillaries in the SV by hemispherical probe. The data points of volume of SV and length of capillaries were normally distributed. The total volume ranged from 0.22 to 0.51mm^3. The volume of SV of each turn and the length of the capillaries in each turn decreased from basal to apical (overall $p<0.001$). The volume of SV and length of the capillaries in each turn though did not show any significant change with age (Volume: basal, middle, apical and total; $p = 0.996, 0.841, 0.763, 0.978$, respectively; capillary length: basal, middle, apical and total; $p = 0.265, 0.069, 0.379, 0.061$, respectively). Hence, human metabolic presbycusis is unlikely due to atrophy of the stria vascularis.

Disclosures: **S. Agarwal:** None. **T.G. Jacob:** A. Employment/Salary (full or part-time):; full time. **C. Kaur:** None. **P. Kumar:** A. Employment/Salary (full or part-time):; full time. **T.S. Roy:** A. Employment/Salary (full or part-time):; full time. **D.N. Bhardwaj:** A. Employment/Salary (full or part-time):; full time.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.09

Topic: D.05. Auditory & Vestibular Systems

Support: Washington State University Undergraduate Research Competition

Title: The roles of inflammation and oxidative stress in age-related hearing loss

Authors: *E. DALE[1], O. MOLANO[1], A. B. COFFIN[2];
[1]Washington State Univ. Vancouver, Washington State University, Vancouver, Vancouver, WA; [2]Washington State Univ., Washington State Univ., Vancouver, WA

Abstract: Thirty-six million Americans suffer from hearing impairment, and over 50% of individuals above the age of 75 experience age-related hearing loss (ARHL). While assistive technologies improve hearing capabilities in some, it is of great interest to prevent ARHL and preserve hearing. This type of hearing loss is attributed in part to damage of the inner ear hair cells, which are the primary sensory cells responsible for the transduction of sound waves into electrical signals to be interpreted by the brain. We proposed that two likely initial causes of ARHL are inflammation and oxidative stress in these sensory hair cells. Zebrafish are an excellent model to test these hypotheses, due in part to the presence of exterior lateral line hair cells, which are homologous to human hair cells. Lateral line hair cells also have rapid turnover, allowing us to study hair cell aging in a period of days rather than years. We hypothesized that inhibiting inflammation or oxidative stress would prolong the lifespan of hair cells. Using

transgenic zebrafish expressing green fluorescent protein (GFP) in hair cells, we pharmacologically manipulated inflammation and oxidative stress to investigate hair cell longevity *in vivo*. Fish were bathed in DAPI to label existing hair cells, then raised in one of our pharmacological modulators. We then discriminated relative hair cell age, as older cells were GFP+ and DAPI+ while newer cells were only GFP+. Our preliminary data demonstrates that broad inhibition of inflammation affected hair cell longevity, but TNF-alpha inhibition did not demonstrate the same changes, suggesting that inflammatory effects are independent of TNF-alpha activation. Incubation in the antioxidant d-methionine did not affect hair cell longevity in a predictable manner. Future work will include further manipulation of inflammatory signaling and oxidative stress in the hair cell aging process, which will increase understanding of ARHL causes and may yield targets for therapeutic development.

Disclosures: E. Dale: None. **O. Molano:** None. **A.B. Coffin:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.10

Topic: D.05. Auditory & Vestibular Systems

Support: NIH/NIA R15 AG073947
NIH/NIGMS Grant GM139762
CURAS SURF Grant

Title: Model of premature aging causes effects to both middle ear and cochlea.

Authors: *N. A. SANDE, M. S. LAURITSEN, G. D. KING;
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Abstract: Age-related hearing loss profoundly impacts millions of people every year. While some change to hearing function is within the confines of normal aging, rate and magnitude of changes to hearing may serve as a prodrome to neurodegenerative disease. Both aging and hearing loss are impacted by genetic and environmental factors. Herein we used a genetic model of premature aging (klotho-deficiency) to determine how deficiency of a single gene normally age-downregulated in the cochlea, impacts hearing. Replicating previous publications, we used used auditory brainstem responses to confirm that model mice are profoundly hearing impaired and also show impairment can be detected as early as 3-weeks old. These tests show the most profound effects to apical and basal hair cell function, consistent with a sensorineural-type impairment. As these results confirm previous observations, we sought to further determine the mechanisms by which klotho-deficiency impairs hearing. Thus undertook a characterization of both the middle ear and cochlea. For all experiments, both male and female mice were utilized in even numbers; n=6-10; and compared against age-matched wild-type control mice. Histology of the middle ear bones show profound bone dysplasia indicating alterations to hearing transduction

from the point of hearing initiation. However, phenotypic change is not limited to only the middle ear. Although histology and IHC of the cochlea confirmed published reports of normal hair cell number, we found that the stria vascularis was physically thicker with abnormal, profoundly decreased expression of transporters important for production of the endolymph, the fluid critical for hair cell transduction of sound into a neural substrate. Together these data indicate age-related, decreased expression of even a single gene can be sufficient to cause changes at multiple loci and thus promote an environment supporting hearing impairment. Although our model is an extreme klotho-deficiency, this protein is downregulated across the body during normal aging and contributes to increased risk of age-related disorders. While hearing impairment is impacted both genetically and environmentally, greater understanding of the genetic underpinnings of age-related hearing loss will allow better prediction of risk for hearing impairment and provide points of intervention to maintain hearing function.

Disclosures: **N.A. Sande:** None. **M.S. Lauritsen:** None. **G.D. King:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.11

Topic: D.05. Auditory & Vestibular Systems

Support: Washington State University Cougar Cage

Title: Testing COVID-19 Therapeutics for Hearing Loss as an Unwanted Side Effect

Authors: *O. MOLANO[1], F. FEARINGTON[2], E. DOPPENBERG[2], E. DALE[1], J. HILL[2], T. HAYWARD[2], A. B. COFFIN[3];
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Abstract: The biomedical community has rapidly developed several therapeutics to treat COVID-19, with over 300 drugs currently FDA- approved or in clinical trials. With so many drugs in development, it's likely that some produce unwanted side-effects. We know that certain drugs cause hearing loss, including specific chemotherapy drugs and antibiotics, by damaging sensory cells in the inner ear. However, COVID-19 drugs have not been assessed for their potential to cause hearing damage. Knowing what drugs are toxic to the inner ear can help minimize potential hearing loss and help develop safer therapeutics. We determined the relative hair cell toxicity of selected COVID-19 therapeutics in the zebrafish. Zebrafish have sensory cells on the lateral line that are similar to human inner ear hair cells. We treated zebrafish with COVID-19 drugs and quantified hair cells to assess damage. We found that hair cell damage was caused by the anti-viral drugs ritonavir and lopinavir. Additionally, we identified that imatinib, commonly used to treat chronic myeloid leukemia, and ivermectin, an anti-parasitic drug, also damaged hair cells. The anti-inflammatory drug dexamethasone, the antiviral remdesivir, and the

antibiotic azithromycin did cause hair cell damage. We next asked if the identified hair cell toxins, imatinib, lopinavir, ritonavir, and ivermectin, affected ribbon synapses. In hair cells, ribbon synapses are structures that anchor synaptic vesicles and these structures can be damaged by known ototoxins. We found that imatinib and ivermectin increased the number of pre-synaptic ribbons in surviving hair cells. We are currently testing these putative ototoxic drugs *in vivo* in rats. Our data suggest that audiometric monitoring may be warranted in patients receiving some COVID-19 therapies.

Disclosures: O. Molano: None. **F. Fearington:** None. **E. Doppenberg:** None. **E. Dale:** None. **J. Hill:** None. **T. Hayward:** None. **A.B. Coffin:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.12

Topic: D.05. Auditory & Vestibular Systems

Title: Mutations in the Unfolded Protein Response Regulator Atf6 Cause ER stress in Organ of Corti and Sensorineural Hearing Loss

Authors: *K. KIM[1], E.-J. LEE[1], E. CHAVEZ[2], K. STEINBERGS[1], L. SAFARTA[1], H. MIN[1], A. RYAN[2], J. H. LIN[1];
[1]Pathology, Stanford Univ., Palo Alto, CA; [2]Surgery and Neurosci., UCSD, La Jolla, CA

Abstract: Activating transcription factor 6 (Atf6) is required for endoplasmic reticulum (ER) function andprotein homeostasis and is a key regulator of the unfolded protein response (UPR). Patientscarrying hypomorphic ATF6 alleles develop the congenital cone photoreceptor disease,achromatopsia, with some patients also reporting hearing loss. Here, we investigate the auditoryfunction of patients homozygous for *ATF6* disease alleles and mice homozygous for *Atf6*deletion. We performed RNA sequencing (RNA-seq) of cochlea from $Atf6^{-/-}$ mice and examinedconsequences of *Atf6* loss by histology of the cochlea. Auditory phenotypes of 4 patientshomozygous for *ATF6* disease alleles, p.Arg324Cys or p.Tyr567Asn, were analyzed byaudiogram. 2-week- and 2-month-old male and female $Atf6^{+/+}$ and $Atf6^{-/-}$ mice on a C57BL/6Jbackground were assessed for the role of *Atf6* in the cochlea. Immunohistochemistry wasperformed on cochlear wholemounts (using MYO7A and phalloidin). The hearing sensitivity ofthe mice was studied by auditory brainstem response (ABR) thresholds. RNA-Seq analysis wasperformed and differential gene expression profile of cochlea from $Atf6^{+/+}$ and $Atf6^{-/-}$ 2-month-oldmice was analyzed. All 3 siblings homozygous for the *ATF6* loss-of-function mutation encodingp.ARG324Cys (age: 49, 51, 52) and 1 patient homozygous for the *ATF6* mutation encodingp.Tyr567Asn (age 14) showed neurosensory hearing loss in both ears. In 2-month-old $Atf6^{-/-}$mice, ABR thresholds were significantly higher ($p < 0.0001$) compared to WT mice; thisdifference was independent of gender. 2-week-old $Atf6^{-/-}$ mice showed no ABR thresholddifferences when compared to $Atf6^{+/+}$ counterparts. On histology, $Atf6^{-/-}$ mice showed

loss ofouter-hair cells at 2 months (*p=0.001*) and inner-hair cell stereocilia disorganization.Transcriptomic analysis revealed abnormal activation of ER-induced genes (*Wilcoxon,P=0.0001*). Based on gene ontology analysis, we found that the genes involved in the UPRpathway were upregulated in the *Atf6*$^{-/-}$ cochlea. Overall, our findings implicate *ATF6* as a novelregulator of cochlear function. Here, we demonstrate that impaired *ATF6* increases ER stressand undermines organ of Corti function. Our findings suggest *ATF6* disease variants causeaudio and visual sensory defects.

Disclosures: **K. Kim:** None. **E. Lee:** None. **E. Chavez:** None. **K. Steinbergs:** None. **L. Safarta:** None. **H. Min:** None. **A. Ryan:** None. **J.H. Lin:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.13

Topic: D.05. Auditory & Vestibular Systems

Support: NIH NIDCD R15DC018935
American Hearing Research Foundation

Title: Targeted deletion of oncomodulin alters inflammatory response of the cochlea after noise damage.

Authors: *W. D. SESE[1], L. K. CLIMER[3], K. MURTHA[1], Y. YANG[1], A. J. HORNAK[1], R. KANE[2], D. D. SIMMONS[1];
[1]Biol., [2]Chem. and Biochem., Baylor Univ., Waco, TX; [3]St. Jude Children's Res. Hosp., Memphis, TN

Abstract: Noise induced hearing loss (NIHL) is at epidemic proportions with an estimated 5% of the global population suffering from this condition. Noise overexposure is marked by loss of sensory hair cells, ribbon synapses, cochlear nerve degeneration as well as elevated hearing thresholds. The mechanisms behind NIHL have not been fully delineated but autophagy, oxidative stress and calcium overload are known contributors. Noise damage to the cochlea also elicits an immune response marked by inflammation and infiltration of immune cells. However, we understand very little about the role the immune system plays in the pathogenesis of NIHL. Targeted deletion of oncomodulin (OCM), an EF-hand Ca^{2+} binding protein, leads to outer hair cell (OHC) dysfunction and hearing loss as well as immune cell dysfunction in the dorsal root ganglion. Our preliminary evidence suggests that deletion of OCM makes the cochlea more vulnerable to noise, raising the suspicion that OCM plays a role in inflammatory responses after noise damage. Here, we used *Ocm*$^{+/+}$ (WT) and *Ocm*$^{-/-}$ (KO) mice on a C57bl/6J background to evaluate immune responses after acute noise damage. Age-matched OCM WT and KO mice were divided into groups of control and noise exposed mice. Mice were either exposed to broadband noise at 106 dB SPL for 2 hours or placed in a soundproof booth with ambient noise

levels. Hearing function was assessed using distortion product otoacoustic emissions (DPOAEs) at three timepoints: pre-noise exposure, immediately following noise exposure, and 4 days after noise exposure. Noise exposure led to higher DPOAE threshold shifts in KO mice compared to WT mice. Ears were then harvested and assessed using antibodies to a pan-leukocyte marker, CD45, and toll-like receptor 4 (TLR4), a pattern recognition receptor (PRR) that recognizes damage associated molecular patterns (DAMPs). After noise exposure, KO mice had higher numbers of CD45+ immune cells than WT ($Ocm^{+/+}$ = 119.3 $\pm$ 20, n = 3; $Ocm^{-/-}$ = 212 $\pm$ 10, n = 3). In general, KO mice had more intense TLR4 immunoreactivity in the sensory hair cells than either noise-exposed or control WT hair cells. Noise-exposed KO mice had higher levels of TLR4 immunofluorescence than control KO mice as assessed by normalized mean gray values ($Ocm^{+/+}$ = 17.26 $\pm$ 4.5, n = 3; $Ocm^{-/-}$ = 33.95 $\pm$ 4.6, n = 3). Our data are consistent with OCM KO mice having greater sensitivity to noise exposure and a more robust immune response. These data also implicate a role for TLR4 inflammatory signalling in the pathogenesis of NIHL and as a potential candidate for therapeutics.

Disclosures: **W.D. Sese:** None. **L.K. Climer:** None. **K. Murtha:** None. **Y. Yang:** None. **A.J. Hornak:** None. **R. Kane:** None. **D.D. Simmons:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.14

Topic: D.05. Auditory & Vestibular Systems

Support: This study was supported by funding from Defense Health Program

Title: Repeated low-level blast exposure causes injuries to auditory and ocular systems

Authors: V. S. SAJJA, A. B. BATUURE, D. M. WILDER, J. C. DEMAR, Y. WANG, J. B. LONG, ***P. ARUN**;
Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: Multiple low-level blast exposures have been linked to impairment of neurosensory systems, prompting concern over the cumulative deleterious effects of blast and the need to define standards to mitigate this risk among Warfighters. There are no set guidelines establishing cumulative limits for number and intensity of blast exposures for Warfighters in training and operational settings. In the present study, we have explored the effect of repeated low-level blast exposures on auditory and ocular systems in a rat model. Anesthetized rats (n=6/ group) were frontally positioned in an advanced blast simulator, which closely mimics “free-field” blast, and subjected to 1, 4 or 14 daily exposures at 4 or 6 psi. Functional assessments were conducted with electroretinograms (ERG) for the ocular system, and distortion product otoacoustic emissions (DPOAE) and auditory brainstem responses (ABR) for the auditory system. Assessments were made either 7 or 28 days following the last exposure. Structural integrity of cochlea was

evaluated using myosin VIIa and phalloidin markers. At 4 psi (1, 4 or 14 exposures), significant decrements in DPOAE thresholds and impaired ABR responses were observed at 7 and 28 days following blast, while significant reductions in ERG A- and B-waves were observed only in the 6 psi/14 exposures treatment group at 28 days following blast. Outer hair cells were completely lost at the base and middle of the cochlea, but remained intact at the apex. Thus, functional assessments of both auditory and visual systems revealed vulnerabilities to low-level repeated blasts resembling those experienced by Soldiers during training and operations, which provides a first step towards identifying tolerable thresholds of blast exposure.

Disclosures: **V.S. Sajja:** None. **A.B. Batuure:** None. **D.M. Wilder:** None. **J.C. Demar:** None. **Y. Wang:** None. **J.B. Long:** None. **P. Arun:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.15

Topic: D.05. Auditory & Vestibular Systems

Title: Exploring the molecular mechanism by which oncomodulin, an EF-hand Calcium-Binding Protein, protects outer hair cells from noise sensitivity

Authors: *K. MURTHA[1], S. BASOOR[1], Y. YANG[1], T. SESE[1], L. CLIMER[2], A. HORNAK[1], D. D. SIMMONS[1];
[1]Biol., Baylor Univ., Waco, TX; [2]St Jude Children's Res. Hosp., Memphis, TN

Abstract: Cochlear outer hair cells (OHCs) play a fundamental role in the hearing sensitivity and frequency selectivity of mammalian hearing. Mitochondria, endoplasmic reticulum (ER), Ca^{2+} channels and pumps, and Ca^{2+}-binding proteins (CaBP) all help control the localization and spread of free Ca^{2+} in OHCs. However, very little is known about the importance of Ca^{2+} banks such as mitochondria and ER and Ca^{2+} buffers in OHC function and survival. The most abundant CaBP in OHCs is oncomodulin (OCM), an EF-hand CaBP belonging to the parvalbumin family. Genetic deletion of *Ocm* causes progressive hearing loss and shortens hearing life span by ~50%. OHCs are vulnerable to Ca^{2+} overload from noise, which can induce mitochondrial-associated OHC death. Ca^{2+} dysregulation is a known factor of acquired hearing loss. Preliminary data show that *Ocm* knockout (KO) mice are more sensitive to noise damage than wildtype (WT) mice. Both WT and KO mice were exposed to 106 dB SPL for 2 hours. Distortion product otoacoustic emissions (DPOAEs) and auditory brainstem responses (ABRs) were measured before and after noise exposure. At 5 days post noise exposure, hearing tests indicated that noise exposed *Ocm* KO mice have high thresholds, indicative of severe hearing loss, while noise exposed *Ocm* WT mice have lower thresholds. The role of three prominent OHC CaBPs was also explored in transfected HEK293T cells. GFP tagged CaBPs (OCM, APV, and sorcin) were transiently transfected into HEK293T cells. To mimic prolonged elevated cytoplasmic Ca^{2+} levels, transfected cells were exposed to the SERCA inhibitor, thapsigargin (Tg). Following Tg

incubation (48 hrs), cells were analyzed via MTS assays (used as a proxy for cell viability) and immunocytochemistry. MTS assays showed that neither OCM, nor APV, increased the viability of cells incubated with Tg. Sorcin expression itself resulted in lower MTS values compared to untreated control groups. Correspondingly, the decrease in viability between untreated and Tg treated groups was the smallest in sorcin transfected cells. Tg treatment also altered mitochondrial morphology and cell size, regardless of the presence or absence of transiently expressed CaBPs. Incubation with Tg resulted in a reduction in cell size and smaller, more fragmented mitochondria. These experiments show that while OCM may protect OHCs from the damage of noise exposure, it does not appear to ameliorate cell stress induced by prolonged ER stress. These studies suggest that OCM relieves Ca^{2+} overload via an alternate mechanism, possibly through mitochondrial-related cell stressors. Our future experiments will explore these mechanisms to define the unique role of OCM in OHCs.

Disclosures: K. Murtha: None. **S. Basoor:** None. **Y. Yang:** None. **T. Sese:** None. **L. Climer:** None. **A. Hornak:** None. **D.D. Simmons:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.16

Topic: D.05. Auditory & Vestibular Systems

Support: R01 DC018003-01 (King)
1IK2RX003271-01A1 (Stewart)
I01RX003250-02 (Altschuler)
R01 AG073157 (Stewart)

Title: The Impact of Noise Exposure on Vestibular-Mediated Motor Performance in Rats

Authors: *D. BARTIKOFSKY[1], D. BAUER[2], M. HERTZ[1], R. A. ALTSCHULER[2], W. KING[2], C. E. STEWART[1];
[1]Res. Service, LTC Charles S Kettles VAMC, Ann Arbor, MI; [2]Otolaryngology-Head/Neck Surgery, Kresge Hearing Res. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: The vestibular system integrates signals related to vision, head position, gravity, motion, and body position to provide stability during motion through the environment. Disruption in any of these systems can reduce agility and lead to changes in one's ability to safely navigate their environment. Causes of vestibular decline are diverse; however, excessive noise exposure can lead to otolith organ dysfunction (Stewart et al., 2020). We hypothesize in the current study that noise exposure can be a source of vestibular damage that leads to decreased vestibular-mediated agility. We aim to determine the effects of noise exposure on stability and balance in rats with a balance beam crossing task. Rats are trained to cross a 1-meter balance beam. All balance beam trials (n=10), regardless of outcome, are recorded and scored for each

rat. Each balance beam crossing is assigned in real-time a score of 1, 2, or 3. An overall score of 10-14 indicates proficiency in the task, while higher scores (up to 30) indicate a requirement for additional baseline training. Each balance beam crossing is objectively timed, using two sensors that mark start and stop times. When rats demonstrate stable crossing times and their crossing scores demonstrate consistent performance and proficiency, they are exposed to noise or sham conditions. Following noise exposure, rats continue to perform the balance beam crossing task 2 times per week, and if deficits are not present, rats may be re-exposed to noise. Sham rats were exposed to the same conditions as noise rats but were not exposed to noise. All rats are being tracked continuously into late adulthood. Rats' crossing behavior rapidly stabilizes and remains proficient beyond the first year of life in the absence of noise exposure. Deficits in motor performance became apparent after noise exposure, evidenced by increased crossing times and balance beam crossing scores. These findings show the impact noise has on the vestibular system, not only at cellular and physiological levels, but at a functional level that may have implications for people that have experienced noisy environments.

Disclosures: **D. Bartikofsky:** None. **D. Bauer:** None. **M. Hertz:** None. **R.A. Altschuler:** None. **W. King:** None. **C.E. Stewart:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.17

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant GR017268

Title: Characterizing the hazardous effects of noise overexposure on hearing and balance functions

Authors: H. SNAPP[1], L. A. VANLOOY[1], B. KUZBYT[1], K. HARRIS[1], ***S. RAJGURU**[2,1]; [1]Otolaryngology, Miller Sch. of Medicine, Univ. of Miami, Miami, FL; [2]Biomed. Engin., Univ. of Miami, Coral Gables, FL

Abstract: Cochlear synaptopathy, a type of deafferentation as a result of noise overexposure, has emerged as a hidden form of hearing loss. When combined with outer hair cell dysfunction, synaptopathy and associated long-term neural degeneration noise-induced hearing loss impairs our ability to communicate in challenging listening environments. Occupational groups such as firefighters are at particularly high risk for noise-induced changes to the inner ear due to chronic exposure to hazardous noise levels. Recent studies have suggested these pre-clinical structural and physiological changes are not detectable by conventional monitoring techniques such as clinical Distortion Product Otoacoustic Emissions (DPOAEs) or Auditory Brainstem Response (ABR). At the same time, changes in vestibular function due to chronic hazardous noise exposure remain understudied. In the present study, we identify early clinical markers of noise-

induced inner ear damage, both to the auditory and vestibular systems, in an occupationally at-risk group of firefighters. We carried out a cross-sectional prospective study in firefighters (n=62 ears) and age- and sex-matched control subjects (n=62 ears). Control subjects demonstrated minimal noise exposure history. Pure-tone thresholds (250-16,000 Hz), DPOAEs, and supra-threshold click and 4 kHz tone burst ABRs, and vestibular-evoked myogenic potentials were used to characterize changes in cochlear and saccular function between groups. We also monitored changes in otolith function using measures of subjective verticality, ocular counter roll, postural control, and functional mobility tasks to assess sway and gait speed. Groups were divided into pre-career (<1 year of service), mid-career (10-19 years of service), and late-career firefighters (20+ years of service) with age- and sex-matched controls. Our results show that firefighters exhibit significant deficits in DPOAEs and ABR wave I when compared with age- and sex-matched controls. DPOAE amplitude was significantly reduced and wave I ABR amplitude was significantly reduced for both click and 4 kHz tone burst conditions, when comparing firefighters to controls. Furthermore, we demonstrate a high incidence of decreased neuro-vestibular function in a cohort of otherwise healthy firefighters. These findings suggest physiological differences in hair cell function and neural response caused by hazardous noise overexposure. Firefighters exhibit these differences despite having near-normal audiometric thresholds. These findings suggest that audiometric thresholds are insensitive to pre-clinical changes in hearing function.

Disclosures: H. Snapp: None. **L.A. VanLooy:** None. **B. Kuzbyt:** None. **K. Harris:** None. **S. Rajguru:** A. Employment/Salary (full or part-time):; Research Health Scientist, Department of Veterans Affairs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RestorEar Devices LLC.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.18

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant R21DC014324
NIH Grant R01DC013798
NIH Grant F31DC018212

Title: Non-invasive hypothermic intervention protects long-term hearing after acute non-traumatic noise exposure in brown norway rats

Authors: *S. RINCON SABATINO[1], R. SANGALETTI[2], C. KING[4], S. M. RAJGURU[3,5]; [1]Biomed. Engin., [2]Otolaryngology, [3]Biomed. Engin. and Otolaryngology, Univ. of Miami, Coral Gables, FL; [4]RestorEar Devices, Kirkland, FL; [5]RestorEar Devices, Kirkland, WA

Abstract: Motivation: Noise-induced mechanical and molecular injury to cochlear hair cells and membranes may permanently affect hearing sensitivity, resulting in a condition known as noise-induced hearing loss. This sensorineural hearing loss has evolved into a severe public health concern afflicting up to 24% of adults and 17% of teenagers in the United States alone. Unfortunately, no approved otoprotective or therapeutic intervention exists to battle the multifaceted response to acoustic injury. In the present study, we evaluate the use of non-invasive therapeutic hypothermia to preserve cochlear structures post-exposure to non-traumatic noise. **Methods:** Male and female Brown Norway rats aged 15-20 weeks were randomly separated into three groups: (1) *Noise+Normothermia*, (2) *Noise+Hypothermia*, and (3) *Hypothermia Control*. Animals in *Noise* categories were subjected to two hours of continuous noise at 105 dB SPL with a narrowband frequency composition of 4-8 kHz. Immediately post-exposure the animals were anesthetized with Ketamine/Xylazine (44/5 mg/kg) for two-hour targeted cochlear temperature management under *Normothermic* (36-37 ºC) or *Hypothermic* (31-33 ºC) conditions. Changes in hearing sensitivity were analyzed with auditory brainstem response (ABR) threshold and amplitude assessments up to 12 months post-exposure. Cochleae were then extracted for histological assessment of hair cell and spiral ganglion survival. **Results:** *Hypothermia* alone did not affect hearing thresholds, animal behavior, or mortality. *Noise-exposed* animals in *Hypothermic* and *Normothermic* groups demonstrated a transient increase in ABR hearing thresholds with significant differences compared to *Non-exposed Control* animals up to 14 days post-exposure. *Normothermic* animals, irrespective of biological sex, demonstrated significantly higher shifts in hearing thresholds at early timepoints than *Hypothermic* counterparts, particularly at mid-to-high frequencies (8-32 kHz). Hearing assessment at 12 months post-exposure revealed noise-accelerated age-related ABR changes for *Normothermic* animals compared to *Hypothermic* animals. **Conclusions:** In a rodent model, localized induction of mild hypothermia to the inner ear demonstrated a feasible, safe, and controlled intervention for acoustic injury. Hypothermia-treated animals showed significant preservation of hearing thresholds compared to Normothermic animals at multiple timepoints up to 12 months post-exposure. Biological sex did not influence the efficacy of hypothermic intervention for acute noise-induced injury with similar early injury and aging response observed in female and male animals.

Disclosures: S. Rincon Sabatino: None. **R. Sangaletti:** None. **C. King:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RestorEar. **S.M. Rajguru:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RestorEar.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.19

Topic: D.05. Auditory & Vestibular Systems

Support: 1I01RX001095-01 of US Department of Veteran Affairs to AGH

Title: The effect of overstimulation on peripheral and central vestibular function

Authors: *S. NAQVI[1], A. PONCE SEPULVEDA[2], R. BRAUN[2], A. HOLT[3];
[1]Wayne State Univ., Detroit, MI; [3]Anat. & Cell Biol, [2]Wayne State Sch. of Med., Detroit, MI

Abstract: The vestibular system is crucial for posture, gait, and the perception of head and body position in space. Damage to this system can manifest as dizziness, imbalance, and poor postural control. Linear acceleration has been reported to result in measurable vestibular short-latency evoked potentials (VsEPs). Manganese acts as a calcium surrogate, accumulating in active neurons. The paramagnetic nature of Mn^{2+} permits visualization of these active neurons. Therefore, we combined VsEP and manganese-enhanced MRI(MEMRI) to assess vestibular function and visualize activity in central neurons responding to repetitive linear acceleration and noise exposure.
Following anesthesia, each male Sprague Dawley rat (n=25) was attached to a mechanical shaker and subjected to jerk stimulation in the naso-occipital plane (640 g/s,3,300 g/s, 5,100 g/s or 8,700 g/s). To assess the impact of noise, subgroups of rats from 640 g/s (n=3) and 3,300 g/s (n=3) were later noise exposed (1/3 octave band noise centered at 1.5 kHz at 120 dB SPL for 6 hours). $MnCl_2$ was administered just prior to stimulation. The stimulation was split into 3 blocks, consisting of 5 trials with 10-minuteintervals between each block. For each trial, 200 jerk pair served as stimuli. Recorded VsEPs were analyzed using custom MATLAB scripts with ANOVAs and T-tests used as appropriate. MEMRI was used to assess Mn^{2+} uptake in vestibular nuclei.
P1 and P2 VsEP amplitudes did not significantly change after repetitive jerks. P3 amplitude dropped after 6,000 jerks at 8,700 g/s ($p<0.05$). P1 and P3 latencies remained constant at each intensity after 6,000 jerks while P2 latency increased at 8,700 g/s($p<0.05$). In noise exposed rats versus baseline, no amplitude differences were found in rats stimulated at 640 g/s, but rats stimulated at 3,300 g/s had waveform modifications($p<0.05$). Latencies were delayed at 3,300 g/s, but remained constant at 640 g/s. The least Mn^{2+} uptake was after 640 g/s and 8,700 g/s stimulation, while the greatest was at3,300 g/s and 5,100 g/s ($p<0.05$). In noise exposed rats, the 640 g/s group had more Mn^{2+} uptake than the 3,300 g/s group.
Irregular fiber activity (P1) appeared to stay constant in response to repetitive linear acceleration, but increased at a mild jerk intensity following noise exposure. Neuronal responses in the vestibular nuclear complex (P2) were delayed after repetitive jerks. Diminished synaptic activity occurred in other vestibular-related brain regions (P3) following intense stimulation and noise exposure at a mild jerk intensity. Our results demonstrate intense stimulation and noise exposure change neuronal activity.

Disclosures: S. Naqvi: None. **A. Ponce Sepulveda:** None. **R. Braun:** None. **A. Holt:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.20

Topic: D.05. Auditory & Vestibular Systems

Support: R01 DC018003-01 (King)
1IK2RX003271-01A1 (Stewart)
I01RX003250-02 (Altschuler)
R01 AG073157 (Stewart)

Title: Transient VsEP Deficits and Recovery are Correlated with Calretinin Expression in Calyx-Only Afferent Terminals

Authors: M. ANDERSON[1], A. KANICKI[1], D. BAUER[1], R. A. ALTSCHULER[1], W. KING[1], ***C. STEWART**[2];
[1]Otolaryngology Head/Neck Surgery, Kresge Hearing Res. Inst., Univ. of Michigan, Ann Arbor, MI; [2]LTC Charles S Kettles VAMC, Ann Arbor, MI

Abstract: Previous research shows 120 dB SPL noise causes long-lasting vestibular hypofunction characterized by decreases in vestibular short-latency evoked potential (VsEP) responses that have not recovered 28 days after noise exposure (1). Rats with VsEP deficits also have a reduction in calyx-only afferent terminal labeling in the striolar region of the saccule (1). We recently showed that 110dB SPL noise exposure caused a transient VsEP deficit that recovered within 7 days after noise exposure (2). The present study examined 110dB SPL noise-induced changes in calyx-only afferent terminals in the otolith organs and semicircular canal cristae that follow the time course of VsEP loss and recovery. Long-Evans rats were exposed to 110dB SPL or sham noise conditions bilaterally with insert earphones for 4 hours under general anesthesia. After a 1- or 7-day recovery period, ears were collected, and vestibular sensory epithelia were immunostained for calretinin and beta-3 tubulin to visualize calyx-only and total calyx terminals, respectively. Immunostained vestibular end organs were imaged with a Leica Stellaris confocal microscope and calyces were counted in striolar regions of otolith organs and central regions of semicircular canal cristae. 110dB SPL noise exposure caused a significant reduction in calyx-only terminals in the otolith organs 1-day after 110dB SPL noise exposure versus sham. 7-days after noise exposure, calyx-only terminal counts were similar to counts obtained from sham-exposed otolith organs, suggesting recovery. There was no significant change in beta-3 tubulin immunolabeling of total calyces at either time point. This indicates that calyces are not lost after noise exposure but also do not express calretinin at the same level as was observed in non-noise exposed tissue. The 110dB SPL noise did not produce changes in the semicircular canal cristae. The association of otolith organ changes with VsEP changes is consistent with a primary influence of otolith organs in generation of the VsEP response to head jerk. The time course of vestibular dysfunction and recovery after noise, measured by VsEP, is mirrored by reduced calretinin immunolabeling of calyx-only afferent terminals 1- but not 7-days after noise exposure.
(1) Stewart CE, Bauer DS, Kanicki AC, Altschuler RA, King WM (2020) J Neurophysiol 12392): 658-669. (2) Stewart CE, Bauer DS, Altschuler RA, King WM (2021)J Neurophysiol 126(5):1547-1554.

Disclosures: M. Anderson: None. **A. Kanicki:** None. **D. Bauer:** None. **R.A. Altschuler:** None. **W. King:** None. **C. Stewart:** None.

Poster

712. Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 712.21

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant DC018003
VA Merit RX003250

Title: Change in head orientation and stability due to the exposure to intense noise or intratympanic injection of sodium arsenilate in rats

Authors: *M. NIWA, M. ANDERSON, D. BAUER, H. N. BECK, W. M. KING;
Univ. of Michigan, Ann Arbor, MI

Abstract: Recent studies have revealed that exposure to intense noise not only damages the cochlea but also affects vestibular parts of the inner ear. This is evidenced by reduced vestibular short-latency evoked potentials and reduced calretinin staining in calyx-only afferents of saccule following noise exposure (Stewart et al. 2020). Here, we aim to study the consequences of noise exposure on vestibular behavior.We measured rats' head angular velocity and linear acceleration using a motion sensor (Yost labs, Ohio) while the animal was subjected to abrupt whole-body rotations about an earth vertical axis. The measurements were made before and after a 4-hour, 120 dB noise exposure or intra-tympanic injection of sodium arsenilate. Arsenilate damages hair cells and synapses in the vestibular end organs, serving as a positive control of vestibular damage. Our report focuses on head orientation and stability during the inter-trial-intervals of the behavioral experiments.Animals exposed to arsenilate showed severe vestibular deficits. For every animal tested (3 males), the distribution of head orientation showed a significant increase in variance after arsenilate exposure (roll and pitch, $p < 0.001$), suggesting the animals' sense of gravity was severely degraded by the lesion. The time the animals heads were motionless was also significantly reduced. For every animal tested, head angular velocity was significantly increased after the lesion ($p<0.001$). These findings demonstrate severe deficits in a rat's ability to stabilize its head after an arsenilate lesion. Animals exposed to noise (5 males and 3 females) showed more subtle, but still significant changes in head orientation and stability. In only 1 of 8 animals did noise exposure result in a significant increase in the variance of orientation pitch and roll, as seen in arsenilate-treated animals. However, a majority showed significant increases in the variance of either pitch or roll, but not both (5 out of 8, $p < 0.05$). Furthermore, 6 out of 8 animals showed significantly reduced pitch angles (chins closer to chest) after noise exposure. These findings suggest the rats' sense of gravity was less accurate after noise exposure although the effect size was smaller compared to the arsenilate animals. Interestingly, noise exposure resulted in some changes in the opposite direction of those seen in arsenilate-treated animals. For example, rats could hold their heads motionless for a significantly longer time after noise exposure (Signed rank test, $p < 0.01$). These findings show that noise exposure does indeed

affect head orientation and stability but does so in a different manner compared to arsenilate exposure.

Disclosures: **M. Niwa:** None. **M. Anderson:** None. **D. Bauer:** None. **H.N. Beck:** None. **W.M. King:** None.

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.01

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant DC019303
NIH Grant DC007690

Title: The effect of encoding cue reliability on the function and development of the barn owl auditory system

Authors: *K. SHADRON[1], J. L. PENA[2];
[1]Albert Einstein Col. of Med., Bronx, NY; [2]Neurosci., Albert Einstein Col. of Med. Dominick P. Purpura Dept. of Neurosci., Bronx, NY

Abstract: In order to accurately perceive the world and respond accordingly, the brain has to deal with noise inherent in sensory cues. One method is for the brain to learn which cues are reliable across contexts and rely on these cues in the future. Previous studies have demonstrated that sensory systems are able to actively learn recent statistics underlying cue reliability and adapt to short term changes. However, relatively little is known about whether and how sensory systems adapt to natural statistics of sensory cues that are expected to be permanent. While humans display biases based on long term patterns of sensory cue statistics, the neural mechanisms underlying this are not fully known. To address these knowledge gaps, we investigated whether the anticipated reliability of binaural spatial cues drives the tuning of neurons that compute sound location in barn owls. Barn owls use the interaural time difference (ITD) to determine azimuthal location. Previous work showed that the signal-to-noise ratio of ITD varies across frequencies in a location dependent manner, based on the acoustical properties of the head. Thus, for a given location, certain frequencies convey ITD cues more reliably, and the neural tuning in the midbrain external nucleus of the inferior colliculus (ICx) reflects this pattern. We hypothesize that if the frequency tuning of the ICx is driven by cue reliability across locations, then altering the pattern of cue reliability should adjust frequency tuning. For this study, two barn owls were raised without the facial ruff, the structure that determines the pattern of ITD reliability. Once they reached adulthood, electrophysiological recordings of the ICx were performed. Results indicate that ICx neurons tuned to frontal locations are tuned to lower frequencies than previously reported in normal owls, consistent with the change in ITD reliability induced by the facial ruff removal. Additionally, recordings of the lateral shell of the

central nucleus of the inferior colliculus (ICCls), immediately upstream of the ICx, show normal tuning to frequencies across the owl's normal hearing range. This suggests that the ruff-cut owls' midbrain is still encoding ITD for these higher frequencies, but aren't using them for sound localization. Additional recordings from two juvenile owls, recorded before the facial ruff fully developed, show similar tuning to ruff-cut owls, suggesting that the high frequency tuning is learned once the facial ruff develops. These data suggest that stimulus statistics are used by the brain to guide neural tuning, and future work will seek to determine if this type of learning is confined to early-life development.

Disclosures: K. Shadron: None. **J.L. Pena:** None.

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.02

Topic: D.05. Auditory & Vestibular Systems

Support: NIH, NICHD

Title: Development of Auditory Brainstem in Fragile X Syndrome Mice

Authors: *A. CHAWLA[1], A. GENSKY[2];
[1]Oklahoma State Univ., Stillwater, OK; [2]Integrative Biol., Oklahoma State Univ., STILL WATER, OK

Abstract: Fragile X Syndrome (FXS) and autism are neurodevelopmental and communication disorders. FXS is a monogenic form of autism. Hypersensitivity to sound and altered binaural hearing are two common symptoms in these disorders. Binaural hearing and spatial acuity are important for localizing a sound source and separating sounds of interest from noise background. Sound information computation starts with the auditory brainstem, and compares the information of interaural timing differences (ITD) and interaural level differences (IID) from both ears. Highly myelinated axons in specific auditory brainstem region encode sound information quickly and precisely. The study of myelination during critical developmental timepoints will help to establish when during development altered hearing ability arises in *Fm*r1 knockout (KO) mice. We are analyzing anatomical markers of myelin including diameter and thickness of myelination, spacing and size of sodium channels (nodes/paranodes), and number and type of oligodendrocytes (mature and proliferating oligodendrocytes with ASPA and Sox-10 antibodies) in *Fmr1* KO mice and controls at several critical developmental timepoints, P9, P12-14, and P21. We are using ABR to measure brainstem specific hearing ability across the same developmental timepoints. The ABR is a non-invasive electrophysiological measure recording a pattern of waveforms that is directly related to the different brain areas that encode sound processing in the auditory brainstem. We are measuring male and female C57BL/6J wildtype, *Fmr1* KO and heterozygote female mice. Preliminary data suggests that similar to adult phenotypes, FXS mice

have altered auditory brainstem development as measured by ABR that may be related to myelination. These findings are important for understanding mechanisms of auditory hypersensitivity in FXS and when during development they arise.

Disclosures: **A. Chawla:** None. **A. Gensky:** None.

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.03

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant DC020109
NIH Grant DC007690

Title: Dual region recordings in the sound localization pathway of barn owls to investigate stimulus selection of salient stimuli

Authors: *A. BAE[1], K. SHADRON[2], R. FERGER[3], J. PEÑA[3];
[1]Albert Einstein Col. of Med. Dominick P. Purpura Dept. of Neurosci., Bronx, NY; [2]Rose F. Kennedy Ctr., [3]Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: Barn owls are specialists in sound localization. Their well-described midbrain stimulus selection network, a circuit containing a map of auditory space dedicated to localizing salient sounds, provides a unique opportunity to study the flow of information between midbrain and forebrain, where a transformation of coding scheme is indicated by the vanishing of a map of auditory space between midbrain and forebrain regions. This project worked towards investigating how the circuit conducts bottom-up relay for salient stimuli in environments with competing sounds. Earlier *in vivo* recordings in the owl's optic tectum (OT) have shown that gamma oscillations are spatially tuned to both visual and auditory information, and may play a role in stimulus selection. However, previous recordings in deep midbrain structures, like OT, have relied on single electrodes in a single region and an open question remains regarding how oscillations contribute to information flow during stimulus selection. Towards this end, we recorded spike responses and local field potentials in OT and one of its downstream forebrain regions simultaneously in anesthetized owls. So far, we observe heterogeneity in tuning properties to binaural cues in the forebrain, ranging from peaked tuning curves to broad tuning to contralateral space. However, while tuning may differ between brain regions, firing rates and gamma power positively correlate both during spontaneous activity in the absence of stimuli and during presentation of stimuli, suggesting connectivity. Future experiments will determine the role of gamma oscillations in promoting stimulus selection during presentation of two competing sounds, and determine whether gamma power is predictive of bottom-up relay towards salient stimuli during sound orientation behavior.

Disclosures: **A. Bae:** None. **K. Shadron:** None. **R. Ferger:** None. **J. Peña:** None.

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.04

Title: WITHDRAWN

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.05

Topic: D.05. Auditory & Vestibular Systems

Support: BBSRC BB/T002085/1

Title: Unravelling the mechanisms underlying song pattern recognition in crickets

Authors: *X. ZHANG, B. HEDWIG;
Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Intracellular recordings of auditory brain neurons indicate a delay-line and coincidence detector circuit underlying auditory pattern recognition in the bi-spotted cricket *Gryllus bimaculatus* (Schöneich et al 2015). Based on this circiuit, a behavioural test exploring the impact of the specific pulses and intervals within a chirp on phonotaxis was performed (Hedwig and Samiento-Pounce, 2017). Here, we explored the roles of the specific pulses and intervals within a chirp play in pattern recognition at both neural and behavioural levels. We first confirmed the morphology of the auditory neurons in the cricket brain. There are at least 51 neurons in the auditory neuropil and the cell bodies are grouped into six clusters. With a novel calcium labeling technique we primarily explored the dynamics of the calcium signal in each cell cluster. Besides the morphological features, we also used behavioural, intracellular recording, and staining techniques to further investigate the neural mechanisms underlying the processing of the specific pulses and intervals. We tested the phonotactic behaviour and pattern recognition neurons in the cricket brain with systematic variations of one pulse duration or inter-pulse interval in the chirps. The recordings of the pattern recognition circuit reveal the neurophysiological response properties of the five neurons in response to these sound paradigms. The pattern recognition circuit filters the temporal patterns of the chirps progressively. The ascending neuron AN1 and the inhibitory neuron LN2 do not show selectivity to specific sound patterns. The tuning of the coincidence detector (LN3) and the feature detector (LN4) to the

stimuli with varied intervals matched the behavioural tuning. We also demonstrate that the non-spiking neuron (LN5) not only provides a delay-line for coincidence detection but also demonstrates intrinsic response properties by an increased amplitude of its post inhibitory rebound tuned to pattern recognition. This expands the previously described function and points toward an adapted neuronal filter mechanism at the level of an individual neuron for the processing of a species-specific auditory pulse pattern. The results also demonstrate that the mechanisms underlying the filtering of pulses or intervals in the pattern recognition circuit may be different. For example, a chirp containing a single long interval is sufficient for reduced activity in LN4 compared to the normal chirp. However, it is required to have at least three consecutive long pulses in a chirp to elicit a reduced response of LN4.

Disclosures: X. Zhang: None. **B. Hedwig:** None.

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.06

Topic: D.05. Auditory & Vestibular Systems

Support: DC016461

Title: Modulation of neural excitability by acetylcholine in the developing gerbil MNTB

Authors: *S. R. WEIMANN, C. ZHANG, R. BURGER;
Lehigh Univ., Lehigh Univ., Bethlehem, PA

Abstract: The medial nucleus of the trapezoid body (MNTB) is the primary source of contralaterally driven inhibition to brainstem auditory circuitry. This output plays a critical role in several computational processes as temporal aspects of sounds are precisely encoded through the calyx of Held synapse. We have previously shown that in adult gerbils, acetylcholine (ACh) modulates sound-evoked responses in MNTB (Zhang et al. 2021). However, the cellular mechanisms through which ACh influences MNTB neurons remains obscure. To investigate these questions, we used gerbils aged P9-36 of both sexes for *in vitro* whole-cell patch clamp and immunolabeling to document physiology and expression of ACh receptors (AChRs) on pre- and postsynaptic elements in the MNTB. MNTB neuron spiking response to depolarizing current was assessed during application of ACh in the presence of nicotinic receptor antagonist mecamylamine, and muscarinic receptor (mAChR) antagonist atropine at several developmental stages. Our results show that ACh potently increases excitability of MNTB neurons via mAChRs, with the effect peaking just before hearing onset. Antibodies directed against M1 and M3 mAChRs were used to profile expression during this developmentally consequential age range. M3 receptors appear prominent in presynaptic terminals prior to hearing onset while M1 receptors were primarily postsynaptic and similar across ages. High M1 expression could indicate cholinergic modulation of outward currents that may mediate the change in excitability.

Outward currents were investigated with voltage clamp. We observed a mAChR-mediated decrease in voltage dependent outward conductance at depolarized voltages prior to hearing onset. We hypothesized that the activation of mAChRs inactivates potassium channels from the Kv7 family, thereby decreasing the outward potassium conductance enhancing MNTB excitability. Application of the Kv7 antagonist, XE 991, yielded the same effect on excitability and outward current as mAChR activation with Oxotremorine. The results were later substantiated by voltage clamp investigation of the Kv7 associated M current (I_M), a hallmark of muscarinic modulation. Our results indicate that cholinergic function is prominent in the developing MNTB and is likely mediated in part by M1 mAChR modulation of Kv7 channels. These data demonstrate candidate cellular mechanisms of cholinergic signaling. Further, the dynamic mAChR expression and physiology of cholinergic signaling components early in development suggests its potential developmental role in shaping MNTB circuitry.

Disclosures: S.R. Weimann: None. **C. Zhang:** None. **R. Burger:** None.

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.07

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant DC10000
NIH Training Grant 2T32DC000046

Title: Electrophysiological correlates of divergent projections in the avian superior olivary nucleus.

Authors: J. F. BALDASSANO, ***K. M. MACLEOD**;
Univ. Maryland, College Park, MD

Abstract: Inhibition is crucial for precise spiking during sensory processing, particularly in auditory processing which is sensitive to changes in the microsecond domain. In the avian auditory brainstem, inhibition stems mostly from the superior olivary nucleus (SON). SON neurons receive excitatory input from the intensity-coding cochlear nucleus angularis (NA) and the coincident detecting nucleus laminaris (NL). SON neurons project back to the ipsilateral cochlear nucleus magnocellularis (NM), NA, and NL. A separate SON population projects to the contralateral SON, but if whether these distinct populations have different physiological properties is unknown. Previous in vitro studies revealed two physiological types based on intrinsic firing properties: a tonic firing neuron and a single-spiking neuron. We describe here a third phenotype, a temporally patterned tonic firing neuron. How in vivo responses in SON correspond with the in vitro responses is unclear, as well whether these cell types correlate with the divergent postsynaptic targets. To investigate how SON neurons respond to more naturalistic, temporally fluctuating inputs, we used in vitro patch clamp electrophysiology in brain stem slices

and applied ‘noisy’ current injections that mimic in vivo activity. Sensitivity to fluctuations was measured as a change in firing rate, while reliability was assessed using a shuffled autocorrelogram analysis. Our results showed that single-spiking neurons (n=15) were the most sensitive to temporally modulated input and had highest reliability, while non-temporally patterned tonic neurons (n=22) were the least sensitive to temporally modulated input and more closely resembled integrators. The temporally patterned tonic neurons (n=31) had moderate sensitivity and reliability in its firing. Intracellular labeling of recorded neurons allowed the reconstruction of the axonal projections. The projection patterns were strongly related to the noise response types. Single-spiking neurons projected medially, toward the contralateral SON or ascending pathways. Temporally patterned tonic neurons projected ipsilaterally and dorsally in a fiber tract toward NM and NL. Finally, the non-temporally patterned SON neurons projected ipsilaterally via two different fiber tracts, either toward NA or toward NL and NM. These results suggest SON neurons have physiological specializations that allow a range of temporally responsivity, consistent with the diversity of in vivo response patterns. The data further suggests that circuit specializations allow the processing temporal information in functionally distinct pathways.

Disclosures: **J.F. Baldassano:** None. **K.M. MacLeod:** None.

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.08

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant R01 DC 019348
NSF Grant IOS 1652432

Title: Functional convergence of bilateral auditory tectothalamic pathways

Authors: *T. T. ADEYELU[1], O. M. OGUNDELE[1], C. C. LEE[2];
[1]Louisiana State Univ., Baton Rouge, LA; [2]Comparative Biomed. Sci., LSU Sch. of Vet. Med., Baton Rouge, LA

Abstract: Ascending information in the central auditory system is conveyed eventually by pathways from the auditory midbrain (inferior colliculus: IC) to the auditory thalamus (medial geniculate body: MGB). These tectothalamic pathways are composed of both excitatory and inhibitory projection neurons, which transfer and modulate this incoming auditory stream. Although the role of the ipsilateral auditory tectothalamic pathways in this process has been intensively investigated, the contribution from the contralateral tectothalamic pathways has been largely ignored. Here we employed a cre-lox approach to examine the neuroanatomical and physiological properties of the contralateral tectothalamic pathways in auditory processing. Floxed viral tracers expressing either mCherry or EYFP were injected bilaterally into each IC of

VGLUT2-Cre or VGAT-Cre transgenic mice. The resultant bilateral terminal fields were then examined in the MGB. In addition, we assessed the functional impact of these projections, by utilizing an optogenetic approach to express halorhodopsin using floxed viral vectors in the Cre-transgenic animals and then recording physiologically from the MGB to acoustic stimuli. From our studies, we found that the MGB terminal fields from bilateral IC tectothalamic projections overlapped on a gross level. On a finer scale, terminal puncta were often closely apposed near presumed cell bodies, suggesting single-cell convergence of these inputs. Physiologically, optogenetic inhibition of contralateral tectothalamic pathways affected the responsiveness and spiking characteristics of MGB neurons to sound stimulation. Together, these data demonstrate a significant role for the contralateral tectothalamic pathways in the bilateral integration of the auditory scene.

Disclosures: T.T. Adeyelu: None. **O.M. Ogundele:** None. **C.C. Lee:** None.

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.09

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant R01DC019341

Title: Central projections of auditory nerve fibers in the Western ratsnake (Pantherophis obsoletus)

Authors: *D. HAN, C. E. CARR;
Univ. of Maryland, College Park, MD

Abstract: All snakes lack tympana and are instead thought to detect vibration through the lower jaw, which is coupled to the inner ear via the columella and quadrate. How snakes process vibrational information centrally is poorly understood. Here we describe the projections of the cochlear branch of the VIIIth nerve in the Western ratsnake (*Pantherophis obsoletus*) using tract tracing, immunohistochemistry and Nissl staining. Injections of biotinylated dextran-amine (BDA) to the basilar papilla revealed projections to two first-order cochlear nuclei, a rostrolateral nucleus angularis (NA) and a caudomedial nucleus magnocellularis (NM). NA receives parvalbumin-positive bouton terminals and forms a distinct dorsal eminence in the fourth ventricle. NA projects to the superior olive and torus semicircularis. NM is small and poorly separated from the surrounding vestibular nuclei but can be distinguished as a small group of calbindin-positive cells. NM projects bilaterally to a second-order target in the acoustic tubercle. Our results show that despite detecting primarily ground-borne vibration instead of aerial sound, the Western ratsnake has the same first-order cochlear nuclei as other reptiles.

Disclosures: D. Han: None. **C.E. Carr:** None.

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.10

Topic: D.05. Auditory & Vestibular Systems

Support: R01 DC0003788
R01 DC017466-01

Title: Mechanisms of interval counting and selectivity in the anuran inferior colliculus: the role of dis-inhibition and 2nd order processing.

Authors: J. M. MCDOWELL[1], *R. K. ALLURI[1], G. J. ROSE[1], A. MUKHOPADHYAY[1], C. J. LEARY[2];
[1]Sch. of Biol. Sci., Univ. of Utah, Salt Lake City, UT; [2]Dept. of Biol., Univ. of Mississippi, University, MS

Abstract: Acoustic communication is important in the reproductive behavior of many animals. In many anurans, temporal intervals between the onsets of successive sound pulses carry information about species identity and call type. Behavioral studies have shown that anurans require a minimum number of consecutive, correct intervals to recognize their conspecific advertisement call, and males of some species closely match the number of note-like advertisement calls of their neighbor. These findings reveal the numerical abilities of anurans. Interval-counting neurons (ICNs), a class of interval-selective cells in the anuran inferior colliculus, represent neural correlates to such behaviors; these cells respond only after a threshold number of sound pulses have occurred with optimal intervals. Using a novel combination of whole-cell recordings with focal pharmacology, *in-vivo*, and by estimating excitatory and inhibitory inputs to ICNs, we investigated the mechanisms that underlie counting. We show that interval counting in the inferior-colliculus is achieved in diverse ways. Most notably, for ICNs that show strong band-pass selectivity for pulse rate i.e., interval selectivity, the interval-counting process rapidly resets following an interval that is 2-3 times the optimal value. For this type of ICN, inhibition rapidly depresses at fast PRs and rebounds following the end of a pulse train; counting results from integration of excitation that temporally summates and inhibition that shows rate-dependent decrease in amplitude during a pulse train, followed by a strong 'off' response; this 'dis-inhibition' enables excitation to depolarize the cell. Attenuating inhibition in these '1st-order' neurons decreased PR selectivity and pulse-number thresholds. Further, we show that some ICNs show little or no evidence of performing this computation, but are highly selective to fast pulse rates. These '2nd-order' ICNs show excitation that is nonlinearly related to pulse number at fast pulse-rates, therefore appearing to receive inputs from other ICNs; inhibition in these ICNs, if present, appears to primarily control response gain. These novel findings provide an unprecedented advance in understanding how the brain counts temporal elements in acoustic signals.

Disclosures: **J.M. McDowell:** None. **R.K. Alluri:** None. **G.J. Rose:** None. **A. Mukhopadhyay:** None. **C.J. Leary:** None.

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.11

Topic: D.05. Auditory & Vestibular Systems

Support: Czech Science Foundation 20-06927S
RVO 86652036
NIH/NIA AG060504
NIH/NIA DC016099
NIH/NIA AG051443

Title: Isl1is necessary for auditory neuron development and contributes towards tonotopic organization

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Abstract: A cardinal feature of the auditory pathway is frequency selectivity represented in the form of a tonotopic map from the cochlea to the cortex. The molecular determinants of the auditory frequency map are unknown. Here, we discovered that the transcription factor ISL1 regulates features of auditory neurons, including the formation of the spiral ganglion neuron (SGN) and peripheral and central processes that shape the tonotopic representation of the auditory map. We selectively knocked out *Isl1* in auditory neurons using *Neurod1*^{Cre} strategies. In the absence of *Isl1*, SGNs migrate into the central cochlea and beyond. The cochlear wiring is profoundly reduced and disrupted. The central axons of *Isl1* mutants lose their topographic projections and segregation at the cochlear nucleus. Transcriptomic and epigenomic analyses of SGNs shows that *Isl1* regulates neurogenesis, axonogenesis, migration, and the functional properties of neurons. Surprisingly, notable auditory processing features are preserved despite the significant hearing impairment, revealing central auditory pathway resilience and plasticity in mutant mice. Mutant mice demonstrate altered acoustic startle reflex, prepulse inhibition, characteristics of compensatory neural hyperactivity centrally. Our findings show that the *Isl1* is one of the obligatory factors required to sculpt auditory structural and functional tonotopic maps. Still, upon *Isl1* deletion, the ensuing compensatory plasticity of the auditory pathway does not suffice to overcome developmental changes at the peripheral sensory organ.
FundingThis research was supported by the Czech Science Foundation (20-06927S to GP), by

the institutional support of the Czech Academy of Sciences (RVO: 86652036 to GP), and NIH/NIA (R01 AG060504, DC016099, AG051443 to BF and ENY).

Disclosures: **G. Pavlinkova:** None. **I. Filova:** None. **K. Pysanenko:** None. **M. Tavakoli:** None. **S. Vochyanova:** None. **M. Dvorakova:** None. **R. Bohuslavova:** None. **O. Smolik:** None. **S. Benesova:** None. **L. Valihrach:** None. **E.N. Yamoah:** None. **J.M. Syka:** None. **B. Fritzsch:** None.

Poster

713. Auditory-Neurophysiology and Anatomy: Midbrain

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 713.12

Topic: D.05. Auditory & Vestibular Systems

Support: NIH R01 DC 17924
R01 DC 18401
National Key R&D Program of China (No. 2020YFB1313502)
Shenzhen-Hong Kong-Macau S&T Program (Category C) of SZSTI (No. SGDX20201103094002009)
University of Macau (File nos. MYRG2018-00146-AMSV, MYRG2019-00056-AMSV)
Science and Technology Development Fund, Macau SAR [File nos. 088/2016/A2, 0144/2019/A3, 0022/2020/AFJ, SKLAMSV (FDCT-funded), SKL-AMSV-ADDITIONAL FUND, SKL-AMSV (UM)-2020-2022]

Title: Sound Localization Deficits and Abnormal Auditory Brainstem Responses in a Computational Model of Fragile X Syndrome

Authors: *B.-Z. LI[1,2,3,4], S. PUN[1], M. VAI[1,2], T. C. LEI[3,4], A. KLUG[3];
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Abstract: Perceptual deficits in spatial hearing are frequently associated with developmental abnormalities in the auditory pathways, but the underlying mechanisms have yet to be completely elucidated. In this study, we investigated the influence of pathological alterations in the sound localization pathway with a computational model of fragile X syndrome (FXS). Fragile X is the most common monogenetic form of autism spectrum disorder and commonly causes auditory processing disorders and aberrant neurodevelopment. Our multiscale computational model, which simulates neuronal dynamics and synthesizes biopotentials, was developed by using spiking neuronal networks with spiking neuron models, connected and distributed to recapitulate the anatomical arrangement within the auditory brainstem. The developmental abnormalities caused by FXS, including hyperexcitability and myelination

deficits, were represented by enhanced excitatory connectivity and slower axonal conduction velocity, respectively. This model was stimulated with encoded cochlear responses using various sound waves containing binaural cues, and analyzed by neural decoding approaches to estimate the amount of spatial information and the precision of binaural detection. Our simulations revealed that both hyperexcitability and myelination deficits in FXS can significantly degrade the binaural integration process and reduce the spatial hearing precision. In addition, we were able to model the synthesized Auditory Brainstem Responses (ABR) through the spiking neuronal network model. The results showed an effect on the attenuated peak III-V amplitudes in FXS, as well as longer peak latencies, which closely match experimental observations. In summary, this work demonstrates that FXS-induced neurodevelopmental abnormalities in the auditory brainstem circuits are sufficient to cause the sound localization deficits and abnormal auditory brainstem responses.

Disclosures: **B. Li:** None. **S. Pun:** None. **M. Vai:** None. **T.C. Lei:** None. **A. Klug:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.01

Topic: D.06. Vision

Support: NIH Grant RF1 MH117015

Title: Using rapidly sampled, high resolution fMRI to measure deviations from linearity in the presence of low frequency oscillations

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Abstract: Despite electrophysiological evidence that the activity of surrounding neurons scales responses through normalization mechanisms in cerebral cortex, the implications of such scaling on response dynamics and population-based signals such as blood oxygenation level dependent (BOLD) signals measured in fMRI remain undetermined. Understanding the effects of surrounding activity, or mesoscopic brain state, on the magnitude and dynamics of impulse response functions is critical for the interpretation of brain activity correlates. For example, even slight changes in the hemodynamic response function (HRF) can result in substantial errors in BOLD based predictions of the timing and location of neuronal activity. In this project, we have approached this issue using an oscillating background of 4 Hz flickering band-passed noise while acquiring high resolution (1.3mm isotropic) rapidly sampled (0.375s) functional neuroimaging of the occipital cortex in human volunteers (n=2). Probe pulses (500 ms vertical gratings, s1:350, s2: 387) were delivered randomly at difference phases of the background sinusoid in 2 retinotopic locations. Participants responded each time they detected a probe. Under this framework we are able to 1) extract estimates of the response amplitude and 2) reconstruct

impulse response functions according to phase from precise retinotopic locations, thereby allowing a systematic examination of reactivity as a function of brain stateIn the BOLD signals from human visual cortex, we observe a nearly linear response modulation in response to the slowly oscillating background at across broad regions of visual cortex however the timing of these responses shows spatial variability. The recovered estimates of the hemodynamic response impulse function show the substantial influence of background contrast, with moderate contrast levels appearing to have a potentiating effect. Further examination of impulse response functions show that the background-dependent modulations cannot be explained by a simple scaling model.These findings highlight several important but often overlooked details in functional neuroimaging. The effects of ongoing activity, often left uncontrolled, induced here using a oscillating background, induce variability in the amplitude of BOLD responses. In addition, accurate modeling of HRF variability, visible here over space, also frequently ignored. Understanding and further modeling of these contributions may make it possible to attenuate such sources of 'neuronal noise' for more accurate and robust fMRI studies.

Disclosures: **L. Dowdle:** None. **L. Vizioli:** None. **G. Ghose:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.02

Topic: D.06. Vision

Support: Research supported by grant number RTI2018-094465-J-I00 funded by MICIN/AEI/10.13039/501100011033 and by "ERDF A way of making Europe" FUNDALUCE (Foundation for Fighting Blindness)

Title: Cross-modal neural rewiring in the dystrophic Royal College of surgeon rat: insights for bionic vision.

Authors: *A. BARRIGA-RIVERA[1,3], D. CARAVACA-RODRIGUEZ[1], S. P. GAYTAN[2]; [1]Dep. Applied Physics III, [2]Dep. Physiol., Univ. de Sevilla, Sevilla, Spain; [3]Sch. of Biomed. Engin., Univ. of Sydney, Sydney, Australia

Abstract: Transformative changes occur in the brain of the blind. The loss of visual inputs produces a cascade of neural reconnections that modify the neural circuits of the visual system. Besides, cross-modal neural rewiring in blind subjects is evidenced by, for example, the activation of the visual cortex by other sensory inputs. Whether said neural rewiring hinders or assists during neural rehabilitation following the reintroduction of the visual input remains uncertain. Here we describe an exploratory study to investigate the effects cross-modal plasticity can have in visual prosthetics by recording auditory evoked potentials (AEPs) from two visual centers in a model of retinal degeneration. The study was approved by the Ethics Committee of the University of Seville. We have chronically implanted three microwire electrodes, one in the

primary visual cortex (V1), and two in the dorsal lateral geniculate nucleous (dLGN) in four dystrophic Royal College of Surgeon rats, aged 14 weeks. After recovery from surgery, the animals underwent auditory training for five consecutive days. Briefly, the animals were introduced within a custom acoustically isolated experimental chamber. First, a 32-kHz 400-ms tone was presented to assess the auditory evoked potentials (AEPs). The tone was repeated 50 times with inter-stimulus time randomly distributed between 3 and 5 s. Then, 25 periods of between 20 and 30 s of white noise were presented with inter-stimulus time between 20 and 30 s. Recordings of the AEPs were conducted for a second time. Successful responses, characterized by the ensemble average, were obtained from two male rats. We characterized the amplitude and latency to the first maxima of the AEPs. Overall, responses in the dLGN and the V1 appeared at 20.2 ± 0.6 ms and 32.8 ± 2.7 ms respectively. The amplitude of the peak in dLGN AEPs at day-5 training was significantly lower compared to those in the day-1 training (p-value=0.09, t-test). In addition, a good linear correlation was obtained over time in both animals (r^2=0.7 ± 0.1, r^2=0.6 ± 0.0). However, no statistically significant differences were observed in V1 responses (p-value=0.16, t-test). In a previous study (Caravaca-Rodriguez *et al.* 2022) we found faster AEPs in the V1 of the anesthetized dystrophic rat compared to sighted individuals. Together, these results suggest that thalamic rewiring may play a more relevant role in the cross-modal adaptation in the RCS rat. Hypothetically, this may be understood as more efficient thalamic connectivity between auditory and visual processing centers. However, the insights in this study require larger cohorts that include non-dystrophic rats, and further histological verification.

Disclosures: **A. Barriga-Rivera:** None. **D. Caravaca-Rodriguez:** None. **S.P. Gaytan:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.03

Topic: D.06. Vision

Support: IBS-R015-D1

Title: The brain optimizes perception in astigmatism through compensatory gain modulation

Authors: *S. SON[1,2], W.-M. SHIM[1,2,3], H. KANG[4], J. LEE[1,2,3];
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Abstract: Most people have some amount of astigmatism, which systematically distorts retinal inputs to the brain. However, in everyday life, our perception is much less distorted. Here, we investigated how the brain compensated for the distorted orientation inputs after long-term exposure to astigmatism. We asked two groups of participants to perform an orientation adjustment task while recording an electroencephalogram (EEG) activity from 64-channels of

active electrodes. One group had chronic astigmatism in which their retinal input had a meridian-specific distortion due to the deformation in the lens (chronic group). The other group had normal vision, where we temporarily induced astigmatic blur by applying a cylindrical lens (control group). The amount of astigmatism induced in the normal-visioned group was matched with that in the chronic group. In the control group, the neural orientation tuning responses represented in the multivariate EEG activities were severely skewed according to the optical characteristics of astigmatism. However, it was far less severe in the chronic group, even if the degree of deformation in retinal inputs were similar to those in the control group. Computational modeling on multivariate EEG responses revealed that the enhancement in the chronic group was due to a simple gain modulation mechanism that enhanced neural responses to the optically blurred orientation and reduced responses to the orthogonal orientation. We further found that the gain modulation gradually stabilized over exposure time. Even in the control group, we found that the gain modulation started to appear after the participants were exposed to astigmatic blur for approximately 30 minutes. Yet, this gain modulation had no visible relationship with the perceptual judgments. On the contrary, the gain modulation was observed throughout the trials in the chronic group and was closely related to both within- and across-participants variability of the perceptual report. These results provide insight into how the brain adapts to systematically biased inputs; the brain is sensitive enough to temporarily re-weight the neural orientation space to fight back the distortion, but it takes time to work stably and functionally. The current research provides a mechanistic understanding of neural compensation for the optical aberration, which can be utilized as a practical guide in clinical situations.

Disclosures: **S. Son:** None. **W. Shim:** None. **H. Kang:** None. **J. Lee:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.04

Topic: D.06. Vision

Support: CIHR grant MOP-119498

Title: Cortical state effects on receptive field responses of early visual cortex neurons

Authors: *J. J. SOORIYAARACHCHI[1], C. ZHAN[2], C. L. BAKER[3];
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Abstract: A visual cortex neuron’s response depends not only on the characteristics of a visual stimulus in relation to its receptive field (RF), but also “brain state” fluctuations which cause substantial trial-to-trial variability. Brain state effects on sensory coding are poorly understood, potentially compromising RF estimation. Here we analyzed the interaction between a neuron’s spiking response and brain state inferred from local field potentials (LFPs) to obtain better

quantitative estimates of neuronal RFs. We used extracellular recordings from the primary visual cortex of anesthetized, paralyzed cats recorded with 32-channel NeuroNexus probes which responded to rapid sequences of natural images (Talebi and Baker, 2012). Low-pass filtering (< 100Hz) was employed to extract LFPs from the raw recorded signals, and single units were isolated using Kilosort software. Phase locking strength (PLS) provided an indication of the relationship between spiking responses and different frequency bands of the LFP signal. We then employed a system identification approach using machine learning, with a model architecture incorporating an LFP-driven filtering pathway in parallel with a stimulus-driven RF pathway, followed by a simple output nonlinearity. The model parameters were estimated with an iterative regression algorithm with L2 regularization, using TensorFlow and Keras on a training dataset, along with a validation dataset for regularization. The variance accounted for (VAF) was used to evaluate the model's predictive performance on a hold-back test dataset. Results from the PLS analysis showed that the spiking responses of neurons are strongly linked to various frequency band oscillations of the LFP signals. The system identification revealed the relevance of LFP frequency bands similar to those found with the PLS analysis, with different neurons recorded simultaneously showing significant relationships with different frequency ranges of the LFP. Incorporating brain state effects provided significant improvements in VAF measures of predictive performance depending on the type of neuron (i.e., simple/complex, oriented/non-oriented etc.), despite the additional model parameters. These findings highlight the importance of incorporating the trial-to-trial variability due to brain state variations in studies of sensory coding at the single neuron level and indicate that the nature of brain state variations may vary substantially across different neurons.

Disclosures: **J.J. Sooriyaarachchi:** None. **C. Zhan:** None. **C.L. Baker:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.05

Topic: D.06. Vision

Title: Functional ultrasound (fUS) as a novel approach to assess the visual system in live mice: from vascular structure to functional responses

Authors: H. VAHERTO, ***K. PALDANIUS**, A. SHATILLO;
Charles River Discovery Services, Kuopio, Finland

Abstract: Variety of neurodegenerative diseases such as Alzheimer’s, Parkinson’s and Batten disease include visual impairments in their pathophysiology. Ideally, translational preclinical disease model should have symptomatic ocular component enabling evaluation of the therapeutic window for new treatments. In vivo assessment of visual system function in rodents is possible using tools such as optical coherence tomography (OCT), electroretinography (ERG) and visual evoked potentials (VEP), which all are used to measure specific aspects of impaired vision.

Direct imaging tools to study anatomy and function are largely limited to methods like confocal scanning laser ophthalmoscopy (cSLO) and in rare applications, MRI. Here we present a novel and versatile in vivo imaging technique, functional ultrasound (fUS), to assess the structure, perfusion, and neuronal responses in the visual brain upon direct stimulation of the mouse eye. The fUS method utilizes latest technological advancements for ultrafast plane-wave acquisition of doppler ultrasound signal with real-time data processing. This approach enables high sensitivity imaging of blood volume changes with unrivaled temporal and spatial resolution. If applied to structural scan, signal can be acquired from a regular 3D power-doppler volume mode (~0.4 mm in-plane resolution) up to a single slice super-resolution ULM image at 0.005 mm in-plane volumetric ocular vessel-maps. Perfusion and structure of the ocular vasculature can be assessed using microbubbles contrast enhanced dynamic scan, to provide relative ocular blood flow (rOBF) via first-pass flow curve of the fUS signal time-course over retinal vasculature. Assessment of the brain responses and integrity of the whole visual pathway with fUS is based on the classical neurovascular coupling mechanisms as in functional MRI (fMRI). We show here, how this is applied using 3 Hz single-eye white LED light stimulation to visualize the brain responses in primary and secondary visual cortex, superior colliculus, and visual relay to entorhinal cortex. Finally, we applied this in a $CLN8^{mnd}$ mouse model of Batten disease, where we show that both low (0.1-0.2 lux) and high (50-60 lux) intensity stimulation completely lack the neuronal response in the visual cortex, whereas high intensity stimulation is still capable of eliciting some signal changes in the superior colliculus.
Taken together, fUS imaging presents promising, highly versatile yet largely unexplored novel method for ocular research. This platform can be utilized both for basic research and pre-clinical drug discovery, allowing screening of the novel compounds targeted for visual system pathologies.

Disclosures: **H. Vaherto:** None. **K. Paldanius:** None. **A. Shatillo:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.06

Topic: D.06. Vision

Support: NSF NCS-FO 2024364

Title: Accounting for visual cortex variability with distributed, brain-wide activity states

Authors: *A. J. LI[1], Z. LU[2], E. T. SHEA-BROWN[2], N. A. STEINMETZ[3];
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Abstract: Generating flexible neural and behavioral responses is a key feature of animal nervous systems. Sensory neuron responses are known to fluctuate on repeated trials of the same stimuli. Aspects of these fluctuations can be attributed to locomotion, arousal, movements, and other

behavioral variables. Other aspects may reflect more cognitive factors, such as attention, metabolic state, or other factors without known labels. Both behavioral and cognitive variables have representations in many brain regions, cortical and subcortical, that underlie brain states, or shared patterns of activity between regions. We hypothesized that such distributed brain states may account for trial-to-trial variability in responses of sensory cortical neurons.
Here, by measuring simultaneously in multiple neuronal populations, we identify brain states that are independent of stimulus information and commonly measured behavioral variables, and which explain trial-to-trial variability beyond that attributable to those factors. We collected high-density neural recordings in mouse primary visual cortex (the "target" region) and other "source" regions, including anterior cingulate area and thalamic nuclei. Animals were awake, alert, and passively viewing multiple types of visual stimuli. Using multiple linear regression, we find that neurons in "source" areas were highly predictive of the target visual cortex population. Behavior (pupil diameter, face movements) and stimulus information predicted up to 10% of visual cortex neuron activity, while including "source" areas predicted up to 15%. Including "source" neurons in the regression specifically improved our prediction beyond what was predictable with behavioral and stimulus features, indicating that a unique component of the variance in visual cortical activity is predictable from activity observed in other brain regions. The results suggest that trial-to-trial variability may be captured or even driven by distributed brain states. We find a similar result when predicting single visual cortex neurons with simultaneous widefield calcium imaging across the cortex, which indicates that bulk population activity in distant cortical areas can also account for aspects of the visual cortex trial-to-trial variability.
We discovered that internally-measurable fluctuations in the activity of distant regions predicts visual cortical activity and accounts for previously unexplained components of trial-to-trial variability. We speculate that these distributed brain states may also relate to behavioral and perceptual variability within animals, or individual differences in behavior between animals.

Disclosures: **A.J. Li:** None. **Z. Lu:** None. **E.T. Shea-Brown:** None. **N.A. Steinmetz:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.07

Topic: D.06. Vision

Support: NIH Grant R01EY031328

Title: Rapid adaptation impacts the population coding of parametric and natural stimuli in mouse visual cortex

Authors: *L. LUO[1], C. LIENKAEMPER[3], Y. CHEN[2], L. L. GLICKFELD[1];
[1]Neurobio., [2]Statistical Sci., Duke Univ., Durham, NC; [3]Mathematics, Pennsylvania State Univ., State College, PA

Abstract: The efficient coding hypothesis proposes that neural systems strive to maximize the mutual information between input and neuronal response using a minimal number of spikes. Adaptation in early visual areas serves to reduce temporal redundancy and benefit coding efficiency. However, it is unknown whether the spatial redundancy of visual stimulus features modulates adaptation to achieve higher coding efficiency. To test this, we performed two-photon calcium imaging in mouse primary visual cortex (V1) and measured adaptation evoked by 100 ms stimuli of different spatial redundancy, namely static gratings (vertical, 0.1 cycles/deg) or natural images. We find that gratings evoke larger rapid adaptation in V1 than the natural images used in our experiments, suggesting that the high spatial redundancy in gratings drive stronger adaptation, facilitating coding efficiency. While consistent with efficient coding theory, this stimulus dependence was surprising since ongoing work suggests that adaptation arises due to short-term synaptic depression, which should not depend on stimulus features. One possible explanation is that neurons that prefer different features undergo different degrees of depression. To test this, we compared the adaptation magnitude as a function of spatial frequency preference. We find that neurons that prefer low (0.04 cpd) and high (0.64 cpd) spatial frequencies exhibit less adaptation than mid spatial frequencies, which could explain observed differences between natural images and gratings since natural images contain more diverse spatial frequencies. To explore the functional consequence of the heterogeneity in adaptation across neurons, we used dimensionality reduction analysis on open-source data from Allen Institute visual behavior dataset. We find that neurons that adapt less encode natural image identity in a lower dimensional space than neurons that adapt more, where their variance can be explained by fewer dimensions and there is strong clustering of population responses according to image identity. This suggests that the less-adapting subpopulation accurately encodes natural image identity, while the more-adapting subpopulation sparsifies the representation. Together, our data reveal how heterogeneous adaptation carries out efficient coding by compressing stimulus redundancy to support both accurate encoding and sparse representations.

Disclosures: **L. Luo:** None. **C. Lienkaemper:** None. **Y. Chen:** None. **L.L. Glickfeld:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.08

Topic: D.06. Vision

Support: NIH Grant EY032102
NIH Grant EY021462
NIH Grant EY032999
NSF GRFP
Whitehall Foundation

Title: Decoding momentary gain variability from neuronal populations

Authors: *C. M. ZIEMBA, Z. M. BOUNDY-SINGER, R. L. T. GORIS;
Ctr. for Perceptual Systems, Univ. of Texas at Austin, Austin, TX

Abstract: Neural activity in visual cortex is well described by models composed of a deterministic tuning function, a stochastic gain, and a point process. Recent work has shown that in area V1 and V2 of macaque monkeys, variability in the gain is tuned to the statistics of the sensory input. This suggests that gain variability may reflect signal rather than noise. Specifically, gain variability appears well suited to inform downstream estimates of perceptual uncertainty. However, this notion critically requires that gain variability can be instantaneously read-out in a neurally plausible manner. Here, we simulated neural population activity and studied the performance of a heuristic decoder of gain variability, derived from the expected variance of mixture distributions. This decoder exclusively relies on operations of summation, squaring, and division, and requires no knowledge of the selectivity or organization of the input population. For small input populations ($N < 10$), the decoder performed poorly. However, with increasing population size, its estimates of gain variability increasingly approximated the ground truth. For large input populations ($N > 100$), the decoder's performance was excellent. We found the decoder to perform robustly at short timescales, across different stimulus strengths, and with realistic levels of correlated spiking variability. Together, our findings show that cross-neuron gain variability can in principle be read-out instantaneously using neurally plausible operations. We conclude that the visual cortex may employ a coding strategy whereby stimulus identity and stimulus uncertainty are encoded independently from each other.

Disclosures: C.M. Ziemba: None. **Z.M. Boundy-Singer:** None. **R.L.T. Goris:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.09

Topic: D.06. Vision

Support: NIH F31 EY031941
NIH R01 EY031328

Title: Synaptic depression of intracortical synapses shapes temporal integration in mouse primary visual cortex

Authors: *J. Y. LI, L. L. GLICKFELD;
Duke Univ., Duke Univ., Durham, NC

Abstract: Adaptation is a fundamental feature of visual processing that enables the nervous system to adjust to specific environmental features over time. Even brief visual stimulus presentations (100 ms) can suppress responses in primary visual cortex (V1) to similar stimuli for seconds (Jin et al., 2019). This form of rapid adaptation is particularly relevant to naturalistic viewing patterns, as saccadic eye movements and changes in natural scenes occur on this time

scale. To investigate the mechanism of rapid adaptation, we used *in vivo* whole-cell recordings to measure subthreshold membrane potential or synaptic inputs in layer 2/3 V1 neurons while presenting static 100 ms gratings. In contrast to studies using seconds-long adapter stimuli, we find no hyperpolarization induced following brief visual stimulus that can explain the observed suppression in spiking following rapid adaptation. Instead, we find that changes in stimulus-evoked PSPs better reflect features of rapid adaptation. We thus performed *in vivo* voltage clamp recordings and measured EPSCs and IPSCs within individual cells. This reveals balanced changes in stimulus-evoked excitation and inhibition that are similar to changes in spike output when comparing the degree, recovery time course, and stimulus-specificity of suppression. The stimulus-specific suppression of both EPSCs and IPSCs implicates a role for plasticity at feed-forward inputs onto excitatory and inhibitory neurons rather than at inhibitory synapses within layer 2/3, which are generally more broadly tuned. Therefore, we reasoned that lasting suppression of synaptic inputs could be due to short-term synaptic depression at feed-forward synapses from layer 4 neurons onto layer 2/3 neurons. To test this hypothesis, we performed *in vivo* silicone probe recordings in V1 and used optogenetics (Scnn1a-Cre x Ai32 mice) to activate synapses from layer 4 neurons onto layer 2/3 neurons. Consistent with an activity-dependent depression mechanism, direct activation of these synapses (in the absence of a visual stimulus) is sufficient to suppress visually-evoked responses in layer 2/3 neurons and occlude adaptation to subsequent visual stimuli. Furthermore, optogenetic suppression of vesicle release probability using the Gi-coupled inhibitory opsin eOPN3 at layer 4 synaptic terminals (again using Scnn1a-Cre mice) also occludes the visually-evoked adaptation in layer 2/3 neurons. Together, our data identify a mechanism for the regulation of temporal dynamics of visual responses that occurs at the level of specific synapses within the V1 circuit.

Disclosures: J.Y. Li: None. **L.L. Glickfeld:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.10

Topic: D.06. Vision

Title: Mesoscopic mapping of the acetylcholine release and neuronal responses to variations of contrast in the mouse visual cortex

Authors: *H. SEDIGHI[1], A.-R. FOFANA[1], S. CHOI[1], M. GUEZZANE[1], Y. LI[2], E. H. VAUCHER[1];
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Abstract: Mesoscopic mapping of the acetylcholine release and neuronal responses to variations of contrast in the mouse visual cortexHossein Sedighi[1], Abdel-Rahamane Kader Fofana[1], Shiwon Choi[1], Mehdi Guezzane[1], Yulong Li[2] and Elvire Vaucher[11]*Laboratoire de*

Neurobiologie de la Cognition Visuelle, École d'Optométrie, Université de Montréal, Canada
[2]State Key Laboratory of Membrane Biology, Peking University School of Life Sciences The basalo-cortical cholinergic system regulates the visual function by modulating the fine tuning of the cortical processing, especially in the mechanisms of cortical plasticity, attention and learning. Particularly, the cholinergic neurons stimulation potentiates the response of visual neurons and their specificity in relation to these functions, as well as contrast sensitivity. The present study aims to compare the pattern and intensity of the acetylcholine (ACh) release and neuronal activity in the visual cortex of mice in response to contrast variations. The mesoscopic imaging of calcium and cholinergic activity was performed in Thy1-GCaMP6s transgenic and AAV-delivered gACh-3.0 awake mice, respectively (4-6-month-old, n=4-6 per group). A luminance based sinusoidal grating (0.03cpd, 1Hz drift, 30%, 50%, 75% and 100% contrast) was displayed (2sec on/8sec off, 10 repetitions) on two gaming monitors (BenQ, 120Hz, 1ms) in the axis of the eyes. Cortical responses (ΔF/F, %) were measured using Modular Optical Imaging System (Labotech, QC) and cmos Scientific camera (ThorLabs, Canada) and at the level of the primary visual cortex (V1) and the extrastriate visual areas (LM, PM, AL). The variation of ACh and calcium signals were analyzed by Imagery Serialized Analysis Toolbox in MATLAB. Both the ACh and calcium signals varied in a contrast-dependent manner in all the visual areas investigated (V1, AL, LM, PM), although the variation was smaller in AL and LM. Compared to the lower contrast (30%), ACh release increase around 240% at 100% contrast in V1 and PM, and 60% for 75% contrast. The maximal ACh release increase reaches only 60% for AL. The GCAMP signals increased up to 400% for 100% contrast in V1 and PM, and 300% in LM and AL. These percentages were around 100% for the 75% contrast. These results suggest that the release of ACh is finely adjusted to the contrast of pattern visual stimuli in all the visual cortical areas of the mice. This is associated with proportional although higher changes of neuronal activity. These neurochemical changes most likely contribute to fine tune the perceptual contrast sensitivity of the mice.

Disclosures: H. Sedighi: None. **A. Fofana:** None. **S. Choi:** None. **M. Guezzane:** None. **Y. Li:** None. **E.H. Vaucher:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.11

Topic: D.06. Vision

Title: Gaba cell-subtypes and layer specific expression of cholinergic receptors in the mouse visual cortex

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Abstract: In addition to its direct role on excitatory cells, acetylcholine (ACh) interacts with the GABAergic cells to control lateral inhibition in the primary visual cortex (V1) and synchronization of cortical networks. Different, sometimes opposite, action however results from nicotinic receptors (nAChRs) and muscarinic receptors (mAChRs) located on different types of GABAergic neurons.In order to better understand the complex interaction of ACh and GABAergic neurons in visual computing, we analyzed single-cell RNA sequencing (ScRNASeq) datasets of the mouse V1.The transcriptomic profile of parvalbumin (PARV), somatostatin (SST) or vasointestinal peptide (VIP) neurons related to the AChR was examined from the datasets of the Allen Institute for Brain Science, according to their taxonomy. UMAP plot was used to generate dimensionality reduction and cluster visualization of the subpopulations of GABAergic cells.Dotplots of the expression of the genes of mAChR subtypes (m1 to m5) and nAChR (α2, α4, α7, β2, and β6) subunits across GABAergic cell types were produced and analyzed. While m1 was poorly but universally expressed in the GABAergic neurons, m2 expression was particularly enriched in the PARV and SST neurons of the infragranular layers. M3 was found in VIP neurons of the supragranular layers as well as in the infragranular SST and VIP neurons. M5 were virtually not found in the GABAergic neurons, except in a small subpopulation of SST neurons.α2 and β3 were particularly expressed in a subset of SST neurons cells, albeit at low expression levels. α4β2 were expressed as a baseline level in SST and VIP cells but not PARV cells. α7 were scarcely expressed within any subtypes of GABAergic cells.These results underline a very potent role of m2 mAChR on the PARV and SST GABAergic infragranular neurons. As this receptor is linked to inhibitory Gprotein (G α q) it could elicit cortical diesinhibition. M3 is also very highly expressed on SST and VIP neurons. M4 action seems distinct from m2, since it is only expressed in basal level in PARV cells.The results also reveal a possible specific action of α subunits in the inhibitory control of V1 by showing their expression on SST neurons. There is no specific expression of m1, α7 and α4β2 receptors on the GABAergic neurons, although they are considered as the main AchR in V1, confirming a potent and maybe exclusive role of these receptors on the excitatory cells compared to inhibitory interneurons.
according to specific markers that determine the neurochemical signature of the cells, as well as their layer specificity (taxonomy is available on website.Using this ScRNAseq dataset, we have determined the cell specificity of the in the V1 of mice.

Disclosures: **F. Meziane:** None. **G. Cagnone:** None. **J. Joyal:** None. **E.H. Vaucher:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.12

Topic: D.06. Vision

Support: 2T32EY007135-26
1R01EY027402-01

Title: V1 ocular dominance is functionally relevant for binocular vision

Authors: *B. A. MITCHELL[1], B. M. CARLSON[1], M. A. COX[2], A. MAIER[1];
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Abstract: Neurons in primate primary visual cortex (V1) combine left and right-eye information to form a binocular output. Models of binocular combination have identified contrast gain-control as a critical process in regulating V1 binocular responses. Recent work from our laboratory and others have suggested that a neuron's monocular preference for eye, i.e., ocular dominance, modulates excitation under binocular conditions. However, it remains unclear the extent to which V1 ocular dominance interfaces with interocular gain-control. Here, we tested the hypothesis that adding ocular dominance information to a model of interocular gain-control improves the model's ability to account for binocular contrast combination in macaque V1. To do this, we recorded V1 spiking activity while animals passively viewed grating stimuli through a mirror stereoscope. Gratings were either presented to one eye (monocular), both eyes with the same contrasts (binocular balanced), or both eyes with different contrasts (binocular imbalanced) at corresponding retinal positions. We then fitted the entire set of V1 contrast responses (C_L, C_R; 5x5) with the interocular normalization model, as well as alternative and traditional models of binocular contrast combination. Goodness of fit (R^2) to the observed data was obtained for each V1 unit and quantitatively compared between models. Interocular normalization outperformed linear summation, quadratic summation, and a similar model to normalization that nonlinearly combines the contrast in the two eyes. Introducing an ocular dominance weight to the stimulus drive (i.e., numerator) of interocular normalization significantly improved model performance, suggesting that V1 ocular dominance may play a larger role in interocular gain control than previously thought. Together, our results extend the interocular normalization framework to the level of spiking responses and provide evidence for a computational role of V1 ocular dominance in binocular vision.

Disclosures: B.A. Mitchell: None. **B.M. Carlson:** None. **M.A. Cox:** None. **A. Maier:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.13

Topic: D.06. Vision

Support: 1R01EY027402

Title: Interocular transfer of adaptation primarily modulates the infragranular layers of V1

Authors: *B. M. CARLSON, B. A. MITCHELL, J. A. WESTERBERG, A. MAIER;
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Abstract: Visual adaptation can have profound effects for a viewer's perceptual state. Some of the main perceptual effects of visual adaptation include motion aftereffects, decreased contrast sensitivity, and the tilt illusion. Interestingly, all these forms of adaptation are phenomenologically effective even if an interocular transfer of adaptation (IOT) paradigm is used. IOT refers to visually adapting one eye with a monocular stimulus and then presenting the test stimulus monocularly to the other eye. Primary visual cortex (V1) has been identified as a locus for IOT effects, but the spatiotemporal mechanism mediating IOT in V1 remains unknown. We evaluated IOT in awake behaving macaques by having them passively view static sinusoidal gratings through a mirrored stereoscope. We performed electrophysiology recordings in V1 via acute laminar penetrations. Cortical depth was determined by profiling the multi-unit-activity, current source density, and power spectral density across the laminar electrode. Orthogonal penetrations were verified by observing overlapping receptive fields across the laminar profile of V1. We found that adapting a static grating to one eye for 800ms and then presenting an identical stimulus to the other eye resulted in a decrease of cortical activity. This decrease in activity was observed as compared to monocular stimulation. 77 multi-units were binned into their laminar compartments of upper, middle, and deep cortical layers. The laminar compartments were then evaluated with a repeated measures ANOVA to compare the effect of IOT on V1 multi-unit response rates. There was a statistically significant difference in response rates between at least two groups ($F_{2,40} = 31.625$, $p < 0.001$, $\omega^2 = 0.386$). A post-hoc Holm's corrected test showed that the deep layers significantly differed from the middle layers ($t = -7.676$, $p_{holm} < 0.001$, Cohen's $d = -1.906$) and upper layers ($t = -5.641$, $p_{holm} < 0.001$, Cohen's $d = -1.401$), while the upper and middle layers did not significantly differ from each other. Bayesian repeated measures ANOVA produced identical results. Taken together, we observed the largest IOT effect in the infragranular layers, suggesting a laminar mechanism for IOT in macaque V1. We will discuss these results and their implications on a potential laminar mechanism for binocular rivalry.

Disclosures: B.M. Carlson: None. **B.A. Mitchell:** None. **J.A. Westerberg:** None. **A. Maier:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.14

Topic: D.06. Vision

Support: NIH EY026878
NIH NS007224
NIH NS041228
NIH EY032555

Title: Anisotropic contextual interactions in the laminar cortical circuit explain visual crowding.

Authors: *M. P. MORTON, S. DENAGAMAGE, N. V. HUDSON, A. S. NANDY;
Dept. of Neurosci., Yale Univ., New Haven, CT

Abstract: Crowding is the inability to recognize objects among clutter. Visual crowding is thought to be the primary limitation on object perception in peripheral vision. The region in visual space over which flanking stimuli impair identification of a target stimulus is known as the crowding zone. Psychophysical studies have identified three main characteristics of crowding zones: 1. They scale linearly with eccentricity (Bouma's Law), 2. Outward crowding stimuli exert a stronger influence compared to inward crowders (inward-outward asymmetry), and 3. Crowding zones are elongated in the radial direction compared to the tangential direction (radial-tangential anisotropy). Although there is robust psychophysical and modeling work describing crowding, our understanding of how crowding stimuli influence information processing in the visual cortex is extremely limited. Additionally, no studies have investigated the neural underpinnings of the radial-tangential anisotropy and inward-outward asymmetry of crowding zones. Our hypothesis is that cortical layer-, cell-class and region-specific interactions underlie crowding and the spatial characteristics of crowding zones. Here, we performed laminar electrophysiological recordings in areas V1 and V4 in the macaque cortex while monkeys viewed stimuli in isolation or with flanking stimuli around them at various spatial configurations. We found that crowding stimuli broaden the tuning curves of neurons in the visual cortex. Additionally, crowding stimuli that produce stronger effects on perception most strongly impair tuning, in a layer-specific manner. These results indicate that spatially anisotropic interactions in the visual cortex can explain the spatial characteristics of crowding zones.

Disclosures: M.P. Morton: None. **S. Denagamage:** None. **N.V. Hudson:** None. **A.S. Nandy:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.15

Topic: D.06. Vision

Support: NIH EY026878
NIH NS007224
NIH NS041228
NIH EY032555

Title: Spatiotemporal Dynamics of Receptive Field Remapping in Area V2

Authors: *S. DENAGAMAGE, M. MORTON, A. NANDY;
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Abstract: Primates use ballistic eye movements called saccades to rapidly shift their field of view and examine objects of interest with high spatial acuity. To maintain perceptual stability despite the rapid retinal motion due to saccades, the visual system transiently shifts receptive fields in anticipation of upcoming eye movements. This phenomenon, termed receptive field remapping, has been observed in many visually driven areas in the primate brain. Neurons, both within and across these brain areas, exhibit remapped sensitivity either toward the post-saccadic location (forward remapping) or toward the saccade target (convergent remapping). However, the neural mechanisms of remapping remain elusive. We hypothesize that cortical layer- and cell-class specific neural modulation around the time of a saccadic eye-movements underlie these different forms of remapping. Here, we use a novel receptive field mapping paradigm in combination with high density laminar electrophysiology to continuously track receptive field shifts around the time of saccades. We find that in primate area V2, receptive field remapping occurs across cortical layers and unit types. We further investigate the dynamics of remapping in individual neural subpopulations, and propose a laminar circuit mechanism for this phenomenon.

Disclosures: S. Denagamage: None. **M. Morton:** None. **A. Nandy:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.16

Topic: D.06. Vision

Support: NIH National Eye Institute #R01 EY030860
Fyssen Foundation

Title: Category representation in the mouse primary visual cortex supports orientation discrimination

Authors: *J. CORBO[1], O. ERKAT[2,1], J. MCCLURE, Jr.[2,1], H. KHDOUR[2,3], P.-O. POLACK[1]; [1]Ctr. for Mol. and Behavioral Neurosci., [2]Behavioral and Neural Sci., Rutgers Univ., Newark, NJ; [3]Ctr. for Mol. and Behavioral Neurosci., Rutgers Univ., Neark, NJ

Abstract: Perceptual discrimination requires the ability to determine that two stimuli are different. It is well established that neuronal representations in sensory cortices (i.e. the specific neuronal activity patterns evoked by the stimuli) are essential for such perceptual choice. Yet, the general principles by which those representations are compared in sensory systems remain paradoxically elusive. Indeed, the resolution of the neuronal population representations is an order of magnitude more precise than the discrimination capabilities of the animals. This large discrepancy between theoretical neural resolution and actual animal discrimination threshold suggests that the integrative mechanisms leading to perceptual decisions are computationally limited. Here, we investigated the relationship between orientation representation in the primary visual cortex (V1) and orientation discrimination. We used calcium imaging in mice performing

a Go/NoGo discrimination task using oriented visual stimuli. Sessions were performed for six consecutive days. Each day, the orientation of the NoGo stimulus was made closer to the Go orientation (from day 1: +90° to day 6: +15°), going across the discrimination threshold of the animals. We found that two oriented cues were perfectly perceived as distinct when there was no overlap between their neuronal representations. However, around the limit of discriminability, V1 activity stopped encoding for the orientation of the visual stimulus. Indeed, the NoGo cues activated neurons tuned for the same domain of the orientation space day after day, despite the change of the presented orientation. Additionally, when the angle between Go and NoGo was reduced enough, the NoGo cues activated neurons tuned for the Go orientation domain, in addition to the persistent NoGo domain. This created a bimodal activation in the orientation space that was likely due to a preferred-orientation-dependent modulation of the neuronal excitability. The relative neuronal activity at those domains correlated with the average choice of the animals. Thus, in the context of the task, V1 seemed to be feeding the decision process with a probabilistic indication that the stimulus belonged to the Go or NoGo category, in a departure from a truthful feature representation.

Disclosures: **J. Corbo:** None. **O. Erkat:** None. **J. McClure:** None. **H. Khdour:** None. **P. Polack:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.17

Topic: D.06. Vision

Support: NIH/NEI Grant R01 EY030860
Whitehall Foundation Grant 2015-08-69
Charles and Johanna Busch Biomedical Grant Program

Title: Time course of the distortions of the orientation representation space induced in V1 by learning

Authors: *O. ERKAT[1,2], J. CORBO[2], J. P. MCCLURE, Jr.[1,2], P.-O. POLACK[2];
[1]Rutgers University-Newark, Behavioral and Neural Sci. Grad. Program, Newark, NJ; [2]Rutgers University-Newark, Ctr. for Mol. and Behavioral Neurosci., Newark, NJ

Abstract: Learning is an essential mechanism that adjusts neuronal processing to adapt the animal behavior to novel contexts. In a recent study, we have shown that learning a visual task is associated with modifications of the neuronal responses in the mouse primary visual cortex (V1) that favor the representation of stimuli relevant to the task but distort the space of orientation representation. Here, we investigated how this distortion of the orientation representation space is established during the time course of training. Our previous results showed that representations of rewarded and non-rewarded orientations were more accurate and stable across trials in trained

mice. This improvement was due to a distortion of the orientation representation space such that stimuli flanking the task-relevant orientations were represented as the task stimuli themselves. This suggested that flanking orientations were generalized as the task cues by the trained mice. We designed a new experiment to determine the time course of this distortion in trained mice. We imaged L2/3 of V1 at several time points during training then after disengaging the mice from the task. We found that the distortion was still present a few days after the animals were disengaged but decayed over days. The disappearance of the distortions in the representation of orientation did not impair the mouse performance when they were asked to perform the Go/NoGo orientation discrimination task again. Our results suggest that the population activity in V1 returns to an unbiased state once expertise is reached, and that this return does not influence the behavioral performance.

Disclosures: O. Erkat: None. **J. Corbo:** None. **J.P. McClure:** None. **P. Polack:** None.

Poster

714. Neural Bases of Adaption and Modulation of Visual Circuits

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 714.18

Topic: B.09. Glial Mechanisms

Support: Canadian Institutes of Health Research Grant FDN-143238
Research Chair from the Fonds de recherche santé Québec 31036
Canada Graduate Scholarships Masters
NSERC Postgraduate Scholarship Doctoral

Title: Radial astrocytes in the developing retinotectal system enhance threat detection and promote visually-evoked escape behavior

Authors: *N. BENFEY[1], A. SCHOHL[2], E. S. RUTHAZER[3];
[1]Montreal Neurolog. Institute-Hospital, Montreal, QC, Canada; [2]McGill Univ., Montreal, QC, Canada; [3]Montreal Neurolog. Inst., McGill Univ. Integrated Program In Neurosci., Montreal, QC, Canada

Abstract: The ability to rapidly shift between distinct behavioral states is crucial to the adaptability and fitness of animals. During early development when animals are at their most vulnerable, being able to rapidly and reliably detect and respond to potential threats in the environment is critical for their survival. Across animals, behavioral state switching is known to be regulated by the release of neuromodulators, and more recently has also implicated the activation of astrocytes. Recent studies have also begun to demonstrate that in some neural circuits astrocytes mediate the effects of neuromodulators. Norepinephrine, a neuromodulator known to be associated with attention, learning and memory, as well as heightened states of vigilance and arousal is also a potent activator of astrocytes throughout the vertebrate brain. Here we investigated how the activation of radial astrocytes in the developing optic tectum of *Xenopus*

laevis by norepinephrine alters visual processing in tectal neurons. We found that radial astrocytes are activated by norepinephrine through alpha-1-adrenergic receptors and that norepinephrine shifts the tectum from a state in which diverse visual stimuli are represented into an encoding state that is preferentially responsive to looming stimuli, which are treated as a threat by the animal, inducing escape behavior. We demonstrate that the targeted chemogenetic activation of radial astrocytes in the tectum is sufficient to reproduce the effects of norepinephrine on tectal circuit function and enhances the detection of looming stimuli by freely swimming animals. Taken together our experiments demonstrate that norepinephrine likely acts directly through astrocytes to mediate a state change in the developing visual system which has important implications for processing of sensory information in developing animals.

Disclosures: **N. Benfey:** None. **A. Schohl:** None. **E.S. Ruthazer:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.01

Topic: D.06. Vision

Title: Behavioral detection of optogenetic stimulation in inferior temporal cortex depends on the content and visibility of the image being viewed

Authors: *E. LOPEZ[1], S. E. BOHN[3], R. AZADI[1], R. LAFER-SOUSA[2], K. WANG[4], A. AFRAZ[4];
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Abstract: While stimulation of low-level visual areas evokes consistent perceptual events, evidence in humans has shown that stimulation of high-level visual areas produces events which differ based on the content of the concurrent visual input. Here we use an optogenetic stimulation detection task in macaque monkeys to provide systematic evidence for the idea that visual input interacts with cortical stimulation in inferior temporal (IT) cortex, a high-level and object sensitive visual area. We chronically implanted LED arrays over a region of central inferior temporal (IT) cortex which had been previously transduced with excitatory opsin C1V1 in two macaque monkeys. The animals were then trained on a behavioral task which consisted of fixation on a target followed by a 1 second presentation of an object image randomly drawn from a set of 39, in addition to a no image condition in which no visual stimulus was presented on the screen. Randomly, in half of the trials a 200ms illumination impulse was delivered to IT cortex in the middle of image presentation. The animals were rewarded for correctly reporting if the trial contained a cortical stimulation impulse or not, and they learned this task significantly above chance level within 17 and 8 days respectively. There was a strong effect of image on the animals' ability to detect cortical stimulation ($p<0.001$ for all), with their performances ranging from 52% to 88% for various objects. Given that detection of cortical stimulation was at or near

its minimum for both animals during the no image condition (<56% for both animals), we also tested how attenuation of the visibility of the images affects detection of stimulation. To do so, we had the animals perform the same stimulation detection task with a set of five object images at four visibility levels in addition to a no image condition. Visibility of the image had a strong effect on stimulation detectability ($p < 0.001$), with the fully visible stimuli producing significantly higher performance compared with the two lower levels of visibility and with the no image condition ($p < 0.001$ and < 0.001). These results reveal that optogenetic stimulation of IT cortex evokes visual events that are easily detectable by subjects, and detectability of these events depends on the content and visibility of the visual input. Concurrent object-related activity in the visual system modulates these events, and thus they are not psychophysically isolated from ongoing visual perception. Our findings shed light on the causal role neuronal activity in IT cortex plays in perception and opens the door for utilizing stimulation of high level visual areas in visual prosthetics.

Disclosures: E. Lopez: None. **S.E. Bohn:** None. **R. Azadi:** None. **R. Lafer-Sousa:** None. **K. Wang:** None. **A. Afraz:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.02

Topic: D.06. Vision

Support: R01EY027853

Title: The impact of visual experience on developing motion functions in ferret visual motion area PSS

Authors: *D. KHAMISS, K. NIELSEN;
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Abstract: Previous studies have shown that visual experience plays a crucial role in the development of basic motion computations in carnivore primary visual cortex (V1). In cats and ferrets, for instance, the development of V1 direction selectivity requires normal visual experience around the time of eye opening. If visual experience is absent or altered during this early period, direction selectivity cannot be recovered with subsequent exposure to normal visual inputs. Conversely, prolonged exposure to simple moving stimuli can accelerate the development of V1 direction selectivity in visually naïve animals. Visual experience also appears to impact the functional development of higher visual motion areas beyond V1, as direction selectivity is drastically reduced in higher-order area PMLS of cats reared under stroboscopic conditions. Our current data suggest a similar situation in the ferret: We find that the developmental status of global motion responses in ferret higher motion area PSS correlates with the duration of patterned visual experience (i.e., the time since eye opening). Here, we thoroughly tested the

impact of visual experience on the development of both simple and complex motion functions in ferret PSS. To that end, we used multi-site silicon probes to record from V1 and PSS in animals with different kinds of visual experience. By recording neuronal responses to a range of simple and complex motion stimuli, we were able to determine the impact of visual experience on both direction selectivity and global motion responses. Our data reveal that, like V1, PSS direction selectivity is impaired if visual experience is absent during an early period around eye opening. Yet, direction selectivity levels remain higher in PSS than V1, consistent with increases in overall direction selectivity observed between V1 and PSS after normal visual experience. At the same time, it appears that the remaining levels of direction selectivity are not enough to support complex motion integration in PSS neurons. These findings reveal a profound impact of visual experience on the functionality of the motion pathway and provide the groundwork for future experiments aimed at determining the role of different visual cues in motion pathway development.

Disclosures: D. Khamiss: None. **K. Nielsen:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.03

Topic: D.06. Vision

Support: Canadian Institutes of Health Research (PJT-180333 and PJT-156029)
National Science and Engineering Research Council of Canada (RGPIN-2020-05739)
Portuguese Foundation for Science and Technology (2020.08995.BD)

Title: The endocannabinoid system is expressed in both visual pathways of the vervet monkey

Authors: *C. MICAELO-FERNANDES[1], H. HAÏMEUR[1], J. BOUSKILA[1], R. M. PALMOUR[2,3], J.-F. BOUCHARD[1], M. PTITO[1,4];
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Abstract: Despite the growing evidence on how cannabis affects several aspects of visual processing, little is known on the anatomical distribution of the endocannabinoid (eCB) system within the visual system. After characterizing the expression of the cannabinoid receptor type 1 (CB1R) from the retina to the primary visual cortex/V1 of the vervet monkey, we now continue to investigate its presence in the higher-order visual areas V4 and V5. Three young male vervet monkeys (*Chlorocebus sabeus)* were used in this study. We used immunohistochemistry and immunofluorescence to compare the expression of eCB proteins - the CB1R and the eCB metabolic enzymes N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) and Fatty

Acid Amide Hydrolase (FAAH) - to that of markers whose cellular and layer distributions are well-defined for the primate visual cortices - the neuronal nuclear antigen (NeuN), the non-phosphorylated neurofilament H (SMI-32) and parvalbumin (PV). CB1R-immunoreactivity in areas V4 and V5 resembled that found previously in V1, although CB1R labelling appeared denser in the former. CB1R was present in axons rich in varicosities located mainly in the supragranular (layers 2-3) and infragranular (layers 5-6) layers. These axons were found in close relationship with SMI-32-positive pyramidal cells and PV-positive interneurons that, complementarily, expressed NAPE-PLD and FAAH in their somas and proximal dendrites. These results suggest that, in primates, eCBs are capable of modulating the neural networks and the outputs of different visual cortices, through different levels of processing and through different processing streams.

Disclosures: C. Micaelo-Fernandes: None. **H. Haïmeur:** None. **J. Bouskila:** None. **R.M. Palmour:** None. **J. Bouchard:** None. **M. Ptito:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.04

Topic: D.06. Vision

Support: ISF grant No. 1485/18 to SGD
"Lev-Zion" scholarship to OK
Bar Ilan University Gonda Multidisciplinary Brain Research Center student travel encouragement scholarship for international conferences to OK

Title: Ffa and ppa display qualitative differences in parafoveal processing

Authors: *O. KREICHMAN[1], S. GILAIE-DOTAN[1,2];
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Abstract: The fusiform face area (FFA) and parahippocampal place area (PPA) are usually defined by their selectivity to a specific visual category, faces or places (respectively), over other categories. FFA and PPA are anatomically adjacent and yet they differ in various functional characteristics such as FFA showing a strong preference to foveal central-field information and PPA showing a significant bias towards peripheral field information. Despite their different visual field (VF) preferences, the sensitivity of these regions to their preferred and non-preferred categories has predominantly been studied centrally. We hypothesized that according to their VF biases, FFA's and PPA's sensitivities to preferred and non-preferred categories would reveal qualitative differences such that face-sensitive FFA would be more sensitive to eccentricity than place-sensitive PPA. Here we parametrically examined the foveal to parafoveal (0°-8°) sensitivities of FFA and PPA with upright and inverted faces and houses (n=29). FFA and PPA

were defined by an external localizer. In line with our hypothesis, FFA's and PPA's activations were modulated differently by eccentricity although our task did not demand any category-specific attention. For their preferred categories, FFA and PPA both displayed reductions in activation with growing eccentricity, however, PPA was less sensitive to eccentricity than FFA with a more moderate reduction in activation than FFA. More importantly, for their non-preferred categories FFA and PPA showed opposite trends: PPA (but not FFA) displayed a qualitatively different behavior to its non-preferred category (faces) relative to its preferred category with an increase in activation with growing eccentricity for faces. These patterns were not task-dependent as they were evident across two experimental paradigms. Although overall activation patterns to inverted stimuli were similar to those observed with upright stimuli, PPA was not deactivated to central inverted faces as it was for upright central faces. Our parafoveal investigations reveal further qualitative processing differences between these category-selective areas. We propose that processing differences between FFA and PPA do not stem solely from their category preferences but may further reflect an antagonistic response of the PPA to central processing demands.

Disclosures: O. Kreichman: None. **S. Gilaie-Dotan:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.05

Topic: D.06. Vision

Title: Hd-tdcs to the lateral occipital complex improves haptic object recognition

Authors: *L. CACCIAMANI, M. MYLOD-VARGAS, A. SELCOV, G. PETERSON, D. TOMER, A. BARBIEUX, C. OSEGUERA;
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Abstract: High-definition transcranial direct current stimulation (HD-tDCS) is a non-invasive brain stimulation technique that has been shown to be safe and effective in modulating neuronal activity. The present study investigates the effect of anodal HD-tDCS on haptic object perception and memory through stimulation of the left lateral occipital complex (LOC), a structure that has been shown to be involved in both visual and haptic object recognition. In this single-blind between-subjects study, blindfolded participants used their right (dominant) hand to perform haptic perception and memory tasks with 3D-printed, novel objects called "Greebles" while receiving 20 minutes of 2 mA stimulation or sham. Those who received left LOC stimulation (vs. sham) showed an improvement in haptic object recognition but not perception. This effect was not observed with right LOC stimulation (ipsilateral to the hand used), as shown in our previous study. The results of this study suggest that HD-tDCS to the left LOC may be used to improve memory of objects perceived via touch. This body of work has potential applications for

improving haptic abilities in those with visual impairments who must rely on their sense of touch to perceive and remember objects around them.

Disclosures: L. Cacciamani: None. **M. Mylod-Vargas:** None. **A. Selcov:** None. **G. Peterson:** None. **D. Tomer:** None. **A. Barbieux:** None. **C. Oseguera:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.06

Topic: D.06. Vision

Support: NIMH ZIAMH002958

Title: The causal link between neural activity in inferior temporal cortex and eye movement

Authors: *R. AZADI[1], J. TAUBERT[2], E. LOPEZ[1], A. PATTERSON[3], A. AFRAZ[1];
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Abstract: Vision is the main driver of eye movement. Low-level visual information has an essential role in saliency map models proposed to predict eye movements. However, the high level structure of visual objects (such as a face) is also a strong predictor of eye movements. Such structure can only be detected and encoded by high-level areas of the ventral visual pathway. In this study we systematically investigated the effect of artificial inactivation of neural activity in inferior temporal (IT) cortex on free-viewing eye movements in macaque monkeys. Vision is the main driver of eye movement. Low-level visual information has an essential role in saliency map models proposed to predict eye movements. However, the structures of visual objects (such as a face) are also strong predictors of eye movement patterns. Such a structure can only be detected and encoded by high-level areas of the ventral visual pathway. In this study we systematically investigated the effect of selectively inactivating different discrete regions of the inferior temporal (IT) cortex on free-viewing eye movements in macaque monkeys. We hypothesized that inactivation of category-selective (such as face-selective) groups of neurons in IT cortex would selectively affect eye movements while free viewing images of different object categories (such as faces). Thus, we first used fMRI localization to map the face- and object-selective patches in two macaque monkeys. Then, we targeted these different functionally-defined patches in IT cortex with microinjections of muscimol, a potent GABA receptor agonist. The results show that the inactivation of the middle face patch in one hemisphere does not disrupt the attraction of eye movements towards faces during free viewing; the animals still found the faces in the large format natural scenes they were presented with and looked at the facial features. However, the animals spent more time looking at the contralateral eye with respect to the targeted hemisphere. Injections of muscimol outside the face patch system evoked a similar pattern of eye movements; however the effect size was significantly smaller. These

results establish the causal role of neural activity in the face-selective neurons in IT cortex and eye movements.

Disclosures: R. Azadi: None. **J. Taubert:** None. **E. Lopez:** None. **A. Patterson:** None. **A. Afraz:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.07

Topic: D.06. Vision

Support: CIHR
NSERC

Title: Dynamics of response accuracy in the visual cortical area 21a

Authors: *L. IKAN, N. CORTES, H. LADRET, L. LAPLANTE, C. CASANOVA;
Univ. de Montreal, Montreal, QC, Canada

Abstract: Our vision is provided by a succession of hierarchical areas containing neurons selectively sensitive to different characteristics of visual stimuli. As the cortical hierarchy progresses, neurons become increasingly selective and sensitive to complex patterns. Recently, our laboratory characterized the dynamics of the orientation responses of neurons of the cat primary visual cortex, V1, using natural stimuli. These experiments showed that very slow dynamics are involved in the processing of low precision patterns. How accuracy affects orientation in higher hierarchical areas is unknown. Here, we studied the difference in response to accuracy in a higher-order cortical area, more precisely in area 21a in the cat, often considered as the homologue of the primate area V4. We hypothesized that, if accuracy follows a hierarchical organization, neurons in 21a will have an amplified (linear) response to accuracy compared to those in V1. We used pseudo-natural visual stimuli with controlled accuracy content, MotionClouds, and recorded the responses of neurons in area 21a to quantified variations in orientation accuracy. Preliminary data indicate that the tuning curve of neurons stimulated with Motion Clouds have amplified response to accuracy compared to those in V1. This data suggests that the cortical ventral stream is involved in accuracy processing.

Disclosures: L. Ikan: None. **N. Cortes:** None. **H. Ladret:** None. **L. Laplante:** None. **C. Casanova:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.08

Topic: D.06. Vision

Support: Princeton University Startup Funds

Title: New sulcal rami in human prefrontal cortex reveal developmental restructuring of visual responses and tissue properties

Authors: *J. K. YAO, Z. YAZDANI, J. GOMEZ;
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Abstract: Despite the known role the frontal lobe plays in visual processing, little is known about the organization of visual function and structure in prefrontal cortex (PFC). Using a novel anatomical parcellation of PFC, we asses if visual category representations can be consistently observed relative to cortical folding and how the organization of these representations and the underlying structure changes across development and differs from that of classic visual cortex. 25 children (ages 5-11) and 20 adults (ages 22-26) completed a visual category localizer and underwent quantitative MRI to acquire maps assessing brain tissue properties. Contrast maps of faces, words, bodies, objects, and places versus all other categories were produced for each subject. Using three rami reliably located along the inferior frontal sulcus, and surrounding sulci as anatomical borders, we created a novel parcellation of 10 regions of interest in VLPFC and quantified average category selectivity in these regions. We include 8 ventral temporal cortex (VTC) regions for comparison. In VLPFC, we find reliable representations of visual categories as well as a lateralization effect whereby word activations increase in the left hemisphere and are pruned in the right, and faces show the opposite trends ($F = 5.83$, $p = 2.21e-5$) - much like in VTC ($F = 22.18$, $p < 2.2e-16$). Additionally, the lateralization of words to the left hemisphere is predictive of reading abilities ($R = 0.62$, $p = 0.002$). In VTC, finer-grained analysis reveals responses to categories that are highly correlated between children and adults, suggesting development simply sharpens existing patterns (RH: $R = 0.94$, $p < 2.2e-16$; LH: $R = 0.97$, $p < 2.2e-16$). However, VLPFC response patterns - particularly in the right hemisphere - are less correlated (RH: $R = -0.03$, $p = 0.84$; LH: $R = -0.69$, $p = 2.12e-08$) and more discriminable (RH: $t = 3.49$, $p = 0.001$, LH: $t = 0.12$, $p = 0.90$) between children and adults. Rather than a simple sharpening of existing patterns as is observed in VTC, these stark differences between child and adult patterns provide evidence for functional restructuring in VLPFC as category responses differentially develop across and within prefrontal cortex. As large functional restructuring is likely paralleled by structural change, we also analyzed the underlying cortical tissue using a large qMRI dataset (N = 107, ages 7-82) and find unique changes in prefrontal tissue composition across development compared to visual cortex. Together, these findings highlight the unique structural-functional development of PFC and stress the importance of the frontal lobe in visual processing.

Disclosures: J.K. Yao: None. **Z. Yazdani:** None. **J. Gomez:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.09

Topic: D.06. Vision

Support: NIH EY016187
NIH P30EY012196

Title: The microarchitecture of face-selective patches in macaques

Authors: *H. OISHI[1], V. K. BEREZOVSKII[3], M. S. LIVINGSTONE[3], K. S. WEINER[2], M. J. ARCARO[4];
[2]Psychology, [1]Univ. of California, Berkeley, Berkeley, CA; [3]Neurobio., Harvard Med. Sch., Boston, MA; [4]Psychology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Face perception is critical for social life, and is supported by a network of connected cortical patches specialized for processing faces. While recent functional MRI (fMRI) and electrophysiological studies have revealed the functional properties of face patches in detail, little is known about the microarchitecture of this specialized cortical system. This gap in knowledge persists because examining the microarchitecture of functionally localized face patches in the same individual requires a rare combination of fMRI localized face patches pre-mortem and histological measurements of microarchitecture post-mortem.
Here, we fill this gap in knowledge by first localizing face patches with fMRI pre-mortem. We then performed histological staining on individual slices of the same macaques. We developed an analysis pipeline for registering fMRI data to histological slices using a reference T1 MRI data. Through these procedures, we localized the face patches along the STS on the histological slices. We analyzed the laminar profile of myelin and cytochrome oxidase within each face patch and along adjacent sections of the STS. We compared the laminar profiles among face patches and between face patches and their adjacent areas. To test the similarity and difference between myelin profiles, we calculated the norm between their profiles.
Laminar organization was heterogeneous across the STS. We found that the myelin profiles varied most widely around layer IV among all areas. The variability of myelin profiles was smaller among ventral face patches than that among dorsal face patches. The laminar profile of myelin was more similar among face patches than between face patches and adjacent STS cortex. This result suggests that face patches develop unique anatomical organizations in the STS. Since face patches typically are localized to focal convex folds along the STS (Arcaro et al. 2020), current analyses aim to resolve the relationship between laminar organization, face patch localization and cortical folding. This work offers a direct bridge between classic parcellations of anatomical architecture to modern parcellations based on functional MRI.

Disclosures: H. Oishi: None. **V.K. Berezovskii:** None. **M.S. Livingstone:** None. **K.S. Weiner:** None. **M.J. Arcaro:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.10

Topic: D.06. Vision

Support: RIKEN CBS institutional funding
JSPS 26290011
JSPS 17H06037
NSERC PGSD
IST-RA
HFSP LT000582/2019
Fujitsu Collaborative grant

Title: Efficient coding of texture images in the mouse visual cortex

Authors: *F. BOLANOS[1,2], J. G. ORLANDI[1], R. AOKI[1], A. V. JAGADEESH[3,4], J. L. GARDNER[3,4], A. BENUCCI[1,2];
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Abstract: Textures are useful visual stimuli for studying the neural underpinnings of object recognition. Textures are sufficiently complex to largely match the statistical properties of other natural images, and, unlike other natural images, they can be precisely parameterized and synthesized. Here, we studied the cortical processing of textures in mice, asking first whether mice could perceptually discriminate visual textures, and then whether the underlying neural architectures shared similarities with those found in primates. We found that mice could distinguish between types of textures, and between textures and spectrally matched stimuli (scrambles) lacking higher-order statistical features characteristic of textures. Mesoscale calcium imaging revealed that the primary visual cortex (V1) and the secondary ventral visual area (LM), were differentially activated by textures relative to scrambles (ΔF/F difference, V1: 0.27% ± 0.04%; LM: 0.50% ± 0.03%), with a stronger texture selectivity in LM than in V1 (V1: d' = 0.41 ± 0.05, s.e.; LM: d' = 0.79 ± 0.05). Similarly, 2-photon imaging recordings, examined with a regressive model, showed that cell responses in LM were better predicted by the higher-order statistics of textures than in V1 (explained variance, V1: 5.27% ± 0.61% s.e., LM: 8.18% ± 0.67%). Furthermore, at the population level, textures clustered in activity subspaces that were more compact (smaller radii and intercluster distances) and separable in LM than in V1, with the distance between clusters significantly correlated with the discrimination performance of the mice.
Together, our results demonstrate texture vision in the mouse, finding a linking framework between stimulus statistics, neural representations and perceptual sensitivity which is a distinct hallmark of efficient-coding computations.

Disclosures: F. Bolanos: None. **J.G. Orlandi:** None. **R. Aoki:** None. **A.V. Jagadeesh:** None. **J.L. Gardner:** None. **A. Benucci:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.11

Topic: D.06. Vision

Support: NIH Grant EY029438
Whitehall Foundation (2016-08-18)

Title: Clustering of visual, choice-related, and presaccadic activity in macaque V3A and CIP

Authors: *Z. ZHU, B. KIM, R. DOUDLAH, T.-Y. CHANG, A. ROSENBERG;
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Abstract: The robust three-dimensional (3D) visual and sensorimotor capabilities of primates are supported by the dorsal visual stream. In particular, 3D visual representations, choice signals, and presaccadic activity converge at the individual neuron level to form experience-dependent sensorimotor associations in area V3A and the caudal intraparietal (CIP) area of macaques. Across sensory and motor cortices, neurons often aggregate into clusters with similar properties. This clustering is thought to reflect a network structure that facilitates efficient neural computation. Evaluating whether such clustering occurs in multimodal areas with sensory and motor-related functions, like V3A and CIP, can therefore provide insight into the wiring principles that support sensorimotor transformations. Here, we assessed the functional clustering of neuronal tuning properties in V3A and CIP using a large database of well-isolated single neurons (V3A: N = 692; CIP: N = 437), with 404 V3A and 244 CIP neuron pairs simultaneously recorded on common tetrodes (Chang et al., 2020 *eLife*; Doudlah et al., 2022 *bioRxiv*). Using correlation and parametric (preference, bandwidth, and sensitivity) based comparisons, we specifically evaluated the clustering of visual, choice-related, and presaccadic properties within and across the areas. For each functional domain (visual, choice-related, and presaccadic activity), we first tested whether the similarity of the tuning properties of the neuron pairs significantly differed from within-area shuffled data. Then, we compared the clustering between areas. For visual activity, V3A and CIP both showed significant clustering and there was no significant cross-area difference in clustering. For choice-related activity, both areas showed significant clustering, but CIP had stronger clustering than V3A. For presaccadic activity, both areas also showed significant clustering, but V3A had stronger clustering than CIP. Across the cortical hierarchy, these findings together suggest that the clustering of sensory properties was similar, whereas presaccadic properties were more clustered in the lower-level area (V3A) and signals associated with perceptual decisions were more clustered in the higher-level area (CIP). More broadly, the results are consistent with the possibility that the organization of primate cortex follows general wiring principles that support efficient neural computation prioritizing specific functions at different processing stages.

Disclosures: **Z. Zhu:** None. **B. Kim:** None. **R. Doudlah:** None. **T. Chang:** None. **A. Rosenberg:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.12

Topic: D.06. Vision

Support: NIH Grant EY029438
Whitehall Foundation (2016-08-18)

Title: Parallel processing, hierarchical transformations, and sensorimotor associations along the macaque dorsal stream

Authors: *R. DOUDLAH[1], T.-Y. CHANG[1], L. THOMPSON[1], B. KIM[1], A. SUNKARA[2], A. ROSENBERG[1];
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Abstract: Visually guided behaviors require the brain to transform ambiguous sensory signals into object-level spatial representations and implement sensorimotor transformations. Specifically, because three-dimensional (3D) orientation and position (i.e., 3D pose) information are confounded in retinal projections, the visual system must solve the inverse problem of creating robust 3D representations to guide appropriate motor responses. These processes are supported by dorsal visual stream areas spanning occipital and parietal cortex. In particular, we hypothesize that brain areas located at the parieto-occipital junction: intermediate visual area V3A and the caudal intraparietal (CIP) area, are critical to forming high-level 3D representations and implementing sensorimotor transformations. To test this, we assessed: (*i*) 3D pose selectivity using planar surfaces, (*ii*) choice-related activity during a 3D orientation discrimination task, (*iii*) presaccadic activity during a visually guided saccade task, and (*iv*) sensorimotor associations. Using laminar array probes, we compared the functional properties of 692 V3A and 437 CIP neurons from three macaque monkeys. First, we observed a continuum of visual responses ranging from lower-level feature selectivity (e.g., binocular disparity) to 3D object-level representations (i.e., 3D pose tuning) in both areas, but found that robust 3D pose representations were most prominent in CIP. Second, our findings revealed that choice-related activity was associated with robust 3D pose tuning and was present in both areas, but to a greater degree in CIP (46% of neurons) than V3A (25%). Importantly, we found no difference between the structure of correlated variability across areas, suggesting that functional correlations between neuronal activity and perceptual decisions were stronger in CIP than V3A. Third, our findings revealed a similar presence of presaccadic activity in V3A (60%) and CIP (63%) that predicted the direction and timing of upcoming eye movements. In addition, presaccadic activity started earlier in V3A (108 ms before eye movement onset) than CIP (102 ms), suggesting hierarchical processing of oculomotor-related signals. Finally, we found that sensory and presaccadic

preferences aligned at the individual neuron level in both areas, with CIP forming stronger sensorimotor associations than V3A. Together, these findings challenge classical notions of sensorimotor dichotomies, argue for a reclassification of V3A as association cortex, and implicate choice-related activity as a novel factor in sensorimotor processing.

Disclosures: R. Doudlah: None. **T. Chang:** None. **L. Thompson:** None. **B. Kim:** None. **A. Sunkara:** None. **A. Rosenberg:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.13

Topic: D.06. Vision

Support: R01 EY018839
P30 EY01730
P51 OD010425
R01 EY029601

Title: Cooling of macaque prefrontal cortex modulates activity of V4 neurons during shape discrimination under partial occlusion

Authors: E. KEMPKES, A. W. BIGELOW, D. A. POSPISIL, *A. PASUPATHY;
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Abstract: Previous research has shown that visual cortical area V4 and prefrontal cortex (PFC) are both involved in the recognition of objects under partial occlusion. Specifically, analysis of neuronal dynamics supports the hypothesis of feedback interactions between PFC and V4 neurons especially when dealing with incomplete information (Kosai et al., 2014; Fyall et al., 2017). The aim of the present research is to use reversible inactivation of PFC neurons through cortical cooling to test for a causal relationship between PFC and V4 during the recognition of objects under partial occlusion. Two male rhesus macaques were trained on a shape discrimination task. On each trial two shapes were presented in sequence. The first, “reference” shape, was presented at central fixation, followed by a second “test” shape that moved behind a multi-slit rectangular window that partially occluded the stimulus. Slit widths were varied to increase difficulty and titrate behavior; unoccluded trials were also included. To perturb activity in the PFC, we designed a hollow metal cooling probe (surface area of 616 mm^2) that could be placed against the cortical surface and cooled by passing chilled ethanol through it. Channels through the probe allowed the insertion of a Neuropixels probe to record PFC activity and a needle thermocouple to measure cortical temperature. Our goal was to modulate PFC activity but not significantly alter behavior, so we modulated surface cortical temperature by ~10° C. During each recording session, we simultaneously studied the activity of V4 and PFC neurons with a Neuropixels probe inserted into each area and we conducted multiple cooling and rewarming

cycles to remove confounds due to drift across time. Results from three sessions reveal that cooling PFC modulates responses of neurons in both regions. Specifically, we found that 31/185 (17%) cells in V4 and 148/300 (49%) cells in PFC showed modulation of test-stimulus evoked activity with respect to cooling of PFC. In both areas we found suppressive and excitatory effects of cooling, in V4 12 suppressive and 19 excitatory, and in PFC 89 suppressive and 59 excitatory. We observed diverse effects of cooling on the time course of mean evoked responses in both PFC and V4, and on the modulation of V4 shape selectivity because of PFC cooling. Our results provide evidence for functional connectivity between V4 and PFC and the potential role of PFC responses in shaping V4 activity during shape recognition under partial occlusion.

Disclosures: E. Kempkes: None. **A.W. Bigelow:** None. **D.A. Pospisil:** None. **A. Pasupathy:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.14

Topic: D.06. Vision

Support: NEI Grant R01 EY018839
NEI Center Core Grant for Vision Research P30 EY01730
NIH/ORIP Grant P51 OD010425

Title: Visual saliency alleviates crowding in macaque area V4 but not V2

Authors: *T. KIM[1], A. K. PASUPATHY[2];
[1]Univ. of Washington, Univ. of Washington, Seattle, WA; [2]Univ. Washington, Univ. Washington, Seattle, WA

Abstract: Visual crowding refers to the phenomenon where a target object that is easily recognized in isolation becomes difficult to recognize when surrounded by other stimuli (distractors). Early studies of crowding have largely focused on local positional interactions between neighboring simple visual elements (e.g., letters and Gabors). However, recent psychophysical evidence demonstrated that global configuration of visual elements also strongly modulates the crowding, and that crowding could occur with more complex stimuli such as object shapes, faces. The neuronal representation of an object is constructed hierarchically along the ventral visual pathway. Therefore, to understand the neural mechanisms underlying the crowding effect, it is necessary to examine both local and global aspects of visual crowding at the level of single unit activity in the visual cortex and compare how these effects differ across the areas along the hierarchy. In this study, we used a set of 2D shape stimuli and investigated how shape selective responses of single neurons in macaque area V2 and V4 of the ventral visual pathway are degraded by various Target-Distractor relationships. In both areas V2 and V4, we found that the crowding effect (i.e., degraded shape selectivity) increased with the number of

distractors and decreased with the distance between target and distractors. The difference between two areas, however, was more pronounced in the effect of global configuration of distractors on crowding. When distractors were grouped separately from a target by distinct size, shape, or color, increased target saliency clearly attenuated the crowding effect in V4, but the attenuation effect was only weakly observed in V2 neuronal responses. Our results suggest a hierarchical model of visual crowding in the ventral visual pathway: while lower-level areas (e.g., V1 and V2) extract preliminary visual features and area V4 may play a critical role in encoding saliency stimuli, thereby support object segmentation by highlighting more informative dimensions from multiple extracted features.

Disclosures: T. Kim: None. **A.K. Pasupathy:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.15

Topic: D.06. Vision

Support: NEI grant R01 EY018839
NEI grant R01 EY029601
NEI Center Core grant for Vision Research P30 EY01730
NIH/ORIP grant P51 OD010425

Title: Joint encoding of form and motion direction in ventral visual area V4

Authors: *A. W. BIGELOW, E. KEMPKES, A. PASUPATHY;
Univ. of Washington, Seattle, WA

Abstract: In natural environments, objects are often partially occluded as they move through a visual scene. While primates are effortlessly able to identify and track these objects, the neural mechanisms underlying this ability are not fully understood. In the macaque monkey, it is known that neurons in visual area V4, a mid-level area in the ventral visual stream (a vital pathway underlying object recognition) are shape selective even under partial occlusion, and many neurons signal an upcoming decision when an animal is tasked with discriminating occluded shapes (Kosai et al. 2014; Fyall et al. 2017). Recently we also demonstrated that V4 houses a single-neuron correlate for long-range motion, a psychophysical percept which is analogous to motion behind occluders. With this in mind, we asked how neurons in V4 integrate information regarding motion direction and shape identity for partially occluded stimuli and whether these signals are encoded in the same or different subpopulations.
We trained two male rhesus macaques on a shape discrimination task. Briefly, the animal fixates at the center of an LCD monitor and views a ‘reference’ shape for 600ms. Following a 200ms inter-stimulus blank period, a ‘test’ stimulus moves behind an occluding window with a single viewing slit of varying width. The test stimulus trajectory and the occluder position overlap the

receptive fields of the V4 neurons being recorded. The animal then reports whether the reference and test shapes are the same or not by saccading to one of two target dots on either side of the screen.
Utilizing a high-density silicon, neuropixels probe, which has 385 channels densely packed along a 1mm shank, we recorded data from 181 neurons across 5 sessions during task performance. We found that neurons in V4 jointly encode both the shape identity and motion direction of the stimulus. Partitioning variance associated with shape and motion direction across time, we found that, for a majority of neurons (110 neurons, 61%), information regarding motion direction emerges earlier than information about shape identity, after controlling for receptive field position. In the case of no occlusion, information regarding shape identity peaks, on average, 40ms earlier. With increasing occlusion levels, shape and motion information emerge later (140ms and 120ms later, respectively), but the precedence of motion direction is maintained. These results imply that neurons in V4 are critical for processing dynamic occluded objects via the joint encoding of shape and motion direction information.

Disclosures: **A.W. Bigelow:** None. **E. Kempkes:** None. **A. Pasupathy:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.16

Topic: D.06. Vision

Support: Chuck Noll Foundation for Brain Injury Research
CMU BrainHub
Pennsylvania Infrastructure Technology Alliance
NSF STTR program
CMU Swartz Center Innovation Fellowship
Neil and Jo Bushnell Fellowship in Engineering
Hsu Chang Memorial Fellowship

Title: Silencemap can provide frequency band inferences about functional silences in object shape processing deficits induced by brain injury

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Abstract: Objective and Rationale: The diagnosis and treatment of many neurological disorders can benefit from a non-invasive monitoring tool to uncover the mechanistic details of neural function and dysfunction. We recently proposed a method, called SilenceMap, for the detection and localization of neural “silences” in the brain using scalp EEG [Chamanzar et al., 2021]. “Silences” are regions in the brain with suppressed neural activity, such as hypoxic or lesioned

tissue in brain injuries and stroke. Another example of regions of silence is the functional lesion in "diaschisis" i.e., loss of function or abnormalities distant from the site of the injury in the brain, which can lead to long-term disabilities in patients with brain injuries. The main goal of this study is non-invasive localization of functional lesions in the brain, and understanding their frequency-domain information. Because SilenceMap relies on scalp EEG, it can leverage EEG's high temporal resolution, and, unlike MRI, it permits the localization of functional lesions across different frequency bands. Methods and Results: Patient SM (male, 47 years) has a severe object and face recognition impairment following a lesion in the right lateral occipital complex (LOC) of the brain. Previous structural and functional MRI (sMRI and fMRI) studies revealed diaschisis in the contralateral regions in the preserved hemisphere of SM. We used the sMRI scan of this patient to extract the real head model for lead-field matrix estimation. A standard EEG grid with 128 electrodes was used to record EEG signals during object presentation (intact and parametrically scrambled) and resting state tasks. Data were also recorded from matched healthy controls to provide a baseline for the regions of silence in SM. Preliminary results indicate that SilenceMap can localize the structural and functional lesions, consistent with previously reported fMRI results [Freud & Behrmann, 2020]. In addition, SilenceMap provides frequency domain information about these lesions not obtainable through fMRI: shape sensitivity reductions, observed in the structurally intact left hemisphere, around the LOC and the occipital lobe more generally, are more pronounced in the lower frequency bands (i.e., Delta and Theta, 1-8Hz). These findings remain to be further validated in a larger group of patients and controls. Conclusions: SilenceMap successfully identified not only the location of the structural and functional lesions, but also the frequency-domain information about these silences that cannot be obtained using fMRI. It may also have applicability in use-cases where access to advanced imaging techniques such as MRI is not possible.

Disclosures: **A. Chamanzar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Precision Neuroscopics (equity and IP holder). **E. Freud:** None. **M. Behrmann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Precision Neuroscopics (founder, IP holder). **P. Grover:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Precision Neurscopics (founder, IP holder).

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.17

Title: WITHDRAWN

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.18

Topic: D.06. Vision

Support: FWO PhD fellowship (fundamental research): ZKD7277
EOS HUMVISCAT: G0E8718N

Title: The competition between word and face selectivity within the occipito-temporal cortex: selectivity to different types of characters clusters together with not only face but also body and hand selectivity

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Abstract: The visual categorization of shapes/objects is a critical process to interpret the world around us. The occipitotemporal cortex (OTC) supports this through 1. areas that selectively activate for a certain category (e.g., the visual word-form area (VWFA) selectively activates when looking at words) and 2. voxels across whole OTC that form different activity patterns per category. The category selectivity in OTC seems to organize according to some dimensions on which categories vary, and animacy has been proposed as a particularly strong organizing principle. It is unclear how this principle relates to the seemingly unrelated observation that selectivity for words competes with faces for cortical territory within OTC (see Dehaene & Cohen, 2010). To shed light on this issue, we investigated the selectivity to visual word forms in relation to dimensions like animacy and to other types of selectivity than to faces. We used 7T fMRI because it allows, within a limited timeframe, the collection of high-quality brain data with a relatively high spatial resolution for many categories. In our study, we presented 19 subjects (11 males) with 20 categories that vary on several dimensions. Using a general linear model, we created maps of category-selectivity on the complete brain surface of each subject. Through multi-voxel pattern analysis (MVPA), we built up the so-called representational space of our data and applied multi-dimensional scaling to transform it into a 2D space. We find that activity selective to words, a fake alphabet and numbers clusters together with activity for faces and other human-related categories included in our category set: bodies and hands. This is in sharp contrast with the series of studies that propose that the competition for cortical territory is specific to words and faces. We also show that in representational space, character-related conditions cluster and separately from them, human-related categories also cluster. We conclude that if competition for cortical territory by selectivity between different categories exists within OTC, it relates to character- and human-related categories more generally.

Disclosures: I. Pillet: None. **B. Cerrahoğlu:** None. **R.V. Philips:** None. **S. Dumoulin:** None. **H. Op de Beeck:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.19

Title: WITHDRAWN

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.20

Topic: D.06. Vision

Support: NSF-GRFP
T32 EY021462
K99 EY032102
EY032999
Whitehall Foundation

Title: Relating V1 population activity to perceptual orientation uncertainty

Authors: *Z. BOUNDY-SINGER, C. M. ZIEMBA, R. L. T. GORIS;
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Abstract: Many perceptual tasks require taking into account the uncertainty of individual perceptual impressions. It is not known how this is done by the neural circuits which mediate perceptually-guided behavior. A large body of theoretical work hypothesizes that neural circuits in sensory cortex play a critical role in assessing perceptual uncertainty. However, direct empirical evidence for this idea is lacking. Here, we studied neural population activity in the primary visual cortex of a macaque monkey performing a task that reveals the animal's subjective sense of perceptual uncertainty. Specifically, the animal judged the orientation of ambiguous stimuli ("clockwise" vs "counter-clockwise") and simultaneously reported their confidence in this decision ("high" vs "low"). Choices were rewarded in such a way that the most profitable strategy required the animal to take into account the uncertainty of the perceptual orientation estimates. Analysis of the choice behavior revealed that high confidence choices were more accurate than low confidence choices, both at high and low stimulus contrast. This pattern of choice behavior suggests that the animal was meaningfully introspecting about the uncertainty of its orientation estimates. We then asked how this choice behavior related to V1 population activity. We developed a decoder that transformed population activity into an estimate of stimulus orientation and an associated estimate of orientation uncertainty. The decoder's orientation estimates were on average unbiased but varied across repeated stimulus presentations.

This variability exceeded variability in the animal's perceptual reports and was not predictive of the animal's perceptual choices. In contrast, trial-to-trial variability in the decoder's estimate of orientation uncertainty covaried with variability in the animal's confidence reports. High confidence choices were associated with a lower degree of orientation uncertainty. This was also true of two aspects of neural activity previously proposed to inform perceptual uncertainty: population rate (the more spikes, the higher the confidence) and gain variability (the lower the gain variability, the higher the confidence). Together, these results provide the first direct evidence that neural activity in early visual cortex informs downstream estimates of perceptual uncertainty.

Disclosures: Z. Boundy-Singer: None. **C.M. Ziemba:** None. **R.L.T. Goris:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.21

Topic: D.06. Vision

Support: NIH K00/R00 Award: 1K99EY032603
NIH Pioneer Award: DP1HD091957
NSF NSF Science and Technology Center: NSF CCF-1231216

Title: Functionally distinct sub-regions of the parahippocampal place area revealed by model-based neural control

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Abstract: Abundant evidence supports a role for the parahippocampal place area (PPA) in visual scene perception, but fundamental questions remain. Here we ask whether the PPA contains distinct sub-regions that encode different aspects of scenes. To address this question, we used data-driven clustering to identify groups of PPA voxels with similar responses to a large set of images in extensively scanned individual brains (185 images, 20 repetitions per image, N = 4). We found that >95% of the variance of PPA voxel responses was explained by just two clusters, mapped approximately along the anterior-posterior axis, consistent with previous findings (Baldassano et al., 2013; Nasr et al., 2013; Cukur et al., 2016; Steel et al., 2021). But what distinct scene features do these sub-regions encode? Responses profiles of the two subregions were quite correlated, and visual inspection of stimuli eliciting high and low responses in each sub-region did not reveal any obvious functional differences between them. We therefore built artificial neural network-based encoding models of each PPA sub-region, which were highly accurate at predicting responses to held-out stimuli (each $R > 0.70$, $P < 0.00001$), and harnessed these models to find new images predicted to maximally dissociate responses of the two sub-

regions. These predictions were then tested in a new fMRI experiment, which produced a clear double dissociation between the two sub-regions in all four PPAs tested (two participants x two hemispheres each): The anterior sub-region responded more to images containing relatively bare spatial layouts than images containing object arrays and textures, while the more posterior region showed the opposite pattern. Taken together, this approach revealed distinct sub-regions of the PPA and produced highly accurate computational models of each, which in turn identified stimuli that could differentially activate the two subregions, providing an initial hint about the functional differences between them.

Disclosures: N. Ratan Murty: None. **F.S. Kamps:** None. **A. Abate:** None. **J. DiCarlo:** None. **N.G. Kanwisher:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.22

Topic: D.06. Vision

Support: NIH Eureka Program

Title: Adaptive coding across features in visual cortex during free-viewing and fixations

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Abstract: Theoretical studies have long proposed that adaptation allows the brain to effectively use the limited response range of sensory neurons to encode widely varying natural inputs. However, despite this influential view, experimental studies have exclusively focused on how the neural code adapts to a range of stimuli lying along a single feature axis, such as orientation or contrast. Here, we performed electrical recordings in macaque visual cortex (area V4) to reveal significant adaptive changes in the neural code of single cells and populations across multiple feature axes. Both during free viewing and passive fixation, populations of cells improved their ability to encode image features after rapid exposure to stimuli lying on orthogonal feature axes even in the absence of initial tuning to these stimuli. These results reveal a remarkable adaptive capacity of visual cortical populations to improve network computations relevant for natural viewing despite the modularity of the functional cortical architecture.

Disclosures: S. Nigam: None. **R. Milton:** None. **S.A. Pojoga:** None. **V. Dragoi:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.23

Topic: D.06. Vision

Support: NWO Vici Grant 016.Vici.185.050 (to S.O.D.).
ERC 339490 'Cortic_al_gorithms'
Human Brain Project (agreements 720270 and 785907, 'Human Brain Project SGA1 and SGA2')
NWO (Crossover Program 17619 'INTENSE'; STW-Perspectief P15- 42 'NESTOR'; VENI 451.13.023

Title: Divisive normalization explains diverse population receptive field properties in human BOLD and non-human MUA.

Authors: *T. KNAPEN[1], M. AQIL[2], N. MÜLLER[4], X. CHEN[5], P. R. ROELFSEMA[3], S. O. DUMOULIN[6], C. KLINK[7];
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Abstract: Divisive normalization implements contextual modulation by dividing a local neuronal response by the response of a wider ‘normalization’ pool. It is able to parsimoniously produce highly diverse output signatures, and is thought to represent a canonical computation re-used across a variety of sensory and cognitive domains. Here, we use detailed characterizations of this mechanism in visual cortex to bridge human 7-Tesla BOLD and primate neuronal responses measured using invasive electrophysiology.
We have recently shown that a population receptive field (pRF) model incorporating divisive normalization outperforms extant models in explaining human single-voxel BOLD responses to a visual-spatial stimulus (Aqil et al, PNAS 2021). It does so by combining surround suppression and response compression to produce position invariance and stimulus size tuning. Thus, the model’s best-fitting parameters characterize the evolution of response properties along the visual hierarchy and the visual field. Here, we apply the same model to electrophysiological responses from a virtually identical experiment conducted in 2 non-human primates (Klink et al, eLife 2021).
We investigated multi-unit activity (MUA) responses from over 1000 electrodes placed in V1 and V4 in each macaque. In MUA recordings from both V1 and V4, the divisive normalization pRF model outperforms extant models. Like in human BOLD, it does so by simultaneously capturing surround suppression and response compression. The parameters that determine these behaviors evolve between V1 and V4 electrodes similarly to how they evolve across the entire visual hierarchy in BOLD.
Our results show detailed congruence between the pRF tuning properties and nonlinear transduction characteristics estimated from MUA and BOLD. These parallels indicate that encoding-model based quantifications may help translate between measurement modalities and

different primate species. Our findings buttress the notion that 7-Tesla fMRI samples the local neural population activations in single voxels, providing further support for the basic assumptions of human functional neuroimaging.

Disclosures: **T. Knapen:** None. **M. Aqil:** None. **N. Müller:** None. **X. Chen:** A. Employment/Salary (full or part-time):; Department of Ophthalmology, University of Pittsburgh Medical Center, PA 15213, US. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); equity/shares in Phosphoenix BV. **P.R. Roelfsema:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); equity/shares in Phosphoenix BV. **S.O. Dumoulin:** None. **C. Klink:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.24

Topic: D.06. Vision

Support: NIH-NEI R00 EY025768
Brain & Behavior Research Foundation #28174
Alfred P. Sloan Foundation FG-2020-13415
NIH-NEIR01 EY028811

Title: Investigating task-dependence of choice probability and noise correlations during task learning and task switching in V4.

Authors: *S. LIU, A. PLETENEV, R. M. HAEFNER, A. C. SNYDER;
Univ. of Rochester, Rochester, NY

Abstract: To better understand neural computations happening in the sensory cortex, we study how the brain combines incoming sensory information (bottom-up) and prior beliefs/knowledge (top-down). Two important quantities for understanding neural representation underlying perceptions are (1) choice probability (CP): how well variation of a single neuron's response to the same stimulus predicts the subject's choice and (2) noise correlation: how responses of pairs of neurons covary around their mean response to a given stimulus. Multiple prior studies have found above chance CPs in the visual cortex, and non-zero noise correlations, which has raised the question of whether they are the result of feedforward or feedback mechanisms. One of the main approaches to study this question is to investigate the relationships between CP and noise correlations and neuronal sensitivity to the task-relevant stimulus (d-prime). A positive CP - d-prime relationship was first revealed in MT with multiple replications of this result; for other areas of the visual cortex (V1, V4) results are still inconclusive. Such a relationship is compatible with both feedforward and feedback mechanisms. Previous studies also showed that both learning and selective attention decreased noise correlations between neurons. On the other

hand, models of hierarchical probabilistic inference predict an increase of noise correlations aligned with d-prime*d-prime (alignment of sensitivity) of neuron pairs over the course of learning due to feedback mechanisms. We will test these predictions using trials that are interleaved such that trial-by-trial task-switching occurs within a session, so that task-related changes CPs and noise correlations can be directly studied. To do so, we used Utah array to record populations of V4 neurons from one macaque monkey while he was (1) learning one coarse orientation-discrimination task and (2) switching between two coarse orientation-discrimination tasks within a session. We found a significant positive correlation between choice probability and task sensitivity (d-prime) of neurons and that this correlation was absent before the monkey learned the task, and increased as the monkey's performance improved. We further found that during task-switching sessions, CP for one task is positively correlated with d-prime of the same task, but not with d-prime with the other task. For a given neuron its CP changed between two tasks in accordance with the change of its sensitivity.

Disclosures: S. Liu: None. **A. Pletenev:** None. **R.M. Haefner:** None. **A.C. Snyder:** None.

Poster

715. Visual Processing Properties in Higher Visual Areas

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 715.25

Topic: D.06. Vision

Support: EY028723
Simons Foundation
UKRI

Title: Spontaneous traveling waves occur in macaque V1 and V4 and can be retinotopically coordinated

Authors: *Z. DAVIS[1], M. MOFRAD[3], A. I. JASPER[5], J. E. SMITH[6], A. KOHN[8], A. J. PARKER[7], L. E. MULLER[4], J. H. REYNOLDS[2];
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Abstract: An important goal of neuroscience is to understand how spatiotemporal patterns of neural activity unfold across the brain and to establish their connection to behavior. We find that local field potentials (LFPs) recorded in Area MT of the marmoset are often structured as intrinsic traveling waves (iTWs) (Davis*, Muller*, et al., Nature, 2020). The likelihood that the monkey will detect a near-threshold target varies systematically with the spatiotemporal alignment of iTWs with the stimulus. Similarly, spontaneous spiking and target-evoked response gain is modulated by the alignment of iTWs. It is unknown whether iTWs occur independently

across cortical areas or are coordinated in space and time. We examined recordings of neural activity made simultaneously from Utah arrays in Areas V1 and V4 of behaving rhesus and cynomolgus macaques. Spontaneous activity in both V1 and V4 exhibit iTWs similar to those observed in marmoset. We find that they are more likely to co-occur across areas than would be expected by chance. This suggests that iTWs are to some degree coordinated across areas. If so, this could serve to align local excitability topographically across these cortical areas, creating transient windows of interareal communication. Consistent with this we find significant phase similarity during iTWs between the two cortical areas. Our results show that, as in marmoset MT, iTWs occur in Areas V1 and V4 of macaque monkeys and that they are to some degree coordinated across areas.

Disclosures: **Z. Davis:** None. **M. Mofrad:** None. **A.I. Jasper:** None. **J.E. Smith:** None. **A. Kohn:** None. **A.J. Parker:** None. **L.E. Muller:** None. **J.H. Reynolds:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.01

Topic: D.08. Multisensory Integration

Support: ERC Grant ERC-2009-AdG 249425-CriticalBrainChanges (Brigitte Röder)
DFG Grant Ro 2625/10-1 (Brigitte Röder)

Title: Sound alters earliest visual cortical processing in sight-restored humans

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Abstract: Neuroscientific research has consistently shown more extensive non-visual activity in the 'visual' cortex (including the primary visual cortex) of congenitally blind humans compared to sighted humans, a phenomenon known as crossmodal plasticity. Whether or not crossmodal activation of the visual cortex retracts if sight can be restored is still unknown. In the present study, we employed visual event-related potentials to investigate persisting crossmodal modulation of the earliest visual cortical processing stages in a rare group of sight-restored individuals who were born pattern vision blind (n = 14). These individuals had suffered from total, dense, and bilateral congenital cataracts, preventing more than diffuse light perception before undergoing surgical sight restoration (mean visual deprivation duration = 42.14 months, range = 1 month - 17.75 years). A hallmark of visual cortical organization and function is retinotopy, i.e., the presence of regular topographic maps of the visual field. In a previous experiment we have reported evidence for a prototypical retinotopic organization and visual

function of early visual cortex, with a typical time course, after sight recovery. In the present study, the participants saw brief circular grating stimuli and/or heard white noise bursts (150 ms) while electroencephalographic activity was continuously recorded. By targeting opposite banks of the calcarine sulcus, where most of the human primary visual cortex is located, we derived an electrophysiological marker of early visual cortical processing that emphasized retinotopic activity while eliminating non-retinotopic and/or common neural activity. Here, we report that the earliest, stimulus-driven visual cortical activity (< 100 ms) was suppressed in the congenital cataract reversal group when concomitant sounds accompanied visual stimulation. In contrast, sounds did not modulate the first visual cortical response in a control group of sight-restored individuals who had suffered a transient phase of later (rather than congenital) visual impairment (n = 15), nor in two groups of typically sighted controls matched to the sight-restored groups for age, sex, and handedness (n = 29). Our results provide strong evidence for persisting crossmodal activity of the visual cortex due to transient congenital visual deprivation. Based on the time course of this activity we speculate that exuberant non-matching (auditory) thalamic input to the visual cortex was less pruned in the congenital cataract reversal group, and thus that the pruning of non-matching thalamic input might take place guided by visual experience during a sensitive period.

Disclosures: **S. Sourav:** None. **R. Kekunnaya:** None. **D. Bottari:** None. **I. Shareef:** None. **K. Pitchaimuthu:** None. **B. Röder:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.02

Topic: D.08. Multisensory Integration

Support: NIH Grant R21 DC-019928
NIH Grant R01 DC-019928
Brooklyn College of CUNY -Reassigned Time to TR
Research Foundation- Theodore Raphan Research Fund from Pheobe Cohen

Title: Temporal habituation of yaw eigenvalue vs direct counter-eigenvector protocols for alleviating pulling sensation symptoms in mal de debarquement syndrome (MdDS)

Authors: *T. RAPHAN[1], S. B. YAKUSHIN[2], J. MARUTA[3], C. CHO[4];
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Abstract: The eigenvectors of the system matrix associated with velocity storage define the central vestibular coordinate basis with which the spatial orientation and acceleration of the head

are represented (Raphan and Sturm, 1991; Raphan et al, 1992). In particular, the yaw eigenvector characterizes the internal representation of the spatial vertical defined by gravity, and is normally aligned with the head yaw axis when upright. A model-based analysis indicates that the pulling sensation of MdDS is due to maladapted misalignment between the yaw eigenvector and the spatial vertical (Yakushin et al, 2022). Optokinetic stimulation (OKS) that targets re-adaption of the yaw eigenvector to realign with the head yaw axis when upright can significantly alleviate symptoms of MdDS. Habituation, or reduction of the time constant of the vestibulo-ocular reflex about the spatial vertical yaw axis, can alleviate these symptoms as well. The treatment effects of these apparently different stimulation protocols may both be explained by re-adaptation of the yaw eigenvector to better align with the head yaw axis when upright. This possibility can be addressed in the relationship between the eigenvalues and eigenvectors of the velocity storage system matrix. The eigenvalues are the inverses of the time constants associated with particular directions of rotational stimulation and define the temporal responses of velocity storage. Habituation, or an increase of the yaw eigenvalue, can redirect the yaw eigenvector and have similar effects to the protocol specifically designed to redirect the yaw eigenvector to align with the head yaw axis using OKS (Yakushin et al, 2022). Thus, the direction and magnitude of perception of tilt during pulling are key parameters of comparison between treatment protocols where the yaw eigenvector is realigned and the yaw eigenvalues are changed using OKS.

Disclosures: **T. Raphan:** None. **S.B. Yakushin:** None. **J. Maruta:** None. **C. Cho:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.03

Topic: D.08. Multisensory Integration

Title: Understanding the Interaction of Conflict-Minimizing and Goal-Seeking Motor Imperatives in Autism Spectrum Disorder

Authors: *S. RENGARAJAN[1], J. CANNON[5], B. BARON[2], N. MOHAN[3], L. CHUKOSKIE[4]; [1]Physical Therapy, Movement and Rehabil. Sci., [2]Khoury Col. of Computer Sci., [3]Mechanical and Industrial Engin., [4]Physical Therapy, Movement, and Rehabil. Sci., Northeastern Univ., Boston, MA; [5]Brain and Cognitive Sci., MIT, Boston, MA

Abstract: According to a classical control-theoretic perspective on self-movement, our brains pilot our bodies to achieve goals, sometimes using open-loop predictive models and sometimes with closed-loop feedback. From this perspective, synchronization of self-motion with a moving target is a simple control problem, where error between body and target is minimized by some combination of responsive and predictive control. However, not all self-movement can be described in terms of goals. A second, more subtle, driver of movement is the reconciliation of multisensory prediction errors. When subjected to a visual/proprioceptive conflict, our bodies respond spontaneously and unconsciously to reduce or resolve it. These two drivers of movement

are unified within the theoretical framework of active inference. To study this dynamic interaction of goal-oriented and conflict resolving motor imperatives, we designed a virtual reality task where participants synchronize a cyclic opening and closing hand movement with an opening and closing target hand. We introduce two perturbations: a transient delay of the target hand, and a transient delay of the image of their own hand. We model responses to these perturbations using an active inference model in which the velocities and positions of the oscillating target and the participant's hand are continuously estimated based on two visual streams of information (target hand and own hand images), one proprioceptive stream, and an internal model of the dynamics of the system and the noisiness of each stream. Preliminary results in non-autistic individuals indicate that delays in visual self-motion cause participants to delay their own motion, demonstrating the multisensory-conflict-reducing behavior. In this context, we aim to study interindividual differences in active inference processes. Certain sensorimotor differences reported in autism, including differences in the weighting of proprioceptive relative to visual input and weaker error correction during entrained finger tapping, could follow from reduced sensitivity to sensory/proprioceptive prediction errors in the context of active inference. We are currently recruiting autistic individuals for this task. Our model suggests that reduced sensitivity to sensory/proprioceptive prediction errors should make autistic individuals less responsive to both types of perturbation compared to non-autistic peers (after controlling for visual attention). This result would establish a link among several sensorimotor differences in autism that can be explained in terms of active inference and would help to identify targets for future interventions.

Disclosures: S. Rengarajan: None. **J. Cannon:** None. **B. Baron:** None. **N. Mohan:** None. **L. Chukoskie:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.04

Topic: D.08. Multisensory Integration

Support: NIH NHLBI Grant 13380745
NIH MH Grant 109429
Grant

Title: Differential effects of external vs. internal attention on sensory responsesin the human insula

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Abstract: Several studies have shown that stimuli from multiple external (i.e., vibrotactile, auditory, visual) and internal sources (i.e., heart, respiration) can evoke robust responses in the insula. Additionally, sensory responses in the insula can be modulated by cognitive (attention) and emotional (fear) signals. These and other findings led to the hypothesis that the insula may represent a crucial structure in which internal and external information is being integrated. We evaluated this hypothesis by recording insular responses in epilepsy patients (N=6) implanted with depth electrodes in the posterior and anterior insula (as well as the auditory, visual and frontal cortices) while they performed an audio-visual oddball task. In this task a stream of 40hz click-bursts were presented at 1.2hz, asynchrononous with flashes at 1.8hz. Patients were instructed to either detect auditory or visual deviants of lower intensity or to pay attention to respiration (counting their breaths). This task allowed us to characterize insular responses to auditory (40hz click-trains) and visual (light flashes) under three attentional conditions (attend auditory vs. visual vs. respiration). We found stronger auditory 40hz frequency-following responses in the posterior insula when subjects attended to the auditory stream vs. when they attended to the other modalities. This attention effect was similar to the profile observed in the auditory cortex (posterior STG) and, to a lesser degree, in the anterior insula. However, anterior insular auditory responses were greatly inhibited when subjects directed their attention to their respiration and only weakly inhibited when attention was directed to the visual stimuli. Conversely, in the auditory and posterior insular cortices, auditory gamma responses were strongly inhibited when attention was directed to the visual stimuli and only weakly inhibited when attention focused on the respiration. These attention-dependent effects in the gamma band (40-hz frequency following responses) were accompanied by effects in the lower frequency bands, including alpha-band power suppression (pre-stimulus) and entrainment at the frequency of the attended and unattended streams. In summary, these results show differential modulation of sensory responses in the human anterior vs. posterior insula by internal and external attention states which supports the hypothesis of the insula playing a key role in integrating internal and external representations.

Disclosures: J. Herrero Rubio: None. **N. Markovitz:** None. **G. Tostaeva:** None. **C.E. Schroeder:** None. **A.D. Mehta:** None. **S. Bickel:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.05

Topic: D.08. Multisensory Integration

Support: JST [Moonshot R&D][Grant Number JPMJMS2012]

Title: Influence of intersecting tactile and visual stimuli on early somatosensory evoked potential components and oscillatory power in the human EEG.

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Abstract: When input from the two sensory systems, which is visual and sensory, the visual information tends to take precedence, whereas the somatosensory information tends to take less precedence (Rock and Victor., 1964) in terms of perception and response speed in object recognition. The integration of tactile and visual stimuli must be taking place at single or multiple stage in the stream of visual- and tactile sensory processing, and it has not been fully investigated when which modality, tactile or visual, takes priority in visual and sensory area in multimodal sensory processing. It can be possible to address this issue by taking advantage of temporal characteristics of somatosensory evoked potential (SEP). The SEP latency from 20 to 65 ms represents the response in the somatosensory cortex (Allison et al., 1991). Also, it can be possible to evaluate the amount of visual information processing using oscillatory power (Becker et al., 2008).
To investigate whether humans prioritize somatosensory or visual information when recognizing physical properties of touching objects in early processing stage, we examined the effects of intersecting tactile and visual sensory inputs when touching an object on early components of SEPs in the somatosensory cortex and oscillatory power in the visual cortex using electroencephalography (EEG).
Twelve healthy participants (eleven males, mean age: 23.46 years; one female, age: 24 years) participated in experiments. During a task in which participants had to discriminate one of two material surfaces as a tactile stimulus, a photo image that matched ('congruent') or mismatched ('incongruent') with the material they were contacting was given as a visual stimulus. A 64 channel-cortical EEG was continuously recorded during the task.
The amplitudes of early SEP components (N20, P25, N33, P43, N57, and P65) recorded from EEG channels over the somatosensory cortex showed no significant difference between the congruent and incongruent conditions. In addition, the oscillatory power of theta, alpha, beta, gamma bands in the occipital areas values using the EEG channels over the visual cortex showed no significant difference between the conditions. Furthermore, multiple regression analyses showed that all SEP components were not predicted by oscillatory power. These results imply no difference in visual and tactile information priority in the early stage of tactile and visual information processing. And the tactile information is not modulated by visual information in the early stage.

Disclosures: Y. Ozawa: None. **K. Uehara:** None. **K. Seki:** None. **N. Yoshimura:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.06

Topic: D.08. Multisensory Integration

Support: MSIT 2022-0-00841
MSIT NRF-2017M3C7A1047227

Title: The effect of optic flows on walking trajectories in the discrepancy between the heading direction and the head position

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Abstract: The visual and vestibular systems are mainly involved in the cognitive process of understanding the heading direction to walk toward a target point. In this process, the optic flow, a movement pattern formed on the retina as the body moves, is used to estimate speed and distance while body balance and spatial orientation are perceived by the vestibular system. In general situations, visual and vestibular signals are given together, so it is critical to study the interaction between such systems for multi-sensory integration. This study aims to investigate the interaction pattern between visual information and vestibular information by observing how the heading direction and walking are continuously performed in the locomotion process. In this study, optic flow and head rotation conditions were designed to manipulate visual and vestibular information in a head-mounted display-based virtual reality environment, and participants walked a distance of 5 meters for 10 trials per condition in an indoor experimental space. The conditions consisted of a total of 7 conditions, provided by manipulating the optic flow to conflict with the rotated head direction (0° center, 30° left, 30° right). A total of 10 participants (male: 4, female: 6, age: 26.20 ± 3.82) participated in this study. To analyze a walking trajectory for each condition, the angular deviation of the maximum horizontally traveled position was calculated and compared with that of the null condition in which neither the head was rotated nor the optic flow was applied. As a result of the experiment, the trajectories were leaned to the opposite direction of the applied optic flow regardless of the head rotation. Our results imply that visual information contributes more critically than vestibular information in the process of walking in a heading direction. Taken together, we suggest that this study will improve the understanding of sensorimotor adaptation and be applied to techniques to reduce cybersickness that often appear during experiences with the head-mounted display-based virtual reality environment.This work was partly supported by Development of IoT convergence care technology through biosignal analysis of whole body PBM (Photobiomodulation) chamber and development of VR (virtual space) solution for visual healing care for chamber users (2022-0-00841) and the Brain Research Program of the National Research Foundation (NRF-2017M3C7A1047227) funded by the Korean government (MSIT).

Disclosures: H. Chang: None. **H. Joo:** None. **J. Ryu:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.07

Topic: D.08. Multisensory Integration

Support: IIS-2006152

Title: Spatial representations of thermal stimuli are influenced by temporal parameters of stimulation.

Authors: *L. A. JONES, A. SINGHAL;
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Abstract: A number of experiments have demonstrated that the spatial representation of tactile stimuli on the skin critically depends on the temporal properties of stimulation as demonstrated by a number of illusions involving mislocalization of the site of stimulation when stimuli are presented in close temporal proximity. Much less is known about spatial-temporal interactions involving the thermal senses, although it is often reported that they are markedly inferior at localizing the site of thermal stimulation and at differentiating two thermal stimuli placed in close spatial proximity. The objective of the present set of experiments was to determine the effects of varying the inter-stimulus interval on the perceived location of thermal stimuli and if the perceived locations differed for warmth and cold. A thermal display comprising three independently controlled Peltier devices provided the thermal inputs to the skin and thermistors recorded the temperatures of the skin and Peltier modules. The area of contact of each module was 418 mm^2. Four 2-second stimuli that either cooled (-8 °C) or warmed (+6 °C) the skin were delivered successively along the ventral surface of the forearms of ten participants. Three of the stimuli were always presented at the same locations and the position of the other stimulus varied across trials. The interval between the presentations was either 0.2 or 4 s. There were 80 trials in total; at the end of each trial participants indicated the perceived location of the first two stimuli using a visual depiction of the forearm presented on a computer screen. The perceived locations were then digitized using the Image Processing Toolbox in MATLAB. The results indicated that cold was more accurately localized than warmth, although the mean errors were still relatively large, at 10 mm for cold and 15 mm for warm stimuli. For both cold and warmth, the perceived location of the second stimulus was dramatically affected by the temporal interval separating the second and third stimulus. When the interval was brief (0.2 s) the perceived location of the second stimulus moved in the direction of the third stimulus and was mislocalized by on average 51 mm and 40 mm for cold and warm stimuli, respectively. At longer inter-stimulus intervals (4 s) there was little change in perceived position. These findings demonstrate that the interactions between spatial and temporal properties of stimulation that are a fundamental aspect of tactile sensory processing also occur with thermal sensing and that there are differences between cold and warmth in terms of localization accuracy.

Disclosures: L.A. Jones: None. **A. Singhal:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.08

Topic: D.08. Multisensory Integration

Support: Pilot grant from NIH COBRE (PG20GM103650)

Title: Sensory Sensitivity Across the Migraine Cycle

Authors: *S. M. HAIGH[1], M. M. CORTEZ[3], L. M. THOMPSON[5], A. CHEVYCHALOVA[2], J. SANTIAGO[2], K. BRENNAN[4];
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Abstract: Sensitivity to visual and auditory stimulation constitute elements of the diagnostic criteria for migraine, and can also occur between headache attacks. However, less is known about sensory sensitivity across the migraine cycle or whether sensory sensitivity can be predictive of migraine-onset. First, we assessed overall sensitivity in visual, auditory, and odor modalities, tactile pain, and motion sickness in 60 individuals with migraine compared to 60 headache free individuals using standardized questionnaires. We found that individuals with migraine reported significantly greater sensitivity in visual and odor modalities and in tactile pain. There were no significant group differences in auditory sensitivity or in motion sickness severity. Second, we assessed visual, auditory, odor, tactile sensitivity, and motion sickness across the migraine cycle by asking 35 individuals with migraine to complete sensory sensitivity questionnaires every day for 30 days. The questionnaires were the same as those used in the first study, except were adapted to focus on sensitivity experienced within the day of ascertainment. 28 participants completed at least half of the required days. 19 participants reported sensitivities the day prior, the day of, the day after, and days outside of the migraine window. The average sensitivity for each modality for each of these days was calculated per participant. Day and sensory modality were compared in the same model. The majority of the participants did not consistently report on their odor and tactile sensitivity and so were excluded from the model. There was a significant interaction between day and sensory modality. Visual sensitivity increased on the day of a migraine compared to the day before and the day after the migraine, but visual sensitivity on the day prior did not significantly differ from other non-migraine days. Motion sickness was reported as only occurring on the day of a migraine and was minimal before and after the migraine day. Auditory sensitivity, on the other hand, significantly increased the day before a migraine compared to other days outside of the migraine day. Auditory sensitivity was reported to be the worst on the day of the migraine. Together, these findings suggest specific types of sensory sensitivity between migraine episodes, and that worsening auditory sensitivity could reflect the changes in neural functioning that precede a migraine. This was despite reports of overall auditory sensitivity being similar in migraine and headache free groups. Therefore, tracking sensory sensitivities over the course of the migraine cycle may help patients to anticipate when their next migraine attack will occur.

Disclosures: **S.M. Haigh:** None. **M.M. Cortez:** None. **L.M. Thompson:** None. **A. Chevychalova:** None. **J. Santiago:** None. **K. Brennan:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.09

Topic: D.08. Multisensory Integration

Support: JST Moonshot R&D Grant Number JPMJMS2013

Title: Self-body illusion for a four-armed avatar in virtual reality environment measured by autonomic responses

Authors: *H. NITO, M. NARITA, K. HIGO, S. SHIMADA;
Meiji Univ., Kawasaki, Japan

Abstract: In this study, we examined self-body illusion for a four-armed avatar in VR space that was operated on by two people. Self-body recognition is considered to be composed of senses of self-ownership and self-agency. We focused on one of the conditions related to the emergence of the sense of self-agency: priority. Priority refers to the subject having a prior thought about their behavior. In this study, we investigated whether there was a difference in self-body recognition when the arms moved as intended in advance or not. Previous studies showed that when a full-body illusion occurs, instantaneous heart rate decreases when the avatar is presented with a threatening stimulus. Instantaneous heart rate and questionnaires were used as indices of self-body recognition. We investigated three experimental conditions: the one-person condition, two-person intention-sharing condition, and two-person intention-unsharing condition. Hereafter, the arm that was directly operated on by the subject will be referred to as the main arm, and the arm that was operated on by the experimenter (in two-person conditions) as the subarm. We employed the task of pressing a button that glowed blue or red. In the one-person condition, the subject was asked to press a button that glowed blue or red. If the button glowed blue, the avatar pressed the button with its main arm, while if the button glowed red, the avatar pressed the button with its subarm. In the two-person conditions, the subarm was operated on by the experimenter. In the two-person intention-sharing condition, the subarm pressed the red button correctly, but not in the two-person intention-unsharing condition: the subarm reached for a location unrelated to the button. After the task was complete, the subject was presented with an image of a knife being dropped from above onto the avatar's subarm, while the subject's heart rate was measured. After that, the subject was asked to complete a self-recognition questionnaire on their avatar's subarm. The results showed that the one-person condition showed significantly higher values than the other two conditions in the self-body recognition questionnaire for the subarm. The score for the two-person intention-sharing condition tended to be higher than that of the two-person intention-unsharing condition. The instantaneous heart rate results also showed significant results. In the case of the knife drop, there was a significant decrease in the one-

person condition, and a decreasing trend in the two-person intention-sharing condition. These results suggest that extended body parts behaving in such a way that they share the same goals with the subject would lead to self-body illusion.

Disclosures: **H. Nito:** None. **M. Narita:** None. **K. Higo:** None. **S. Shimada:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.10

Topic: D.08. Multisensory Integration

Support: European Research Council SELF-UNITY 787386
Swedish Research Council

Title: Body ownership information, perceptual processing, and conscious awareness

Authors: *R. C. LANFRANCO[1], M. CHANCEL[2], H. H. EHRSSON[1];
[1]Dept. of Neurosci., Karolinska Inst., Solna, Sweden; [2]Univ. Grenoble-Alpes, Grenoble, France

Abstract: The sense of owning one's body arises from the integration of multiple sensory signals. Is this sense prioritised by awareness in that it enters awareness as soon as it is sensorily processed? To induce and manipulate body ownership, researchers typically use the rubber hand illusion (RHI), which involves stroking a person's hand (hidden behind a screen) alongside a visible fake rubber hand placed in front of them; this induces the feeling that the rubber hand is their own. Most RHI studies rely on subjective reports and indirect measures to assess body ownership. We developed a two-alternative forced-choice (2AFC) paradigm that objectively quantifies body ownership in a bias-free manner by simultaneously inducing the RHI with two rubber hands. Graded stimulation asynchronies between the two rubber hands are introduced using robot arms, and participants must report which rubber hand feels most like their own; in another experiment, they must also rate the clarity of their body ownership. Here, we present five 2AFC experiments that have been analysed under type-1 and 2 signal detection theoretic frameworks to test how different visuo-tactile manipulations modulate perceptual and metacognitive sensitivities to body ownership information. We found that body ownership is very sensitive to tactile stimulation incongruencies: stimulation asynchronies of 30-50 ms caused noticeable changes in hand ownership, leading to above-chance perceptual and metacognitive discrimination performance. In addition, body ownership information becomes available for awareness as soon as is processed in perception. Furthermore, other multisensory manipulations like varying the congruence between the materials stimulating the rubber hands and the real hand, or visually occluding the robot movements, exclusively modulated perceptual bias. Overall, participants exhibited a perceptual bias favouring the rubber hand closer to their body; this bias decreased in magnitude as stimulation asynchronies increased. Using this novel paradigm, we show how the temporal, spatial, and tactile congruence principles of body

ownership modulate body ownership information processing and perceptual bias during the RHI, and that body ownership information is prioritised for conscious awareness.

Disclosures: R.C. Lanfranco: None. **M. Chancel:** None. **H.H. Ehrsson:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.11

Topic: D.08. Multisensory Integration

Support: This research is supported by an NIDCD grant.

Title: Impact of auditory system impairments on eye-movement-related eardrum oscillations (EMREOs)

Authors: *C. KING[1], S. LOVICH[2], D. KAYLIE[2], C. SHERA[3], J. M. GROH[1];
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Abstract: Eye movements are critical to linking vision and spatial hearing - every eye movement shifts the relative relationship between the visual (eye-centered) and auditory (head-centered) frames of reference, which requires constant updating of incoming sensory information in order to integrate the two sensory inputs. Previous neurophysiological studies have revealed eye movement-related modulation of the auditory pathway. We recently discovered a unique type of low frequency otoacoustic emission that accompanies eye movements. These eye movement-related eardrum oscillations (EMREOs) occur in the absence of external sound and carry precise information about saccade magnitude, direction, and timing (Gruters et al 2018, Murphy et al 2020).
However, it is not well understood how these eye movement-related effects in the auditory periphery contribute *mechanistically* to hearing. Two auditory motor systems may be involved in generating EMREOs: the middle ear muscles and/or the cochlear outer hair cells. To gain insight into which systems are involved and how they contribute, we are presently investigating the EMREOs in human subjects with dysfunction involving these systems compared to a normal hearing population. The impact of hearing loss on the EMREO is examined by comparing responses from individuals with different hearing pathologies to population data from normal hearing subjects.
We find that EMREOs are abnormal in subjects with hearing impairment, most commonly with the EMREO being abnormally small in individuals who have impaired outer hair cell or stapedius function. Future work is needed to assess if patients with these types of hearing loss have specific impairments in the perceptual process of integrating visual and auditory spatial information.

Disclosures: C. King: None. **S. Lovich:** None. **D. Kaylie:** None. **C. Shera:** None. **J.M. Groh:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.12

Topic: D.08. Multisensory Integration

Title: Mixed Polyneuropathy and Brain Fog sequelae of Post-Coronavirus Disease 2019

Authors: D. SUÁREZ-SÁNCHEZ[1], O. A. JARAMILLO-MORALES[2], M. FERNÁNDEZ-MOYA[2], M. MENDOZA-NAVARRO[1], *N. V. VEGA-CABRERA[3];
[1]Med. Educ. and Res., Mexican Social Security Inst., México, Mexico; [2]Nursing and Obstetrics, Univ. of Guanajuato, Irapuato, Mexico; [3]UNAM, Mexico, Mexico

Abstract: Coronavirus disease 2019 (COVID-19) can directly or indirectly affect the central and peripheral nervous systems, resulting in cognitive impairment, memory problems, and a wide range of neuromuscular involvement, including neuropathies. However, the long-term neurological complications of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection are not clear. The aim this study was to analyze a case report the presence of neurological sequelae due to post-Coronavirus disease 19 in a patient without apparent previous neurological symptoms. Clinical case: A 46-year-old patient, with no relevant history for the described condition, who, after severe COVID-19 infection, started a mixed neuropathy and mental fog syndrome as the main sequel. Multiple laboratory and imaging studies were performed during and after his hospital stay, and it was corroborated by an electromyography that it occurred from a neuropathy triggered by COVID-19 infection. Conclusions: This case provides additional evidence that mixed neuropathy and brain fog syndrome are potential complications of post-coronavirus disease 2019 syndrome

Disclosures: D. Suárez-Sánchez: None. **O.A. Jaramillo-Morales:** None. **M. Fernández-Moya:** None. **M. Mendoza-Navarro:** None. **N.V. Vega-Cabrera:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.13

Topic: D.08. Multisensory Integration

Support: ANER Grant-RoborSelf Bourgogne-Franche Comte Region

Title: Motor intentionality influences social perception of robots

Authors: D. FARIZON, P. DOMINEY, ***J. VENTRE-DOMINEY**;
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Abstract: In a previous study we demonstrated that robotic telepresence can induce a sensation of embodiment into robots promoted by reciprocal and synchronous facial stimuli, including intentional movements and passive tactile stimulations. Here we investigate in a series of experiments how changes in spatial perspective will impact embodiment and social attitude towards the robot. We used a similar paradigm than in our previous telepresence studies, but here the subject and the robot are facing each other. In this face to face condition, two experiments were realized: -in Experiment 1, 16 subjects (mean age=26 ± 4.6) were tested in the Motor induction condition where their head movement pilots the head of the robot. In Experiment 2, 24 subjects (mean age= 24 ± 4.3) were tested in the Tactile induction condition, where their face and that of the robot were brushed. Each subject was exposed to two sessions: synchronous & asynchronous with either a humanoid robot (iCub) or a cartoon like robot (Reeti). Order of robot type and synchrony was balanced. After each session, the subject was requested to respond to a questionnaire evaluating the level of embodiment into the robot including the sensation of Enfacement, Location and Agency. Once before and once after each session the social attitudes were evaluated using a questionnaire on the feeling of likeability and closeness toward the robot. The embodiment, the likeability and closeness scores were each quantified on the individual quote of subjective scale. The different variables of embodiment and of social features were analysed using a mixed repeated measures ANOVA and post-hoc specific pairwise comparisons with a Bonferroni test. In Experiment 1 of motor induction, the embodiment scores increase significantly in synchronous vs asynchronous reciprocal movements (Syn effect : $F(1, 14) = 24.14$, $p< 0.001$; Cat x Syn interactions : $F(2,30)= 31.42$, $p<0.001$) in particular for the sensation of agency ($p< 0.001$). The scores of social states are enhanced in synchronous vs asynchronous condition and more for closeness (Syn effect : $F(1,15)= 8.77$, $p=0.0097$) than likeability (Syn effect : $F(1,15)= 4.0\ 4$, $p=0.063$). In contrast, in Experiment 2 where the embodiment is promoted by tactile manipulation the scores of embodiment and social states remain low with no significant difference between synchronous vs asynchronous stimulation. When comparing these results with those of telepresence, we found consistent findings between these two types of human-robot interaction. We conclude in the existence of a generalized processing in human-robot interactions where motor intentionality is crucial to induce changes in social perception of robots.

Disclosures: D. Farizon: None. **P. Dominey:** None. **J. Ventre-Dominey:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.14

Topic: D.08. Multisensory Integration

Support: JST Moonshot R&D Grant Number JPMJMS2013.

Title: Enhancement of sense of embodied self on a VR avatar operated by two people through intention sharing: a NIRS study.

Authors: *M. NARITA, H. NITOU, K. HIGO, S. SHIMADA;
Meiji Univ., Kawasaki-shi, Japan

Abstract: The sense of embodied self consists of senses of self-ownership and self-agency. The sense of agency arises when an individual has an intention to move in advance and the movement is carried out in accordance with the intention. On the other hand, the research on sharing a VR or robot avatar body with others has been increasing in the recent years. In this study, we investigated the effect of intention sharing between two people cooperating on a VR avatar on the sense of embodied self. Participants wore a head-mounted VR device to operate an avatar. Their brain activity during the task were measured by multi-channel (48-ch) near-infrared spectroscopy (NIRS). The avatar had four arms, one pair (main-arms) of which was controlled by the participant and the other (sub-arms) by the experimenter. We employed a task of pressing buttons that glowed blue or red. If the button glowed blue, the participants were asked to press it with the main-arms, while, if the button glowed red, the experimenter responded with the sub-arms. The experiment consisted of two phases: learning and experimental phases. There were two conditions in the learning phase: shared-intention and unshared-intention conditions. In the shared-intention condition, the sub-arms pressed the button glowed red correctly (correct behavior). In the unshared-intention condition, the sub-arms pressed a button that did not glow (error behavior). In the experimental phase, the participants observed that the sub-arms performed both correct and error behaviors. The questionnaire results showed significantly higher scores in the shared-intention condition than in the unshared-intention condition for both senses of ownership and agency on the VR avatar. A 2-way ANOVA on the NIRS results showed significant interactions (intention sharing × correct/error) in the left premotor cortex ($F(1, 24) = 5.97$, $p = 0.022$, $\eta\_G^2 = 0.06$) and right supramarginal gyrus ($F(1, 24) = 5.70$, $p = 0.025$, $\eta\_G^2 = 0.03$) in the experimental phase. The brain activity in the shared-intention condition when the sub-arms performed the correct behavior were higher than those in the unshared-intention condition (left premotor cortex: $F(1, 24) = 7.01$, $p = 0.014$, $\eta\_G^2 = 0.09$, right supramarginal gyrus: $F(1, 24) = 3.25$, $p = 0.084$, $\eta\_G^2 = 0.05$). These results indicate that even without moving parts of the avatar's body on their own, sharing intention enhances the sense of self for the VR avatar operated by two people.

Disclosures: **M. Narita:** None. **H. Nitou:** None. **K. Higo:** None. **S. Shimada:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.15

Topic: D.08. Multisensory Integration

Support: NIH Grant 2T32MH064913-16
NIH Grant R01MH102272

Title: Putting the self in context: A preliminary study of interoceptive-exteroceptive integration in autistic and neurotypical individuals

Authors: *A. R. ZOLTOWSKI[1], C. A. CONVERY[2], E. EYOH[4], J. M. QUINDE-ZLIBUT[1], B. KECELI-KAYSILI[3], B. LEWIS[2], C. J. CASCIO[2];
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Abstract: The perception of cues signaling biological needs (i.e., interoception) is crucial for maintaining physical/emotional health. Autistic individuals experience sensory differences in other modalities, so understanding whether these differences extend to interoception may help promote autistic health. However, individual differences in interoception have been difficult to study, partly since internal signals often do not reach conscious awareness outside of biologically relevant contexts. Measures of interoceptive-exteroceptive (IE) integration may help to understand the perception of these signals relative to environmental cues that contextualize their interpretation, such as perceiving and interpreting a heart rate change in a gym versus home environment. Thus, to study different aspects of IE integration, we analyzed relationships between three tasks with different stimulus modalities and time scales: a Method of Constant Stimuli (MCS) task to test perceived synchrony of individual heartbeats and visual stimuli as a function of temporal offset (Brener and Ring, 2016), Legrand et al.'s (2022) heart rate discrimination (HRD) task to test discrimination of heart versus auditory *rate* changes (not requiring perception of individual beats), and Walsh et al.'s (2019) respiration integration task to test whether breathing synchronized with a moving visual stimulus improves subsequent visual speed discrimination relative to an exteroceptive-only baseline. Participants included $n = 9$ neurotypical (7 female, 2 male) and $n = 3$ autistic adults (1 female, 2 male) who had biologically plausible parameter values in all three tasks. Across groups, wider temporal binding windows between heartbeats and visual stimuli were highly correlated with less sensitive heart rate discrimination ($r = 0.72$, $p < 0.01$). Though improvements in detecting visual speed changes with synchronized breathing were not significantly correlated with either cardiac task, there was a slight tendency for individuals with wider cardiovisual bindings windows to improve more in the breath synchronization condition ($r = 0.17$, n.s.). This preliminary finding is in line with the multisensory principle of inverse effectiveness. Our results suggest that these tasks may indeed index some shared and some distinct aspects of IE integration; for example, single heartbeat integration may impact the ability to contextualize heart rate changes related to threat. Future work in larger samples will study relationships between these measures, diagnostic group status, and physical/emotional health outcomes.

Disclosures: A.R. Zoltowski: None. **C.A. Convery:** None. **E. Eyoh:** None. **J.M. Quinde-Zlibut:** None. **B. Keceli-Kaysili:** None. **B. Lewis:** None. **C.J. Cascio:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.16

Topic: D.08. Multisensory Integration

Support: Chair in Neuroscience UAM-Fundación Tatiana Pérez de Guzmán el Bueno (C.C and I.P.-S.)
German Federal Ministry of Education and Research (01GQ1902 to N.P.-G.)
European Union's Horizon 2020 Research and Innovation Programme (785907 - Human Bain Project SGA2 to N.P.-G. and K.Z.)
European Union's Horizon 2020 Research and Innovation Programme (945539 - Human Brain Project SGA3 to N.P.-G. and K.Z.)
Boehringer Ingelheim Fonds (I.P.-S.)
Universidad Autónoma de Madrid (I.P.-S.)
Beatriz Galindo senior research position in the Faculty of Medicine at Universidad Autónoma de Madrid (BEAGAL18/00098 to MA.G-C))

Title: Noradrenaline innervation and adrenoceptors in the human thalamus

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Abstract: Thalamic noradrenaline (NA) modulates sensory transmission as well as higher order processing through the thalamus. Yet, the precise distribution of NA axons and receptors throughout the human thalamus is unknown.
We have mapped NA axons, as well as Alpha-1 and Alpha-2 adrenoceptors, in the human thalamus. Immunohistochemistry against NA transporter (NA axons), and quantitative autoradiography with the ligands [3H]-Prazosin (Alpha-1 adrenoceptor), [3H]-RX-821002 (whole Alpha-2 adrenoceptor population), and [3H]-UK-14,304 (high-affinity state Alpha-2 adrenoceptor) were used.
Our results show that almost all human thalamic nuclei receive NA innervation, except for the visual relay nucleus (lateral geniculate), almost devoid of NA axons. The most innervated are the midline and intralaminar nuclei. Dense NA axon innervation is also present in some sensory relay nuclei, mostly somesthetic (ventral posterolateral) and auditory (medial geniculate), as well as in some association nuclei (lateral posterior, some regions of mediodorsal, and oral pulvinar). Alpha receptor distributions are, in general, coincident with NA axon distributions. Midline, mediodorsal (particularly medially), posterior intralaminar (parafascicular) and limitans nuclei show high Alpha-1 and Alpha-2 receptor concentrations. Non-matching NA innervation and receptor distribution patterns are also present: the anterior intralaminar nuclei have very low Alpha receptor concentrations relative to their NA innervation; other nuclei exhibit high Alpha receptor concentrations (Alpha-1, Alpha-2, or both) with moderate or low NA axon densities (e.g. anterior complex, lateral geniculate, inferior pulvinar).

Alpha-2 receptor distributions revealed by [3H]-UK-14,304 and [3H]-RX- 821002 ligands are in general comparable, with the remarkable exception of somatosensory relay nuclei, as well as the oral pulvinar and supragenicular nuclei. In those nuclei, Alpha-2 receptor concentration revealed by [3H]-RX-821002 ligand is higher than that revealed by [3H]-UK-14,304. Thus, those nuclei likely have a lower proportion of high-affinity Alpha-2 receptors than other thalamic nuclei.
The distributions of NA axons and Alpha adrenoceptors in the human thalamus suggest critical and specific roles for NA in modulating limbic, multimodal, and sensory association thalamocortical circuits. In particular, our results point to a more prominent role in modulating somatosensory transmission and processing in the human thalamus than in other primate species.

Disclosures: I. Pérez-Santos: None. **N. Palomero-Gallagher:** None. **M. García-Cabezas:** None. **K. Zilles:** None. **C. Cavada:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.17

Topic: E.04. Voluntary Movements

Support: NIH grant R34NS111669-01
NIH grant R01NS121919-01
NIH grant UF1NS116377

Title: Joint coding of visual input and eye/head position in V1 of freely moving mice

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Abstract: Visual input to the brain during natural behavior is highly dependent on movements of the eyes, head, and body. Neurons in mouse primary visual cortex (V1) respond to eye and head movements, but how information about eye and head position is integrated with visual processing during free movement is unknown, since visual physiology is generally performed under head-fixation. To address this, we performed single-unit electrophysiology in V1 of freely moving mice while simultaneously measuring the mouse's eye position, head orientation, and the visual scene from the mouse's perspective. We mapped spatiotemporal receptive fields using a generalized linear model (GLM) that predicted the activity of V1 neurons based on gaze-corrected visual input. Critically, a large fraction of visually-responsive neurons showed tuning for eye position and head orientation. Incorporating these variables into the GLM revealed that visual and positional signals in most neurons are multiplicatively integrated, consistent with computation via gain fields and nonlinear mixed selectivity. These results provide new insight

into coding in mouse V1, and more generally provide a paradigm for performing visual physiology under natural conditions, including active sensing and ethological behavior.

Disclosures: E.T.T. Abe: None. **P.R.L. Parker:** None. **E.S.P. Leonard:** None. **D.M. Martins:** None. **C.M. Niell:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.18

Topic: D.08. Multisensory Integration

Support: Institutional funds from Penn State College of Medicine

Title: Acoustic parameters underlying sound-symbolic mapping of auditory pseudowords to different domains of meaning: a machine learning approach

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Abstract: Sound symbolism refers to non-arbitrary mapping between the sound of a word and its meaning, e.g., auditory pseudowords like “bouba”/“kiki” are perceived as sounding rounded/pointed, respectively. Previously (Lacey et al., 2020, Cog Sci, 44:e12883), we showed that ratings of 537 pseudowords on a rounded-to-pointed scale were significantly correlated with three acoustic parameters measuring spectro-temporal properties (spectral tilt (ST), temporal fast Fourier transform (FFT), speech envelope (SE)) and six voice parameters measuring voice characteristics (harmonics-to-noise ratio (HNR), pulse number, fraction of unvoiced frames (FUF), mean autocorrelation, shimmer, jitter). Here, we used a machine learning approach to investigate which combinations of these parameters best predicted ratings of the same set of pseudowords on scales representing categorical opposites for seven meaning domains: shape (rounded/pointed), size (small/big), brightness (bright/dark), weight (light/heavy), texture (hard/soft), arousal (calming/exciting) and valence (good/bad). Pairwise dissimilarities between all pairs of pseudowords were computed for each parameter: for spectro-temporal parameters, we rescaled the pairwise dissimilarity values, computed from corresponding Pearson correlations ($1-r_p$), to lie between 0 and 1; for voice parameters, we rescaled their values to 0 - 1, and computed pairwise absolute differences. Subsequently, we evaluated all 511 possible parameter combinations using a k-nearest-neighbors algorithm ($k = \sqrt{537} \approx 23$). For each combination, we iteratively computed the Euclidean distance in n-parameter space between each pseudoword and the remaining 536 to find its 23 nearest neighbors. The algorithm predicted a rating for each pseudoword based on the modal perceptual rating of its neighbors. Finally, we used the Spearman correlation between predicted and perceptual ratings to quantify the algorithm’s

performance. The best performing model for shape (r =.59), weight (r=.45) and texture (r=0.53) comprised four parameters: FFT, ST, SE and FUF. Different four-parameter models best predicted ratings for brightness (r=0.52; FFT, ST, FUF and HNR) and size (r =.45; ST, SE, pulse number and FUF). A two-parameter model with FFT and SE best predicted valence (r=.0.66), and a five-parameter model comprising FFT, ST, SE, FUF and HNR best predicted arousal (r=.51). These results show that sound-symbolic mappings rely on different patterns of multiple parameters depending on the meaning domain. This approach could be applied to real words to measure the degree of sound-symbolic mapping in natural languages unconfounded by semantic bias.

Disclosures: V. Kumar: None. **A. Hoffmann:** None. **K. L. Matthews:** None. **S.A. Lacey:** None. **L. Nygaard:** None. **K. Sathian:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.19

Topic: D.08. Multisensory Integration

Support: JPMJMI19D1
JPMJMI17DC

Title: Odor representation in the human piriform cortex modulated by verbal labels revealed by 7T MRI

Authors: *T. OKUMURA[1,2], I. KIDA[1], A. YOKOI[1], T. NAKAI[1], S. NISHIMOTO[1,3], K. TOUHARA[2], M. OKAMOTO[2];
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Abstract: It is well known that olfactory perception is influenced by verbal labels. Previous studies showed verbal labels modulate the secondary olfactory areas, such as anterior cingulate and medial orbitofrontal cortices. However, it is still unclear whether the verbal labels could modulate the odor representation in the primary olfactory cortex, especially the piriform cortex. Here, to examine whether verbal labels modulate ensemble patterns of piriform activities evoked by the same olfactory inputs, we measured piriform activity for 8 verbally labeled odorants, 4 odorants presented with 2 different, but congruent words (e.g., labels “Mint” and “Eucalyptus” for an odorant, menthol) using a 7T MRI in 1 mm isotropic resolution (N=25). We conducted searchlight leave-one-subject-out decoding analysis, which showed that ensemble patterns of the piriform activities to identical odorants could be distinguished when different words were used as labels in 3 subregions within the piriform cortex, the bilateral junctions of the frontal and temporal parts and the left postero-temporal area. Note that odor dissimilarity ratings showed that participants perceived identical odorants differently when they were presented with different labels. To examine whether subregions modulated by labels overlap with areas that represent

differences of olfactory inputs, we also conducted the same analysis to stimulus pairs with different odorants labeled by identical words. Significant differences were again observed in the bilateral junctions, but regions modulated by olfactory inputs were closer to the temporal part compared with subregions modulated by labels. In addition, odorant difference was not found in the left postero-temporal area, where label difference was found. These results suggest that verbal labels modulate piriform ensemble patterns in subregions different from those modulated by olfactory inputs. Finally, we assessed the functional connectivities between piriform subregions and regions outside of the piriform cortex using beta series correlation analysis. Significant functional connectivities were found between the piriform subregions modulated by labels and regions associated with semantic, memory or language processing: left temporal pole, hippocampus or left medial frontal lobe. These results suggest that feedback from semantic, memory or language areas may enable modulation of odor representation in ensemble patterns of the piriform activities.

Disclosures: **T. Okumura:** None. **I. Kida:** None. **A. Yokoi:** None. **T. Nakai:** None. **S. Nishimoto:** None. **K. Touhara:** None. **M. Okamoto:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.20

Topic: D.08. Multisensory Integration

Support: Radboud Excellence Fellowships

Title: Facilitative effects of seeing gestures on processing speech when watching and hearing yourself compared to another person

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Abstract: Language is inherently multimodal: spoken words are typically coupled with gestures that carry semantic meaning. Most notably, iconic hand gestures, i.e. movements depicting actions and objects, form an integral part of speakers' utterances. One fundamental question is how iconic gestures influence speech processing and what neurocognitive mechanisms underpin it. This multi-session behavioral and EEG study investigated the production and perception of audiovisual gesture-speech utterances in the same set of individuals. First, we hypothesized that iconic gestures precede the speaker's spoken utterances thereby giving them predictive power. Second, we expected observers to be more tolerant to visual leading asynchronies in speech-gesture utterance perception. Further, they should be more sensitive to audiovisual asynchronies when listening to/watching their own gesture-speech utterances than that of other individuals. To

test these hypotheses, we recorded audio, video and kinematics when participants produced pre-defined action sentences together with an appropriate iconic gesture. Kinematic analyses showed that iconic gestures preceded and thereby potentially predicted the production of the action verb. Yet, their kinematics varied substantially between and within individuals. Next, the same participants were presented with a subset of those movies at variable audiovisual asynchronies in a simultaneity judgment task. As expected, we observed an asymmetry in the audiovisual temporal binding window. Observers were better at detecting asynchronies when the spoken words preceded the gestures and more tolerant to visual leading asynchronies. Critically, this temporal binding window was narrower when they were presented with audiovisual movies of themselves rather than another speaker, suggesting that asynchrony detection can be rendered more precise by prior sensorimotor experience involved in producing gestures-speech utterances. In a final electroencephalography (EEG) session, we investigated the neural mechanisms underlying audiovisual speech-gesture integration. Observers were presented with synchronous and asynchronous speech-gesture and unisensory auditory speech stimuli – again produced by themselves and others. Multivariate EEG decoding techniques will assess to what extent iconic gestures speed up speech comprehension by predicting semantic content prior to the occurrence of the action word they relate to, and whether or not this brain mechanism of semantic facilitation relies on individuals' sensorimotor experience, clarifying the critical role of gestures in audiovisual communication.

Disclosures: **T. Vercillo:** None. **U. Noppeney:** None. **J. Holler:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.21

Topic: D.08. Multisensory Integration

Support: NIH-R01HD062744(David Reinkensmeyer), University of California
NSF Award # 1532239
NIH P41-EB018783-07 (J.R.Wolpaw)
Stratton VA Medical Center
NYS Spinal CordInjury Research Board (J.R.Wolpaw).

Title: Neural Correlates of Bilateral and Unilateral Proprioception in People with Musical Instrument Training

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Abstract: Introduction: Proprioception is crucial for adroit movements but its neural mechanisms are not fully understood. A better understanding can aid the development of therapies for sensory-motor therapy. Here, we used electroencephalography (EEG) to assess neural correlates of proprioception in dexterous-trained participants vs. controls in bilateral and unilateral hand-position tasks.
Methods: Twenty people-11 controls (3 f/8 m, 32.2±15.4 yrs) and 9 music-instrument skilled (3f/6m, 38.6±18.0 yrs; 8 piano/ 1 guitar; training of 30.9±17.9 yrs)-participated in two active proprioceptive tasks: i) bilateral hand-position-matching, and ii) unilateral hand-position-replication. A baseline hand-movement task without proprioceptive matching was also conducted. Hands were not visible in all tasks. Motion tracking recorded hand movements. 32-channel EEG was acquired simultaneously (G.tec amplifier, BCI2000, 512 Hz). Auditory cues signaled movement onset. Based on literature, we assess event-related spectral perturbation (ERSP), specifically μ (8-12Hz) and low-β (12-18Hz) (Lβ) bands, in the contralateral sensorimotor region, at movement onset (200-400 ms) and offset (400-800 ms). We analyze proprioceptive accuracy and ERSP features between conditions (bilateral vs unilateral) and between groups (control vs. skilled). Wilcoxon signed rank and rank sum tests were used for comparisons, and Hedges' g for effect size. Data was collected with informed consent (University of Idaho, IRB).
Results: *Proprioceptive errors:* Skilled group had significantly smaller errors (15.9±8.7 mm) than controls (25.5±12.3 mm), ($p= 0.029$, $g= 2.00$); difference was significantly larger for the unilateral task ($p= 0.03$, $g= 1.94$).*Movement vs proprioception:* Skilled group had significantly less μ and Lβ power during proprioception, at onset (μ: $p= 0.01$, $g= 1.58$; Lβ: $p= 0.01$, $g= 1.32$) and offset (μ: $p= 0.002$, $g= 2.60$; Lβ: $p= 0.01$, $g= 1.88$), compared to controls at onset (μ: $p= 0.12$; Lβ: $p= 0.10$) and offset (μ: $p= 0.09$; Lβ $p=0.06$).
Bilateral matching vs position replication: Skilled group had no significant difference for μ and low-β suppression neither at onset (μ: $p=0.97$; Lβ: $p=0.59$) nor offset (μ: $p=0.85$; Lβ: $p=0.75$); whereas control group had a significant reduction in Lβ power during bilateral task at onset (μ: $p=0.14$; Lβ: $p=0.0005$, $g=1.13$) and offset (μ : $p=0.18$; Lβ: $p=0.002$, $g=1.37$).
Conclusion: Compared to controls, people with musical instrument training show: a) higher proprioceptive accuracy, b) reduced μ and Lβ power during proprioceptive matching compared to active hand movement, and c) less difference in μ and Lβ power for bilateral vs unilateral proprioception.

Disclosures: S. Rueda: None. **J.C. Perry:** None. **E.C. Wolbrecht:** None. **D. Gupta:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.22

Topic: D.08. Multisensory Integration

Support: NIH Grant DC016297
UR Del Monte Pilot Grant

Title: Visual speech tracking and linguistic processing in Deaf individuals

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Abstract: Access to the visible articulations of speech benefits the neural processing and comprehension of audible speech signals. Visual speech can restore acoustic speech that is degraded by noise and provides strong predictions to the auditory system as to when speech will occur and what is being said. There is also evidence that the visual system does more than supplement the auditory system during speech perception. Previously we've shown that the visual system does its own linguistic analysis and that this process is related to lipreading performance. However, these findings were based on data collected in normal hearing subjects, leaving open the possibility that the visual system is recapitulating a linguistic representation borrowed from auditory cortex. Moreover, little is known about how visual speech is processed in individuals that rely on lipreading for speech comprehension. To address these questions, we recorded high-density EEG from Deaf individuals while they lipread continuous, naturalistic, visual-only speech. In addition to natural speech, we also presented time-reversed speech and speech where the form of the lips was masked but their temporal dynamics were preserved. We analyzed EEG responses based on the motion signals present across the entire frame, the lip movements themselves, and the linguistic signals embedded in the speech. These analyses within a Deaf sample and their comparison to hearing individuals provide insight into how visual cortex is capable of linguistic processing independent of prior acoustic experience.

Disclosures: A.R. Nidiffer: None. **M.W.G. Dye:** None. **E.C. Lalor:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.23

Topic: D.08. Multisensory Integration

Support: Institutional funds from Penn State College of Medicine

Title: Understanding selective adaptation and the McGurk effect

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Abstract: In the McGurk effect (McGurk & MacDonald, 1976) visual speech presented concurrently with incongruent auditory speech can influence how speech is heard (e.g. auditory 'ba' + visual 'da' is heard as 'da'). A compelling example of multisensory integration, substantial research indicates that the McGurk effect is robust and occurs early in perceptual processing. One exception to this research concerns phonetic selective adaptation in which

repetitive exposure to a phonetic category exemplar shifts a perceiver's phonetic boundaries to be closer to the presented category. For example, after repeated exposure to audio-only 'ba', listeners identified fewer items that were intermediate between 'ba' and 'da' as 'ba' (Roberts & Summerfield, 1981). The same study also found that, despite reliably producing illusory perceptions of 'da', repeated exposure to a McGurk stimulus produced selective adaptation to the unperceived auditory channel, 'ba'. This finding is generally taken as evidence that selective adaptation reflects perceptual operations that occur prior to multisensory integration, a challenge to accounts that assume multisensory integration is complete early during perception. The objective of this research was to better understand the relationship between the McGurk effect and selective adaptation. Following an a priori power analysis 24 participants (6 male) completed 3 selective adaptation sessions; audio-only 'ba', visual-only 'da', and a McGurk auditory 'ba' + visual 'da' (separate days, counterbalanced order). Results show that the McGurk stimulus produced a selective adaptation effect directionally similar to the adaptation effect of the audio-only 'ba', replicating prior work (i.e. Roberts & Summerfield, 1981). Interestingly, the adaptation effect produced by McGurk stimuli was significantly smaller than the adaptation effect produced by audio-only stimuli. Moreover, this effect also interacted with individual differences in the McGurk effect, with differences between adaptation produced by audio-only and McGurk adaptors being greater for participants for whom the McGurk illusion was more reliable. This finding suggests that, contrary to prior conclusions, phonetic selective adaptation may be sensitive to multisensory integration.

Disclosures: **J. Dorsi:** None. **L.D. Rosenblum:** None. **S. Zadoorian:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.24

Topic: D.08. Multisensory Integration

Title: Visual speech processing interfaces with areas selective for spoken words in ventral and dorsal speech pathways

Authors: *L. CHANG[1], S. R. DAMERA[1], B. W. STEVENS[2], S. P. EBERHARDT[3], E. AUER, Jr.[4], L. E. BERNSTEIN[4], M. RIESENHUBER[1];
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Abstract: Perceiving spoken speech typically involves auditory (i.e., spoken words) and visual cues (i.e., lipreading). Cortical models of auditory processing propose an architecture consisting of ventral and dorsal streams (Rauschecker & Scott, 2009; Hickok & Poeppel, 2007). For auditory speech processing, the ventral pathway is specialized for spoken word recognition; recent evidence supports the existence of an auditory word form area (AWFA) in the anterior

superior temporal cortex (aSTC) with neuronal populations tightly tuned to whole spoken words (DeWitt & Rauschecker, 2012; Damera et al., SFN, 2022), paralleling the visual word form area for reading. In contrast, the dorsal stream is thought to map speech sounds to articulatory networks via areas such as the posterior STC (pSTC) and the premotor cortex (PMC; Wilson et al. 2004). In contrast to auditory speech, the pathways underlying visual speech processing are still poorly understood. Prior research has shown that the so-called temporal visual speech area (TVSA) in the ventral pSTC responds more to visual speech than non-speech gestures (Bernstein et al., 2011; Bernstein & Liebenthal, 2014). Yet, it is unclear if and how the TVSA interfaces with the dual-stream pathways for speech processing. We hypothesized that visual speech interfaces with both streams — activating the AWFA and PMC, as well as coupling between these areas and the TVSA. To test our hypotheses, we first conducted two localizer scans to identify regions-of-interests (ROIs) individually in 15 subjects: an auditory word localizer probing selectivity for spoken real words, pseudowords, and scrambled words, and a visual speech localizer (based on Bernstein et al., 2011) consisting of a one-back task with stimulus blocks comprising speech, non-speech facial gestures (e.g., gurn, chew, smile), or scrambled speech and non-speech gestures. To define the ROIs, we used contrasts reflecting selectivity for auditory and visual speech to isolate clusters for the PMC, AWFA, and TVSA. Supporting our hypotheses, we found activation in all three ROIs during visual speech processing — with the AWFA showing selectivity for visual speech over gestures ($p=0.02$) like the TVSA ($p<0.01$) — as well as significant functional connectivity between the TVSA and the PMC and AWFA ($p<0.05$). Our findings provide further insight into how visual speech processing involves coupling with the dual-stream auditory speech network: integration in the dorsal stream could subserve the learning of speech articulation as part of an inverse model (Chevillet et al., 2013), whereas integration in the ventral stream is compatible with this stream's role as the speech comprehension pathway.

Disclosures: **L. Chang:** None. **S.R. Damera:** None. **B.W. Stevens:** None. **S.P. Eberhardt:** None. **E. Auer:** None. **L.E. Bernstein:** None. **M. Riesenhuber:** None.

Poster

716. Cross-Modal Processing Including Language and Music

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 716.25

Topic: D.08. Multisensory Integration

Support: NRF of Korea, Basic Science Research Program (2020R1A2C2007770)
NRF of Korea, Basic Science Research Program (2019R1A2C2005213)
NRF of Korea, Basic Science Research Program (2020R1A4A1018714)
NRF of Korea, Neurological Disorder Research Program (2020M3E5D9079913)
SNU, Creative-Pioneering Researchers Program

Title: Neural representation of tactile and visual braille during cross-modal working memory

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Abstract: The human ability to predict the tactile sensation of an object they see or to visualize an object being touched is particularly useful when one of the sensory modalities is inaccessible. The neural process of transformation from one sensory modality to another should be essential to this ability. Prior studies have shown that the intraparietal sulcus (IPS) and superior parietal lobule (SPL), located between the visual cortex and the somatosensory cortex, are involved in the integration process of the two sensory modality information. However, the nature of the information processed in these regions during cross-modal transfer remains unclear. To investigate the neural representations during the cross-modal transfer process, we measured cortical responses based on functional magnetic resonance imaging while participants performed delayed match-to-sample tasks. In the tasks, the participants were asked to maintain a tactile or visual braille stimulus and had to determine whether the tactile or visual braille given at the test phase matched the maintained tactile or visual braille. Most participants were successful in retaining the tactile or visual information during the delay in both within-modality tasks (visual-to-visual or tactile-to-tactile) and cross-modality tasks (tactile-to-visual or visual-to-tactile). While braille identity could be decoded from the neural responses in the IPS and SPL during the delay period in both within-modality and cross-modality tasks, the level of decoding was greater in the cross-modality tasks than in the within-modality tasks. Moreover, significant common representations for individual braille stimuli between tactile and visual modalities were found in the IPS and SPL. These results suggest that cross-modal stimulus features are retained and utilized in the parietal associate cortex including IPS and SPL during cross-modal transfer process.

Disclosures: D. Park: None. **Y. Ryoo:** None. **K. Lee:** None. **S. Hwang:** None. **H.F. Kim:** None. **S. Lee:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.01

Topic: E.01. Eye Movements

Support: NIH Grant EY014263
NIH Grant EY032066
NIH Grant P30 EY003039

Title: Electrical microstimulation of the central mesencephalic reticular formation (cMRF) elicits disjunctive saccades in the rhesus monkey

Authors: *J. J. QUINET[1], K. SCHULTZ[2], P. J. MAY[3], P. D. GAMLIN[2];
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Abstract: The vast majority of orienting gaze shifts performed by primates are to targets that lie at both a different distance and eccentricity than the current eye position. Therefore, typical eye movements consist of both a change in the vergence angle between the eyes and a change in conjugate gaze angle. These two categories of eye movement occur simultaneously, but have distinct neural properties, as well as complex interactions, that are still poorly understood. Earlier studies of the cMRF found that electrical microstimulation evoked contralateral conjugate saccades (Cohen et al. 1986) or, at some sites, disjunctive eye movements (Waitzman et al. 2008). Based on our recent anatomical studies (May et al. 2019), we hypothesized that the cMRF plays a role in controlling not only saccades and vergence, but also their interaction. Our recent cMRF recording experiments have confirmed this role by demonstrating the existence of not only near and far response neurons, but also a previously undescribed cell class, saccade-vergence burst neurons, that discharge only during disjunctive saccades (Quinet et al. 2020). The present study further investigates the role played by the cMRF in disjunctive saccades. We studied the effects of electrical microstimulation when an animal fixated at different distances. Binocular eye movements were recorded using the scleral eye coil technique. A monkey was trained to perform a variety of eye movements and to fixate targets located either on a tangent screen (95 cm away) or a LED located from 15 to 60 cm away. Electrical microstimulation was applied in the cMRF at sites where near/far responses were encountered. Stimulation was applied when the monkey was fixating a far or a near target, or during ongoing symmetric vergence movements. The initial horizontal eye position was varied during near target fixation. We found 38 sites at which contralateral conjugate saccades were evoked when the animal was fixating the far target (95 cm). At 20 sites, when the animal's eyes were converged, electrical stimulation evoked divergent disjunctive saccades that were unaffected by initial horizontal eye position. Further, as convergence angle increased to view nearer initial fixation targets, the evoked saccadic amplitude inequality also increased. At a few sites, when the stimulation was applied during ongoing symmetric vergence eye movement, a disjunctive saccade was evoked. The results provide additional evidence supporting the hypothesis that the cMRF is involved not only in the control of conjugate saccades, but also in the binocular control of disjunctive saccades through projections to both the supraoculomotor area and extraocular motoneurons.

Disclosures: J.J. Quinet: None. **K. Schultz:** None. **P.J. May:** None. **P.D. Gamlin:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.02

Topic: E.01. Eye Movements

Support: Deutsche Forschungsgemeinschaft HO 1639/5-1
Graduate School of Systemic Neurosciences (GSN)
Deutsche Forschungsgemeinschaft CRC 870

Title: Histochemical correlates of firing characteristics in the oculomotor system of rhesus monkey

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Abstract: Quick and accurate eye movements are achieved through precise and well-timed firing of various neurons in the oculomotor circuit, which is determined by their cell characteristics. To date, intrinsic membrane properties of motor and premotor neurons for saccade generation have not been studied in monkey brainstem. Motoneurons (MNs) of extraocular muscles are classified by their innervation of slow contracting, fatigue-resistant multiply-innervated (MIF) or fast-contracting, fatigable singly-innervated (SIF) fibers. A previous concept that MIF MNs mediate slow eye movements or gaze holding, whereas SIF MNs generate fast eye movements, has been challenged recently. Electrophysiological recordings in cat revealed that both groups are active for all eye movements with a burst/tonic discharge, albeit with different dynamic properties. Therefore, our first aim was to establish ion channel and transmitter profiles of SIF and MIF MNs to investigate their differences. Our second aim was the investigation of intrinsic membrane properties of premotor burst neurons (BNs), which relay calculated saccadic signals to MNs. BNs supposedly express low-voltage activated (LVA) cation channels, which produce post-inhibitory rebound bursting phenomenon. The overarching aim of this study was therefore to establish the histochemical profiles of oculomotor neurons with respect to their fast-firing and bursting capacity. Therefore, we evaluated the expression of proteins regulating firing patterns of MNs and BNs in the monkey brainstem with immunohistochemistry. We showed that voltage-gated potassium channels Kv1.1&Kv3.1 were expressed in fast-firing neurons of the saccadic circuitry; including tonic-firing omnipause and vestibular Y- group neurons, but not in MIF MNs. Moreover, MIF and SIF MNs differed in their LVA channel (Cav3.1& HCN1) expression. Lastly, excitatory BNs of the vertical and inhibitory BNs of the horizontal saccades similarly expressed LVA channels, as suggested by neuromimetic models of eye movements. According to these models, saccadic disorders such as progressive supranuclear palsy are explained by a dysfunction of LVA channels in BNs. Here, we provided the histochemical substrate for this hypothesis. Overall, this research solidified histochemistry as a valid tool of assessing physiological properties of various neurons in the monkey ocular motor system. This enables post-mortem evaluation of human clinical cases with saccadic disorders. Establishing histochemical profiles of different neurons, related to their firing patterns, will pave the way for pharmacological treatments of oculomotor symptoms in a variety of disorders.

Disclosures: Ü.S. Mayadali: None. **C. Zeeh:** None. **H. Straka:** None. **A.G. Shaikh:** None. **A.K. Horn-Bochtler:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.03

Topic: E.01. Eye Movements

Title: Concurrent programming of voluntary and involuntary saccades in the primate frontal eye field

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Abstract: Classical views hold that there exists a saliency map in the brain which determines the location of a saccade in a winner-take-all fashion, i.e., once a saccade program is made, it cannot be overwritten. However, there is mounting evidence that the appearance of a sudden-onset distractor in a display shortly before saccade initiation can capture spatial attention and modulate saccade trajectory, even though the initial plan has already been made to move the eyes straightly elsewhere. This unresolved competition as a consequence of concurrent programming of a voluntary saccade to the defined saccade target and an involuntary saccade to the sudden onset can lead to saccades curved towards or away from the distractor depending on temporal factors. In order to better understand the neural mechanisms underlying such concurrent programming and curved saccades, we recorded from single neurons in the FEF of two rhesus monkeys shifting gaze to a target while an isoeccentric distractor appeared either left or right of the target at various moments after target presentation, (distractor-target onset asynchrony). We found that saccades curved toward or away from competing distractors as function of distractor-target onset asynchrony relative to saccade reaction times (RT)—the longer the distractor processing time, the more saccades curved away from the distractor, and the shorter the distractor processing time, the more saccades curved toward the distractor. Moreover, the average population activity of the FEF neurons (n=104) in a brief pre-saccadic interval was correlated with the amount of saccade curvature toward the distractor in the response field or away from the distractor outside of the motor field. Contrary to the view that covert attention plays no role in saccade generation once a saccade is programmed, our results revealed that monkeys' attention can be captured to more than one location in a display during saccade preparation. Investigating the FEF neural activity also supported the notion that the oculomotor target selection is not a complete winner-takes-all process. A distractor can transiently coactivate a competing saccade which is integrated with the primary target's saccade, ultimately leading to curved saccade. It remains to be further investigated how various types of FEF neurons (visual, visuomotor, motor) contribute to the programming of curved saccades.

Disclosures: H. Ramezanpour: None. **J. Schall:** None. **M. Fallah:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.04

Topic: E.01. Eye Movements

Support: F31EY033667

Title: The influence of reward expectations and motor planning on visuomotor responses in the primate frontal eye field

Authors: *A. ALERS[1], M. A. SOMMER[2];
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Abstract: Frontal eye field (FEF) visual responses are sensitive to the relevance of a stimulus to eye movements. These visual responses are also modulated by reward. However, it is unclear whether neurons are sensitive to both factors independently or if sensitivity to one drives the influence of the other. We recorded from neurons in the FEF of a monkey while it performed a Go/NoGo delayed saccade task. On Go trials, the animal made a delayed saccade into the receptive field of the neuron. In NoGo trials, the stimulus disappeared at the end of the delay period, instructing the animal to maintain fixation. Across blocks of trials, we altered either the ratio of Go to NoGo trials, the delay between stimulus onset and Go/NoGo signal, or the ratio of liquid reinforcement on Go to NoGo trials. We compared activity in the fixation, visual, and premotor periods between each condition and a baseline block preceding it. We found that visuomotor activity was modulated significantly and distinctly by each condition. Our early results suggest that the effects of changes to saccade probability or timing are modest compared to those of a change in reward ratio between Go/NoGo trials. Our results provide evidence that FEF neurons may be more sensitive to expectations of reward than movement.

Disclosures: A. Alers: None. **M.A. Sommer:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.05

Topic: E.01. Eye Movements

Support: NIH Grant EY030667
NIH Grant EY022854

Title: Spatiotemporal features of population activity in monkey superior colliculus during saccades to stationary and moving targets

Authors: *F. YANG, C. BOURRELLY, N. J. GANDHI;
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Abstract: The Superior Colliculus (SC) is a laminar subcortical structure essential for converting visual inputs into motor commands for eye movement generation. Neurons in the intermediate layer of SC burst spikes when a visual stimulus is presented in their response field and when initiating a movement of that vector. The SC also has a topological structure in each layer. When presenting a stationary visual stimulus, the population movement response is represented as a Gaussian mound of activity centered at the respective location on the SC map. However, it is unclear how the population activity evolves for interceptive saccades directed to a moving target. Previous single electrode studies have demonstrated that the movement fields of individual neurons shift for interceptive saccades and that the shift depends on target speed and motion direction. One hypothesis is that the population activity in SC still encodes the interceptive saccade, likely through a profile that is skewed form of a Gaussian mound. Another hypothesis is that downstream structures are needed to encode the amplitude correctly. In this situation, the center of the population activities is shifted for different target conditions while likely preserving the Gaussian shape. We investigated the population activity in the intermediate layer of SC of two monkeys producing interceptive saccade towards a target moving at different speeds and in various directions. Neural activity was recorded along the dorsoventral axis of SC with a multi-contact laminar electrode. We used the movement field and stimulation parameter to determine the locations of the neurons and combined neurons recorded on different days together with a normalization method to generate the population activity in the SC map. Our preliminary result shows that the population activity lags when a moving target is presented. When the target starts in the periphery and moves inward toward fixation, the population activity is on the caudal side of the SC compared to the stationary saccade of the same amplitude. For outward target motion, the population activity is on the rostral side of the SC. The population activity lags more with a higher speed target. Preliminary result shows that the shape of the population activities also changes compared to the stationary target condition, although further analysis is needed for confirmation. We also investigated the visual response of the SC during target motion and observed propagation in the SC map as the target image sweeps across the retina.

Disclosures: F. Yang: None. **C. Bourrelly:** None. **N.J. Gandhi:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.06

Topic: E.01. Eye Movements

Support: NIH Grant R01-EY030669

Title: Enhancement of superior colliculus activity associated with saccades to an extended object

Authors: *C. CONROY[1], H. ADELI[2], A. LEITE[3], G. J. ZELINSKY[3], R. M. MCPEEK[1];
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Abstract: Superior colliculus neurons were recorded while rhesus monkeys made saccades to locations orthogonal to the cells' response fields. The saccade goal was an exogenous cue presented either overlapping a larger figure that extended into the cell's response field (single-figure condition) or at the same location but overlapping a second smaller figure, disconnected from a larger figure, which extended into the cell's response field (multi-figure condition). In the multi-figure condition, the smaller figure (i.e., the figure at the saccade goal) was created by introducing a discontinuity into the larger figure from the single-figure condition. This discontinuity was introduced far outside the response field of the recorded cell to ensure that the response-field stimulus was the same in both conditions. We found that the cell's activity was enhanced in the single- versus multi-figure condition: that is, when the saccade goal was connected to a figure that extended into the cell's response field, saccades were associated with enhanced peri-saccadic activity compared to when the same saccade was made with the same response-field stimulus but the saccade goal was disconnected from the figure in the response field. This suggests that the primate superior colliculus represents saccade goals in terms of visual perceptual objects rather than (or in addition to) particular locations in space. This further suggests that, in addition to its role in visual spatial attention, the superior colliculus may play a role in object-based shifts of attention, at least when the object to be attended is the target of an impending saccade.

Disclosures: C. Conroy: None. **H. Adeli:** None. **A. Leite:** None. **G.J. Zelinsky:** None. **R.M. McPeek:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.07

Topic: E.01. Eye Movements

Support: Dept. of Physiology and Biophysics collaborative grant

Title: Dissecting the circuit for saccadic suppression in mouse SC

Authors: *J. HUNT, A. POLEG-POLSKY, G. FELSEN;
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Abstract: Virtually all animals, including mice, 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 more 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. 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 across the visual-motor axis of the SC while mice made SC-dependent saccades. Headfixed mice were placed within an immersive visual arena and shown a low-contrast sinusoidal 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 extra-saccadic visual responses. We found that a subset of visually-responsive SC neurons exhibited suppression around the time of saccades. These data are the first to demonstrate that visual responses 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. **A. Poleg-Polsky:** None. **G. Felsen:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.08

Topic: E.01. Eye Movements

Support: NIH Grant EY024831
NIH Grant EY030667
NIH Grant EY022854

Title: Sensorimotor transformation along the dorsoventral axis of the superior colliculus: onset analysis of spiking activity and local field potentials

Authors: *C. BOURRELLY, N. J. GANDHI;
Univ. of Pittsburgh, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The superior colliculus (SC) is essential for mediating visually-guided saccades. It is well known that the SC is functionally organized along it dorsoventral axis: neurons in superficial layers present a visual response, neurons in deeper layers exhibit a movement response, and neurons in intermediate layers show both visual and movement responses. It is commonly accepted that the spiking activity is the output of neurons, while the nature of the

local field potential (LFP) is still debated. One hypothesis is that they can represent the input. Indeed, it has been shown that in cortical regions, the onset of LFP fluctuation precede the spikes during the sensory response, whereas the spikes lead the LFP modulations during the motor response. We tested whether similar onset order is also present in the SC and, furthermore, whether the effect varied with the depth or type of SC neurons. Using multi-contact laminar electrode inserted orthogonal to the SC surface, we simultaneously recorded across depth spiking and LFP activities in two rhesus monkeys performing a visually guided delayed saccade task. Since neurons along the dorsoventral axis have similar optimal response fields, we focused our analysis on trials in which the stimulus was presented near this location. At each depth, both spiking activity and LFP waveforms exhibited similar temporal profiles, particularly in the visual epoch. In accordance with our prediction, the categorization of the LFP across depth revealed a visual preference for the most superficial layers, a movement preference for the deeper layers, and both visual and movement responses for intermediate layers. Interestingly, the switch from visual to motor preference occurred on deeper channels for the LFP signal. The average and the trial-by-trial analysis of the relative timing between the onset of LFP modulations and the onset of the spiking activity revealed a depth-dependent effect. The LFP modulation seemed to occur slightly earlier than, or at least at the same time as the visual burst on superficial layers. During the motor epoch, the motor burst strongly leads the LFP onset for deeper layers. Collectively, the relative timing of transient changes in LFP and spiking activities follow the order reported in visuo-oculomotor regions in the cortex, although the lead in LFP modulation during the visual response is much smaller. All together, these results are consistent with the hypothesis of the input-output transformation in the SC.

Disclosures: C. Bourrelly: None. **N.J. Gandhi:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.09

Topic: E.01. Eye Movements

Support: NIH Grant EY024831
NIH Grant EY030667
NIH Grant EY022854
NIH MH 5R90DA023426-15 Interdisciplinary Training in Computational Neuroscience

Title: Contextual effects on population representation of sensory and motor responses in the superior colliculus

Authors: *E. AYAR[1], M. R. HEUSSER[2], C. BOURRELLY[1], N. J. GANDHI[1];
[1]Univ. of Pittsburgh, [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Sensorimotor transformation is the process of first sensing an object in the environment and then producing a movement in response to that stimulus. For visually-guided eye movements, known as saccades, neurons in the superior colliculus (SC) emit a burst of spikes to register the appearance of a visual stimulus and many of the same neurons discharge another burst to initiate an eye movement. We investigated whether the neural signatures of sensation and action in SC depend on context. Unlike previous studies that considered this question with a focus on individual neurons, we examined the population response. Spiking activity along the dorsoventral axis was recorded with a laminar probe as Rhesus monkeys generated saccades to the same stimulus location in tasks that require either executive control to delay saccade onset until permission is granted or the production of an immediate response to a target whose onset is predictable. Using dimensionality reduction and discriminability methods, we first verified that the subspaces occupied during the visual and motor epoch were distinct within each task. Surprisingly, the low-dimensional spaces spanned by sensation and action epochs were also differentiable across tasks. These results imply that cognitive processes associated with task requirements are multiplexed in SC population activity during both sensation and action, and that downstream structures could use this activity to extract cognitive context. They also suggest that the entire manifolds associated with sensory and motor responses, respectively, may be larger than the subspaces explored within a certain set of experiments.

Disclosures: E. Ayar: None. **M.R. Heusser:** None. **C. Bourrelly:** None. **N.J. Gandhi:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.10

Topic: E.01. Eye Movements

Support: UWM research Growth Initiative Award

Title: Intra- and Inter-individual variation in saccade accuracy and motor attention fields in human parietal cortex

Authors: *W. E. HUDDLESTON[1], M. PENNING[1], L. SODERBECK[1], A. S. GREENBERG[2], E. A. DEYOE[3];
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Abstract: One critical component of voluntary saccadic eye movements is the planning of saccade trajectory. Selecting a particular movement, out of many options, may occur through an attentional mechanism. We, and others, have previously demonstrated the existence of such a topographic map of intended saccade trajectories in human parietal cortex. A primary aim of this

study was to identify the relationship between eye movement accuracy and motor attention fields (MAFs) found in human parietal cortex. An MAF represents the macroscopic spatio-temporal pattern of attentional modulation distributed across the entire expanse of a neural map of possible saccade trajectories. fMRI can be used to record the modulatory effect experienced by single voxels (population motor attention field, pMAF) within such a map and, via computational modeling, estimate the macroscopic topography of the MAF. Thirty-four participants (7 males, 32.7 years, range 20-54 years) completed a delayed saccade task during fMRI at 3T (GE Premier). Concurrently, we recorded eye movements (Eyelink 1000; SR Research) to determine initial saccade accuracy. Participants selectively attended to a centrally presented RSVP stream surrounded by 24 static peripheral targets (radius 8°). Every 4 s, a letter 'N' appeared in the central RSVP stream to cue the participant to prepare a saccade to the next target in the clockwise direction, creating a drifting focus of motor attention (i.e., saccade intention) across the saccade trajectory map. However, participants delayed saccade execution until a rarely presented letter 'X' appeared in the RSVP stream (approx. 4-5 times per run for a total of 19 saccades to unique targets). Seventy-two percent of participants with usable eye-tracking data (n=29) demonstrated excellent shifting of motor attention throughout the task, with 88% of saccades located spatially within one target of the cued location. fMRI data were used to constrain a model of the size and shape of the motor attention field, the voxel's pMAF. Parameters used in the analysis included fit (correlation coefficient), SNR, and field diameter. Consistent with the variability observed both within and between participants on saccade endpoint accuracy, pMAF parameters also varied considerably. The relative distribution of the location and parameters of the pMAFs support the notion of an attentional process computationally aiding in the selection of voluntary eye movements. Our results also highlight the importance of individual differences when determining potential cortical correlates of behavior.

Disclosures: W.E. Huddleston: None. **M. Penning:** None. **L. Soderbeck:** None. **A.S. Greenberg:** None. **E.A. DeYoe:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.11

Topic: E.01. Eye Movements

Support: Australian Research Council (DE180100344)
Australian Research Council (DP200100179)
National Health and Medical Research Council of Australia (APP1185442)
Australian Government Research Training Program (RTP) Stipend Scholarship

Title: Topgraphic and laminar organisation of saccade-related response field properties in the marmoset posterior parietal cortex

Authors: *J. F. D'SOUZA[1], S. L. CLOHERTY[2], N. S. C. PRICE[1], M. A. HAGAN[1];
[1]Physiol., Monash Univ., Melbourne, Australia; [2]Engin., RMIT Univ., Melbourne, Australia

Abstract: The posterior parietal cortex (PPC) has been implicated in the control of visual behaviours such as saccadic eye movements. However, the topographic organisation of the PPC has been notoriously difficult to rigorously study in macaques, as many areas are embedded in sulci. Fortunately, the common marmoset (*Callithrix jacchus*) is a promising new model for exploring the saccade-related response field properties in PPC, specifically related to the existence of stereotypical topographic and columnar organisational patterns of saccade direction tuning. The lissencephalic marmoset cortex offers a solution to the traditional problem of accessibility, and recent studies have confirmed that they can be trained to perform visual behaviours, such as saccades, in a manner comparable to macaques. Here, we present preliminary findings from a single male marmoset, trained to reliably saccade to 8 equally spaced target locations (at 5 degrees eccentricity) around the visual field (performing an average of 300 trials per session), while implanted with a semi-chronic 32-channel laminar array (100um contact spacing), allowing simultaneous recordings across all layers of cortex. Across two arrays (each yielding approximately 5 weeks worth of data), a significant portion of task-responsive units were tuned for a particular saccade direction (array 1: 72%, 176/246 units, array 2: 16%, 58/357 units, $p < 0.05$, random permutation test, corrected for multiple comparisons). In both arrays, there were consistent depth dependent differences in saccade-related response field (RF) properties, such that the superficial and deeper parts of cortex were tuned to slightly different saccade directions compared to more intermediate depths. These depth dependent differences were also consistent across the 5 weeks of recordings in both arrays, supporting the existence of a columnar organisation of saccade direction tuning RF properties in PPC. Furthermore, given the close penetration proximity of these two arrays (approximately 0.5 mm apart), their partially overlapping RFs in the contralateral visual field indicate the existence of a stereotypical topographic organisation of saccade direction tuning in PPC. With additional penetrations sampling adjacent regions of cortex, we can accurately characterise the topographic and columnar organisational patterns of saccade-related RF properties in PPC.

Disclosures: J.F. D'Souza: None. **S.L. Cloherty:** None. **N.S.C. Price:** None. **M.A. Hagan:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.12

Topic: E.01. Eye Movements

Support: CIHR Project and Foundation grants
CIHR Fellowship
Christine Mohrmann Fellowship

Title: Effects of ketamine on the interaction between lateral prefrontal and posterior parietal cortices in macaque monkeys

Authors: *L. MA[1,2], K. D. JOHNSTON[3], S. EVERLING[4];
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Abstract: Acute administration of a subanesthetic dose of ketamine is an effective model for creating schizophrenia-like symptoms, such as working memory deficits, in non-human primates. Previously, we demonstrated an impairment in the performance of a rule-based working memory task involving pro- and anti-saccades. Correlated with this deficit was a reduction in rule information encoded in both spiking and oscillatory activities in the lateral prefrontal cortex (LPFC). Since working memory engages an extended network, it is critical to analyze how the dynamic interactions between brain regions influence the process in real time. Therefore, we simultaneously recorded both spiking activity and local field potentials from the LPFC and posterior parietal cortex (PPC) in two rhesus macaques as they performed the task, both before and after ketamine injection. Like in the LPFC, ketamine weakened oscillations in the alpha/low beta range (9-20Hz) in the PPC. Additionally, ketamine reduced spike-field consistency (SFC), estimated as the mean resultant length, both within and between the two regions. This effect was found in all frequency bands from theta to high gamma. To understand how ketamine affects rule coding, we calculated task selectivity, defined as the difference between mean resultant lengths associated with the two rules, divided by the sum across both rules. We found that task information was reduced in the SFC between LPFC spikes and PPC field potentials in the low gamma band. These results support a role of LPFC-PPC interaction in working memory.

Disclosures: L. Ma: None. **K.D. Johnston:** None. **S. Everling:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.13

Topic: E.01. Eye Movements

Title: Microsaccades to the midpoint between targets and attention-related changes in V4 neuronal activity

Authors: *S. WILLETT, J. MAYO;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Microsaccades are small, ballistic eye movements that occur during fixation and are thought to indicate the locus of covert attention. Attentional cues can alter the frequency, direction, and amplitude of microsaccades as well as modulate neuronal firing rates across visual

and oculomotor areas. Still, the precise relationship between covert visual-spatial attention and microsaccades is ambiguous, due in part to various experimental designs. Most studies probing the attention-microsaccade relationship present a visual cue on every trial that is 100% valid (always predictive). It is difficult to uncover the interaction between microsaccades and attention using this approach because it does not incorporate the dynamic cue validities and temporally unpredictable target changes that occur in naturalistic environments. Here, we analyzed how attentional cueing affected microsaccade behavior and how microsaccades modulated neuronal firing rates in area V4 of macaque monkeys.
Two monkeys were trained to perform an orientation change-detection task in which two Gabors were presented simultaneously. We recorded the activity of both the left and right V4 with 48 channel arrays (96 channels across both hemispheres) while monkeys maintained fixation until one of the two continuous and sinusoidally modulated Gabors changed in orientation (500-5500 ms, exponential distribution). The monkey reported detection of the orientation change by making a saccade to the changed target. Attention was visually cued to a particular location in space on instruction trials at the start of each trial block. Attention was visually cued to a location during instruction trials at the start of each block. During 'cued' blocks, the change occurred with 80% likelihood at the cued location and 20% likelihood at the other location. During 'neutral' blocks, visual cues were shown at both stimuli locations during instruction trials, and the change occurred at a 50% likelihood at each location.
We found that microsaccades from both monkeys were directed towards the midpoint between the two targets. In sessions that only contained 80/20% blocks the microsaccade direction was slightly biased towards the cued direction, and this bias was reduced in sessions that included neutral blocks. As expected, we observed modulation of V4 neuronal activity in the presence of microsaccades. Modulation of V4 activity depended on whether microsaccades were directed towards or away from the cued location and whether that location was within or outside of the neuronal receptive field. Our data suggests that the microsaccades are not a reliable measure of covert-visual spatial attention in more natural tasks.

Disclosures: S. Willett: None. **J. Mayo:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.14

Topic: E.01. Eye Movements

Support: H2020 European Research Council (imove 755745)

Title: Organization of reward and movement signals in the basal ganglia and cerebellum

Authors: *N. LARRY, G. ZUR, M. JOSHUA;
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Abstract: A hierarchical organization of the motor system suggests that along the motor circuitry, reward information is transformed into specific motor signals. Thus, we expect that areas at the top of the motor hierarchy will contain signals that are more closely related to reward whereas areas closer to the motor periphery will contain signals related to the details of movements. In accordance, the basal ganglia are thought to be more closely linked to reward processing whereas the cerebellum is more closely linked to the kinematic details of behavior. Recent findings of reward signals in the cerebellum challenge this view. Although cerebellar reward signals resemble those in the basal ganglia, the comparison is problematic since previous studies probed activity in areas that control different behaviors and in different animals. Here we compared the coding of motor and reward signals directly in both areas to study how reward and movement signals are organized in the motor circuitry.
We recorded from eye-movements related areas in the basal ganglia and cerebellum of the same monkeys while they were performing saccade and smooth pursuit tasks in which we manipulated reward probability. We recorded from Purkinje cells and other neuron types from the oculomotor cerebellar vermis, and two areas within the basal ganglia: the caudate and the substantia nigra pars reticulata (SNpr). To compare these populations, we partitioned single-neuron activity into reward expectation, reward outcome, and movement components.
On a global scale, consistent with a hierarchical organization of the subcortical networks, the basal ganglia coded the expectation of reward, while the reward expectation signals in the cerebellum were relatively small. However, at a more local scale, reward information in the basal ganglia increased rather than decreased between the input and output structures. In contrast to a hierarchical organization, the SNpr, and not the cerebellum, had the most pronounced coding of eye movement direction, both during saccades and pursuit. During reward delivery, reward signals between the basal ganglia and the cerebellum were comparable.
Thus, responses in the basal ganglia and cerebellum are not organized hierarchically to transform reward information into movement. Instead, the larger responses in the basal ganglia suggest that it is a part of the network that drives eye movement whereas the cerebellar vermis modulates eye movement. This modulation could be necessary to fine-tune behavior or correct errors.

Disclosures: **N. Larry:** None. **G. Zur:** None. **M. Joshua:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.15

Topic: E.01. Eye Movements

Support: PGC2018-094654-B-100 supported by MCIN/AEI/10.13039/501100011033, FEDER
P20_00529 Consejería de Transformación Económica, Industria y Conocimiento, Junta de Andalucía-FEDER

Title: Vegf is an essential retrograde trophic factor for motoneurons

Authors: P. M. CALVO, R. G. HERNÁNDEZ, R. R. DE LA CRUZ, *A. M. PASTOR;
Univ. De Sevilla, Univ. De Sevilla, Sevilla, Spain

Abstract: VEGF was initially discovered due to its angiogenic activity and therefore named vascular endothelial growth factor. However, its more recently discovered neurotrophic activity may be evolutionarily more ancient. Our previous work showed that all the changes produced by axotomy on the firing activity and synaptic inputs of abducens motoneurons were completely restored after VEGF administration. Therefore, we hypothesized that the lack of VEGF delivered by retrograde transport from the periphery should also affect the physiology of otherwise intact abducens motoneurons. For VEGF retrograde blockade, we chronically applied a neutralizing VEGF antibody to the lateral rectus muscle. Recordings of extracellular single-unit activity and eye movements were made in alert cats before and after the application of the neutralizing antibody. Our data revealed that intact, non-injured abducens motoneurons retrogradely-deprived of VEGF exhibited noticeable changes in their firing pattern. There is a general decrease in firing rate and a significant reduction in eye position and eye velocity sensitivity, i.e., a decrease in the tonic and phasic components of their discharge, respectively. Moreover, by means of confocal immunocytochemistry, motoneurons under VEGF blockade showed a marked reduction in the density of afferent synaptic terminals contacting with their cell bodies. Altogether, the present findings demonstrate that the lack of retrogradely delivered VEGF renders abducens motoneurons into an axotomy-like state. This indicates that VEGF is an essential retrograde factor for motoneuronal synaptic drive and discharge activity.

Disclosures: P.M. Calvo: None. **R.G. Hernández:** None. **R.R. de la Cruz:** None. **A.M. Pastor:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.16

Topic: E.01. Eye Movements

Support: Smith-Kettlewell Eye Research Institute

Title: A new model of binocular control demystifies the ‘remarkable saccade’

Authors: *S. HEINEN, A. CHANDNA, D. SINGH, S. N. WATAMANIUK;
Smith-Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: Most eye movement models have a single input, and generate a single command that drives both eyes. This architecture is based on Hering’s laws depicting a unitary command that rotates the eyes conjugately, and another unitary command that rotates them oppositely for vergence. Unitary commands are assumed for strabismus diagnosis and intervention, and are reflected in the documented physiology of oculomotor structures. However, our recent results during monocular viewing cast doubt on a unitary vergence command as they show

asynchronous rotation of an occluded eye during midline vergence (Chandna et al., 2021). Theoretical independent control of each eye could substitute for vergence, but pure independent control fails to account for inappropriate conjugate rotations during asymmetric vergence to targets aligned on one eye (The Remarkable Saccade; Enright, 1992), neither can it account for established sluggish midline vergence. Here we introduce a hybrid model incorporating elements of both conjugate and independent control. The core of the model is a rapid conjugate system that outputs a unitary command with a brainstem origin. Mutual inhibition is incorporated between rightward and leftward conjugate components. In parallel with the conjugate system, slow, independent, right and left eye controllers located in cortex generate signals that sum with the conjugate ones to generate vergence and other asymmetric eye movements. The model incorporates a "virtual" target to inform an unseeing covered eye about the target. Negative feedback acts on perception, as evidence suggest that eye movements minimize location error to the perceived and not retinal targets. The model generates rapid saccades, asymmetric eye movements, slow midline vergence and inappropriate rotations like the remarkable saccade. The results suggest separate right and left eye signals are generated by cortical structures, and that vergence anomalies could be caused by dysfunction of these controllers.

Disclosures: S. Heinen: None. **A. Chandna:** None. **D. Singh:** None. **S.N. Watamaniuk:** None.

Poster

717. Neural Mechanisms of Visual Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 717.17

Topic: E.01. Eye Movements

Title: Memory-guided saccade variability in Parkinson's disease

Authors: *L. JIANG, H.-C. LEUNG;
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Abstract: Saccadic eye movements engage a distributed network of brain areas that are under complex neurochemical modulation. Whilst numerous studies examined the mean tendency of saccades, the variability of saccadic behavior and its neural basis is still poorly understood. Here we use Parkinson's disease (PD) as a model to investigate the dopaminergic (DA) modulation of memory-guided saccades (MGS) in comparison to visually-guided saccades (VGS). We recorded eye movements in 13 early-stage PD patients on (PD ON) and off (PD OFF) their DA medication and 12 age-matched healthy controls (HC) while they performed MGS and VGS tasks. Analysis of primary saccade latency and endpoint error of MGS revealed several disease and medication effects. First, relative to HC, PD exhibited greater variability but similar mean errors in MGS endpoint distribution. Second, latency distribution was more variable in PD ON than in PD OFF and HC. Intriguingly, both prolonged mean latency and more frequent short-latency express saccades (< 150 ms) were observed for the MGS condition. Third, both PD and

HC showed trial-by-trial saccade endpoint error and gain as a nonlinear function of saccade latency, with error decreased and gain increased with latency up to 150-200 ms and then plateaued. Compared to PD ON and HC, PD OFF showed more hypometric short-latency express saccades during MGS but more hypometric medium-latency saccades (150-350 ms) during VGS. Finally, express saccade rate correlated positively with disease severity, verbal memory, and processing speed across the subjects with PD. Medication effects on express saccade correlated with Levodopa Equivalent Daily Dose (LEDD). Taken together, our findings suggest an association between memory-based saccadic response variability and nigrostriatal dopamine dysfunction in early-stage PD.

Disclosures: L. Jiang: None. **H. Leung:** None.

Poster

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.01

Topic: E.04. Voluntary Movements

Support: Wellcome Trust 222851

Title: Long-term motor learning creates structure within neural activity space that shapes subsequent adaptation

Authors: *J. C. CHANG[1], M. G. PERICH[2], L. E. MILLER[3], J. A. GALLEGO[1], C. CLOPATH[1];
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Abstract: Animals take a long time to acquire new motor skills, but can quickly adapt learned movements in response to environmental perturbations. How animals adapt is likely influenced by the movements they already know, but the nature of this interaction is unclear. Long-term learning likely causes lasting changes in neural connectivity, which may shape the neural dynamics that can be produced. To examine how a neural population's existing activity repertoire affects its ability to change its activity, we modeled motor cortical neural dynamics during skill learning and subsequent adaptation using recurrent neural networks. We trained networks on motor repertoires of different sizes, from one to four movements. We hypothesized that having larger motor repertoires would facilitate adaptation since the activity already exists within a larger portion of neural activity space. Indeed, networks with larger repertoires could adapt to visuomotor rotation perturbations more quickly. In particular, multi-movement networks adapted significantly faster than single-movement networks. To understand how learning multiple movements impacts the underlying dynamics, we compared how networks with different repertoires performed the same movement. Multi-movement networks had more constrained, robust, and predictable neural dynamics than single-movement networks, with the dynamics

structurally organized in neural space in congruence with the motor output organization. Critically, when we disrupted this structure in neural space by changing how the network inputs were "encoded"—from angular to categorical target cues—, the differences in adaptation between multi-movement networks disappeared. This showed that existing structure in neural space can facilitate adaptation, but under limited circumstances. First, adaptation was facilitated only when the structure in the inputs, the neural space, and the perturbation were all congruent: networks with angular inputs adapted faster to angular rotations, but those with categorical inputs adapted better to target reassociations. Thus, adaptation is affected by the specific organization of dynamics within neural space, and external cues during learning can shape this representation. Second, adaptation was facilitated when only small changes were required: under large perturbations, networks with larger repertoires adapted slower than those with smaller ones. Thus, there may be a fundamental trade-off in skill-acquisition: learning more movements creates more defined structure in neural space, which facilitates adaptation that requires small changes, but hinders adaptation that requires larger changes.

Disclosures: **J.C. Chang:** None. **M.G. Perich:** None. **L.E. Miller:** None. **J.A. Gallego:** None. **C. Clopath:** None.

Poster

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.02

Topic: E.04. Voluntary Movements

Title: Thalamocortical mediated dendritic reorganization in PT neurons during motor learning in the primary motor cortex

Authors: *M. ABBOUD, J. SCHILLER, Y. SCHILLER;
Fac. of Medicine, Dept. of Neurosci., Technion - Israel Inst. of Technol., Haifa, Israel

Abstract: The primary motor cortex (M1) is a central cortical brain region responsible for motor learning, planning and execution of dexterous movements. Layer 5 pyramidal tract (PT) neurons are the main output neurons of M1 relaying motor commands to lower brainstem and spinal cord execution centers. PT neurons are characterized by a large tuft tree in layer 1 featuring extensive dendritic arborizations, which integrate cortical and subcortical input information. Importantly, PT neurons' tuft dendrites are active structures that carry out complex computations, directly influencing signal propagation to the soma, affecting its output and ultimately shaping motor performance. An important subcortical brain region that provides wide excitatory innervation to PT neurons' tuft dendrites is the motor thalamus, which was shown to be important for motor learning and performance. Still, the way in which tuft dendrites' activity evolves throughout motor learning to support motor representation and the role of the direct thalamocortical inputs in the process remains unclear. Towards this end, we use two-photon calcium imaging of tuft dendrites of PT neurons, combined with chemogenetic manipulations of thalamocortical inputs

in awake head-fixed mice throughout the learning process of a hand-reach task. We observe major changes in tuft dendrites' activity during the progression of the learning process; these changes are strongly dependent on intact thalamocortical activity, as chemogenetically blocking this activity leads to a significant decrease in tuft dendrites' activity along with disruption of motor learning.

Disclosures: M. Abboud: None. **J. Schiller:** None. **Y. Schiller:** None.

Poster

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.03

Topic: E.04. Voluntary Movements

Support: ISF Grant 890015

Title: The role of VTA dopaminergic system in M1 network plasticity during motor learning

Authors: A. GHANAYIM[1], H. BENISTY[2], A. COHEN-RAMON[3], S. SCHWARTZ[1], R. TALMON[4], *J. SCHILLER[5];
[1]Technion Med. Sch., Haifa, Israel; [2]Yale, Yale Med. Sch., New Haven, CT; [3]Computer Sci., [4]Electrical Engin., Technion, Haifa, Israel; [5]Neurobio., Neurobio., Haifa, Israel

Abstract: The primary motor cortex (M1) and its dopaminergic ventral tegmental area (VTA) inputs, play a major role in motor learning. However, the cellular and network mechanisms by which the dopaminergic VTA inputs affect M1 during learning of dexterous tasks is unknown. In this work, we investigated the role of VTA projections in shaping the network activity in M1 during motor learning. Toward this end, we used two-photon calcium imaging in head fixed mice performing a hand reach task, combined with chemogenetic and pharmacological manipulations using DAT-Cre animals. We find that silencing VTA projections to M1, significantly affected motor learning and adaptation of a learnt task. Inhibition of the VTA dopaminergic projections prevented motor learning progress in beginner mice, in addition, expert mice failed to adapt to a new target location. Our analysis shows that the activity as well as network connectivity of layer 2-3 pyramidal network gradually transforms and converges to a stable ensemble configuration throughout the training process. Importantly, this progression in network activity and connectivity configuration of layer 2-3 neurons was markedly modulated as a result of silencing the VTA dopaminergic projections. Overall, our results imply that VTA dopaminergic innervation to M1, play a substantial role in shaping the reorganization of the layer 2-3 neuronal network activity of M1 and controlling motor learning and adaptation.

Disclosures: A. Ghanayim: None. **H. Benisty:** None. **A. Cohen-Ramon:** None. **S. Schwartz:** None. **R. Talmon:** None. **J. Schiller:** None.

Poster

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.04

Topic: E.04. Voluntary Movements

Support: NIH 1R01NS123074-01A1
NIH 1R01MH126516-01A1
NIH 1R56MH126516-01
University of Texas at Dallas

Title: Locus Coeruleus stimulation paired with motor training induces plasticity in rat primary motor cortex

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Abstract: Motor cortical plasticity has been shown to depend on noradrenergic neuromodulation from noradrenaline (NA) synthesizing nucleus in the locus coeruleus (LC). The LC-NA system is known to be involved in diverse brain functions including sensory perception, attention, learning and memory. Previous studies suggest that optogenetic stimulation of the LC paired with sensory and spatial experiences induce experience-dependent plasticity in rodent sensory cortices and in the hippocampus. However, the influence of LC stimulation on motor cortical plasticity remains unclear. In this study, we investigate whether optogenetic stimulation of the LC paired with skilled forelimb training is sufficient to induce plasticity in the motor cortex (M1). Male and female TH-Cre+ Long-Evans rats were trained on a skilled reaching lever pressing task emphasizing the usage of the proximal forelimb musculature. Once animals reached the performance criteria, they received a final five sessions of training paired with optogenetic stimulation of the LC delivered at 3, 10, or 30 Hz. Within twenty-four hours of the last stimulation session, intracortical microstimulation was performed to acquire somatotopic motor cortical maps. Our preliminary data suggest that lever pressing paired with 10 Hz LC stimulation resulted in the expansion of the task-relevant proximal forelimb representation in M1. However, training-paired stimulation at 3 or 30 Hz had no significant effect on the motor maps. LC stimulation may also impact task performance. Interim findings indicate that during optogenetic stimulation sessions, rats that received 3 or 30 Hz LC stimulation performed more trials compared to rats that received 10 Hz LC stimulation. These preliminary results suggest that brief, training-paired stimulation of the LC at intermediate frequencies is sufficient to induce experience-dependent plasticity in M1, while lower and higher frequencies may be more effective at altering ongoing motor performance. Further research is needed to understand the mechanisms underlying frequency-dependent effects of LC stimulation on neuroplasticity and behavior.

Disclosures: C. Tseng: None. **C.A. Thorn:** None.

Poster

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.05

Topic: E.04. Voluntary Movements

Support: NSF GRFP DGE-1746045

Title: Stability of motor cortical coding and cross laminar network structure over days in a dexterous reach-to-grasp task

Authors: *E. A. DE LAITTRE[1], J. N. MACLEAN[2];
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Abstract: The stability of the relationship between neural activity and a given external variable is an active area of study in many areas of neuroscience (Liberti, Schmid, et al, 2022; Driscoll et al, 2017; Gonzalez et al, 2019). In motor control there is conflicting evidence as to the stability of the relationship between motor cortical activity and movement (Chestek et al, 2007; Rokni et al, 2007; Huber et al, 2012; Peters et al, 2017). In addition it is far from clear whether the laminar position of a neuron corresponds to the stability of the mapping between neuronal activity and kinematic variables over days.

We have collected an extensive neural and behavioral dataset spanning 24 consecutive days while mice learn a difficult skilled reach-to-grasp task (n=5 mice, 24 days per mouse). We built upon the Whishaw single pellet reaching task, which requires both precision paw placement and spatiotemporally coordinated digit control (Whishaw and Pellis, 1990; Chen et al, 2014). We adapted the task to a self-initiated, freely moving paradigm and increased task difficulty to maximize the variance of paw and digit movements elicited and minimize automaticity once the task is well learned. Notably mice are unable to perform the Whishaw task when motor cortical activity is disrupted (Guo et al, 2015; Sauerbrei et al, 2020) making it an appropriate task for studying the stability of motor cortical representations. We reconstruct the kinematics of the wrist and digit joints during reaching from high speed videography using DeepLabCut (Mathis et al, 2018; Nath, Mathis et al, 2019).

We address the question of representational drift in motor cortical coding and cross-laminar functional relationships using fine-grained behavioral descriptions of paw and digit kinematics and the activity of large numbers of neurons across cortical layers tracked across days. Specifically we record calcium fluorescence changes in large populations of neurons (~400 neurons per mouse) in caudal forelimb motor cortex of unrestrained mice using a lightweight head-mounted miniscope coupled with a prism (Inscopix). When inserted into the cortex the prism allows for simultaneous recording of superficial (putative L2/3) and deep (putative L5) layers. We leverage tools from information theory and network science to quantify and compare the functional relationships (statistical dependencies) between pairs of neurons within and across layers, within and across days. This approach allows us to pinpoint which pairwise relationships

between neurons (or network-wide patterns of relationships) within the cortical column correspond to fine motor skill and delineate the stability of these relationships across days.

Disclosures: E.A. de Laittre: None. **J.N. MacLean:** None.

Poster

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.06

Topic: E.04. Voluntary Movements

Support: Natural Sciences and Engineering Research Council of Canada (NSERC RGPIN-2017-06434, D.F.C.)
Natural Sciences and Engineering Research Council of Canada (NSERC RGPIN-2021-03909, B.A.K.)
Natural Sciences and Engineering Research Council of Canada (Undergraduate Student Research Award, SRU)
Canadian Foundation for Innovation (CFI-JELF 37382, D.F.C.)
Canada Research Chair (B.A.K.)

Title: The effects of sleep deprivation on motor learning in mice

Authors: *D. F. COOKE[1,2], S. R. U[3], A. VIRK[3], M. HAFEZI[1,2], A. R. MCINTOSH[1,2], D. MARIGOLD[1,2], B. KENT[2,3];
[1]Biomed. Physiol. and Kinesiology, [2]Inst. for Neurosci. and Neurotechnology, [3]Psychology, Simon Fraser Univ., Burnaby, BC, Canada

Abstract: Sleep is important for optimal learning and memory. To evaluate how 24 hours of sleep deprivation affects motor learning, mice (c57BL/6) were taught the pasta matrix reaching task (testing ongoing; total n=20) and horizontal ladder walking test (n=20). The pasta matrix reaching task assesses reaching behavior while the horizontal ladder walking test assesses reaching, walking, limb placement, and interlimb coordination. Mice were sleep deprived for 24 hours following Day 1 or Day 4 of training using gentle touch with a soft paint brush when any behavioral signs of sleep were observed. By comparing the effects of sleep deprivation following Day 1 and Day 4, we can assess how sleep deprivation affects learning at different stages of the learning curve. Preliminary analysis of ladder data suggests that animals' performance improved (paw placement errors decreased) across at least 5 days of testing on moderately challenging uneven rung spacing, but 24 hours of sleep deprivation on Day 1 or Day 4 had minimal impact on performance. The present study will serve as a pilot to inform future research on the effects of sleep deprivation on motor learning in mice.

Disclosures: D.F. Cooke: None. **S.R. U:** None. **A. Virk:** None. **M. Hafezi:** None. **A.R. McIntosh:** None. **D. Marigold:** None. **B. Kent:** None.

Poster

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.07

Topic: E.04. Voluntary Movements

Support: NIH R01 NS125298
NIH R01 NS091010
NIH R01 DC018545
NIH R21 NS112750
NSF 2024776
Simons Collaboration on the Global Brain Pilot Award

Title: Functional characterization of input-defined neurons within the primary motor cortex during motor learning

Authors: *A. RAMOT[1,2,3], F. H. TASCHBACH[4,1], A. WU[1,2,3], Q. CHEN[1,2,3], Y. HU[1], Y. YANG[1,2,3], K. M. TYE[4], M. K. BENNA[1], T. KOMIYAMA[1,2,3];
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Abstract: The primary motor cortex (M1) is a central locus for motor learning and execution. Like other cortical regions, the functional properties of M1 neurons are highly heterogeneous, but the origins of this functional heterogeneity are poorly understood. Here we investigate the contributions of long-range inputs to the functional heterogeneity among M1 neurons during two weeks of training in a lever-press task. This motor learning paradigm induces movement kinematics that are reproducible from trial to trial, a key feature of learned motor skills. We first investigated the activity patterns of three major sources of long-range projections providing inputs to M1 L2/3 neurons, primary somatosensory cortex, contralateral M1, and motor thalamus, by performing *in vivo* longitudinal calcium imaging of input axons expressing axon-GCaMP6s while mice are trained in the task. We found that movement-related activity patterns of different input streams are distinct, with thalamic inputs providing the strongest movement-related signal compared to the other two inputs, especially during movement initiation. In order to examine how these inputs relate to the activity of M1 L2/3 neurons, we established a methodology to identify neurons that respond to specific inputs by combining two-photon calcium imaging of M1 neurons with optogenetic stimulation of specific inputs. We then imaged the same neurons throughout training. We found that M1 neurons that respond to different inputs show distinct activity patterns during motor learning. For instance, M1 neurons that are excited by thalamic inputs show stronger movement-related activity, mirroring the activity of thalamic input axons. These thalamus-responsive neurons have higher movement decoding accuracy, which increases through training. Taken together, we demonstrate that the functional properties of individual M1 neurons are at least partially defined by their responses to long-range inputs and propose that the thalamus-M1 L2/3 pathway is a main driver of learned movements.

Disclosures: **A. Ramot:** None. **F.H. Taschbach:** None. **A. Wu:** None. **Q. Chen:** None. **Y. Hu:** None. **Y. Yang:** None. **K.M. Tye:** None. **M.K. Benna:** None. **T. Komiyama:** None.

Poster

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.08

Topic: E.04. Voluntary Movements

Support: NIH/NINDS NS091144
Aligning Science Across Parkinson's ASAP-020551
Stanford School of Medicine Dean's Postdoctoral Fellowship
Parkinson's Foundation Postdoctoral Fellowship

Title: Motor learning induced transcriptomic changes in motor engram neurons

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Abstract: Motor learning induces profound structural and activity changes in both presynaptic primary motor cortical (M1) neurons and postsynaptic striatal spiny projection neurons (SPNs). Recent study revealed the reactivation of motor engram neurons while mice perform an already learned motor task. However, the molecular profile of motor engram cells and the mechanism underlying transcriptome regulation involved in 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 the formation of motor memory. We trained TRAP mice to perform a forelimb reaching task and labeled cells that are specifically activated in the early and late stages of training. Using scRNA-seq, we identified engram neurons in diverse neuronal populations in addition to corticostriatal projection neurons. By calculating the percentage of TRAP cells in each given cell type, we analyzed whether one given cell type is preferentially activated during different stages of motor learning and identified two GABAergic interneuron populations in M1 and the striatum, respectively, that were significantly more activated in different stages of motor training, suggesting that these interneurons may be involved in motor learning. In addition, we found significant differential expressed genes in early and late stages of learning that are associated with synaptic functions and movement disorders. Results gained from scTRAP-seq and subsequent validations identified novel cell types in corticostriatal circuits involved in motor learning, and provided mechanistic insights into pre- and postsynaptic genes that regulate 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

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.09

Topic: E.04. Voluntary Movements

Support: 1F31DC019307
1R01DC018802

Title: Activity in mouse motor cortex reflects action and its expected sensory consequences

Authors: *B. E. HOLEY, D. M. SCHNEIDER;
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Abstract: In addition to controlling movement through its descending projections to the brainstem and spinal cord, the motor cortex also sends copies of motor-related signals, termed corollary discharge, to sensory regions of the cortex. Within sensory cortex, corollary discharge signals can be integrated with ascending sensory input to augment neural responses to self-generated sensory cues. Traditionally, models of motor-sensory learning presume that corollary discharge signals stably reflect movement regardless of its sensory outcome, while learning and encoding the expected outcome of an action happens downstream areas that receive corollary discharge signals (e.g. within sensory regions). Here, we show that in addition to encoding movement, motor cortical corollary discharge signals explicitly encode the expected sensory consequences of an action. We recorded neural activity in a prominent motor-related input to the auditory cortex -- secondary motor cortex (M2) -- as mice operated a lever that produced a predictable sound. During a sound-generating movement, many M2 neurons exhibit mixed selectivity of movement and sound signals, consistent with local motor-auditory integration within M2. Although activity in the broader M2 population tiles time throughout the duration of a sound-generating movement, M2 cells that send axons to the auditory cortex concentrate their activity in a narrow window around the time of the expected self-generated sound. This temporally precise concentration of sound-anticipating activity in M2-to-AC cells matches the temporally precise movement-related signals observed in auditory cortex. Moreover, sound-anticipatory activity is not present in naïve mice nor M2 cells that send projections to V1, indicating that it is learned through motor-sensory experience and selectively routed to modality-specific downstream targets. Together, these findings reveal that M2 integrates signals related to movement and the acoustic consequence of action, and exhibits learned sound-anticipating activity that it selectively routes to auditory cortex.

Disclosures: B.E. Holey: None. **D.M. Schneider:** None.

Poster

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.10

Topic: E.04. Voluntary Movements

Support: NIH R25 (S.E.A.)

Title: Emergent population dynamics in a disinhibitory circuit compartmentalizes preparation and movement

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Abstract: A principle for neural computation is orthogonalized population dynamics to support distinct processing. For example, skilled movement control demonstrates population dynamics that compartmentalizes preparation from execution. The circuit motifs that give rise to compartmentalized dynamics are not known. We hypothesized that disinhibition, where inhibitory neurons inhibit other inhibitory neurons and organize pools of excitatory neurons, would demonstrate emergent orthogonalized dynamics with skill learning. We used endoscopic imaging techniques to track over days the activity of single vasointestinal peptide (VIP) expressing interneurons. These longitudinal recordings demonstrated emergence of orthogonalized VIP population dynamics. Strikingly, we could trace changes in dynamics to altered activations of a small subset of neurons. To verify that VIP dynamics are compartmentalized, we temporally shifted a predictive cue; this resulted in compartmentalized activation of preparatory dynamics. Our results reveal how emergent disinhibitory population dynamics support learning and may play a role in regulating population dynamics.

Disclosures: S. Arroyo: None. **S. Barati:** None. **K. Kim:** None. **F. Aparicio:** None. **K. Ganguly:** None.

Poster

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.11

Topic: E.04. Voluntary Movements

Support: CIHR grant PJT-166014
UNIQUE-IVADO Postdoctoral fellowship

Title: Changes in dorsal premotor cortical activity during learning of a decision-making task

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Abstract: Many neurophysiological studies have shown that while a monkey deliberates between reaching to one of two targets, neurons in dorsal premotor cortex (PMd) often reflect a competition between representations of both actions. For example, in the "tokens task", these representations are continuously modulated by the changing sensory evidence favouring each choice and temporal biases related to the urgency to act, until the combined activity reaches a state where commitment to a choice is made (Thura & Cisek 2014, Neuron). Interestingly, the commitment to a choice appears to occur in PMd, and not in prefrontal cortex, where traditional theories would generally place cognitive processes such as decision-making. However, like most neurophysiological studies these observations were made in highly trained animals, and it is unclear whether similar results would be found when a monkey learns a novel task for the first time. Here, we investigate changes occurring in PMd while a monkey is being trained to perform the tokens task, using chronically implanted GrayMatter micro-drives with 32 independently moveable electrodes, allowing us to record individual task-related neurons over many weeks. On the first day of learning the tokens task, we presented the monkey with two target circles and then, ~1s later, all of the tokens jumped into one of them. The monkey was rewarded if he reached to that target after a GO signal. At first, the monkey tended to choose his favored target (left) but after about 78 choices he abruptly started making the choice instructed by the tokens. Coinciding with this moment, PMd activity responded less to the appearance of the two targets, and began to respond to the token jump event, predicting the monkey's decision. We found a similar pattern in the local field potential (LFP) across 14 PMd channels. In particular, LFP responses in the alpha band decreased for target onset and increased after the token jump. Most notably, early alpha ERPs clearly aligned to the token jump even on the first trials, but then an additional positive ERP, about 500ms later, gradually emerged as the monkey learned. Over the next five days, both the neural spiking and LFP responses to the token jump increased and shifted earlier in time. A few days later, we began to vary the number of tokens jumping into each target, rewarding the monkey for reaching to the target that received the majority. As soon as the monkey learned this "more is better" rule, both neural spiking and LFP activity reflected the level of evidence as well as the choice. Taken together, these results suggest that PMd is involved in action selection even when an animal is first learning a new task.

Disclosures: T.R. Peel: None. **L. Demange-hamel:** None. **T. Deng:** None. **P.E. Cisek:** None.

Poster

718. Neurobiology of Motor Learning During Reaching

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 718.12

Topic: E.04. Voluntary Movements

Title: Interaction of motor learning and tDCS at 2 V/m in rats

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Abstract: Background: One promising application of tDCS is to modulate motor excitability and motor learning. Human and animal studies have demonstrated that anodal tDCS increases motor evoked potential (MEP). However, it is not clear that changes in TMS-evoked MEP have any actual relevance to normal behavior. Functional and structural changes in the primary motor cortex (M1) have been associated with motor skill learning. Therefore, tDCS human and animal studies have targeted this region to modulate motor learning. A recent study has found that offline application of anodal tDCS can improve speed and accuracy tradeoff in the reaching task in adult mice.Methods: Here we tested for the first time tDCS concurrently with a behavioral learning task in rodents. The pellet-reaching task we use here in rats is a classic model of motor learning involving synaptic changes in the motor cortex. We developed a new electrode montage that trades off intensity with electrochemical stability over 10 training sessions while maintaining animal safety and mobility. We measured field intensity intracranially and built a computational model to match our electrode montage. Animals were trained for 20 min with concurrent tDCS over 10 daily sessions. MEP was measured with direct cortical microstimulation in a terminal experiment under anesthesia. Results: We measured field magnitudes intracranially with this configuration and determined that 150μA current results in 2V/m fields in M1. We improved the experimental methods to allow concurrent training and simulation and a longer stimulation period that parallels the motor learning time course. This novel protocol will serve as a basis for systematic experimentation with intensities comparable to human tDCS. A linear mixed effect model finds an interaction between days with the stimulation condition at 2 V/m.

Disclosures: F. Vasheghani Farahani: None. **M. Voroslakos:** None. **N. Khadka:** None. **M. Bikson:** None. **J.H. Martin:** None. **L. Parra:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.01

Topic: E.04. Voluntary Movements

Support: KU Leuven Research Fund (C16/15/070)
Research Foundation Flanders (G089818N)
Excellence of Science (EOS) grant from the Fonds Wetenschappelijk Onderzoek – Vlaanderen (FWO)
Fonds de la Recherche Scientifique – FNRS under EOS Project No. (EOS 30446199, MEMODYN)

Title: White matter microstructural and neurochemical mechanisms underlying age-related differences in motor performance

Authors: *A. RASOOLI[1], H. ZIVARI ADAB[1], S. CHALAVI[1], K. CUYPERS[2], O. LEVIN[1], T. DHOLLANDER[3], D. MANTINI[1], S. P. SWINNEN[1];
[1]Dept. of Movement Sci., K.U.Leuven, Leuven, Belgium; [2]Univ. Hasselt, Univ. Hasselt, Diepenbeek, Belgium; [3]Murdoch Children's Res. Inst., Melbourne, Australia

Abstract: Human aging has a vast effect on different organ systems and the brain is no exception. A set of functional, structural, and neurochemical changes occur in the brain as a result of the process of aging. These changes result in behavioral deficits referring to cognitive and motor function. Specifically, motor deficits result in increased dependency of older adults and reduced quality of life. Prolongation of a healthy life for older adults has pivotal socioeconomic benefits, justifying a comprehensive investigation of age-related motor deficits. Here, we investigated the age-related differences in motor performance, neurometabolites, white matter (WM) microstructure, and the relationship between them, across the adult lifespan.Seventy-six right-handed participants (40 males), aged between 20 - 75 years (mean ± std: 49.79 ± 16.86), without any history of neuromuscular disorders performed a multi-limb reaction time (ML-RT) task in which they reacted to 4 cues representing the different limbs and various interlimb combinations (Boisgontier, 2014). MRS data (1.5 x 1.5 x 1.5 cm) were acquired from the left M1 (main voxel) and the occipital cortex (control voxel) and the level of N-acetylaspartate (NAA), Creatine (Cr), and Choline (Cho) were obtained in these two voxels. To quantify WM microstructure, the average apparent fiber density (FD) was calculated in both M1 and Occ voxel WM masks. Three-way mediation analysis was used to investigate the relations between age - WM FD - ML-RT, age - neurometabolites - ML-RT, and age - neurometabolites - WM FD.Age was positively associated with ML-RT and negatively with WM FD and NAA level in the M1 voxel. Thus, with advancing age ML-RT became longer and WM FD and NAA level in motor cortex decreased. Interestingly, both NAA and FD of the M1 voxel mediated the effect of age on ML-RT. More interestingly, the aforementioned results were only present in the M1 voxel and not in the Occ control voxel. Finally, we found that age-related differences in the FD of the M1 voxel were significantly mediated by the level of NAA.In conclusion, older adults were found to be slower than their younger counterparts. Aging had a significant negative effect on the WM FD and NAA in the motor cortex rather than Occ. Additionally, the decreased FD and NAA were potential mediators of this motor deficit in older adults. Moreover, NAA has shown to be involved in various neural processes related to WM structural integrity, including myelination and osmoregulation. Hence, as NAA in the M1 significantly mediates the age-related changes in fiber density, we tentatively conclude that reduced NAA may result in FD decrease which may give rise to the slowness in reaction performance.

Disclosures: A. Rasooli: None. **H. Zivari Adab:** None. **S. Chalavi:** None. **K. Cuypers:** None. **O. Levin:** None. **T. Dhollander:** None. **D. Mantini:** None. **S.P. Swinnen:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.02

Topic: E.04. Voluntary Movements

Title: Hippocampal Theta Activity During a Novel Rodent String-Pulling Task

Authors: G. R. HOLGUIN, A. K. TAPIA, A. VISHWANATH, R. RAMAMOORTHY, G. JORDAN, S. A. MIRON, E. C. VIGIL, A. L. WEBSTER, S. L. COWEN;
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Abstract: It is well established that the hippocampus plays a vital role in learning, memory, and spatial navigation. Performing these functions requires the integration of spatial and motor information. Involvement of the dorsal hippocampus in processing sensorimotor information is suggested by the strong relationship between locomotor activity and the frequency and power of the 5-12 Hz hippocampal theta oscillation. The current study seeks to elucidate whether this relationship holds during a skilled, fine-motor string-pulling task. While string-pulling tasks have been used for decades to study animal learning and behavior, they have rarely been used to investigate the neural correlates of motor behavior and have never been used to investigate hippocampal function. Unique features of rodent string-pulling tasks include the presence of vigorous forelimb (but not hindlimb) motor activity and the absence of movement through space. We developed an automated version of the string-pulling task that monitors pulling length and speed and dispenses food (liquid Ensure) after a predetermined length of string is pulled. To investigate the relationship between hippocampal theta and string-pulling activity, local-field potentials were recorded in the hippocampal CA1 region from Sprague Dawley rats (N=4) during string pulling and traversal of a circular track. Paw movement was automatically tracked using DeepLabCut. Preliminary analyses revealed increased theta power during string-pulling relative to non-pulling bouts in 3 of 4 rats; however, theta power and frequency were diminished when compared to track-running. Furthermore, while a clear 16Hz theta harmonic was observed during track running, it was not present during string pulling. These preliminary observations suggest that, while theta oscillations are clearly present during a vigorous fine-motor task, reduced sensorimotor drive (e.g., reduced vestibular, optic flow, and hindlimb activity) during string-pulling may decrease hippocampal theta frequency and power and eliminate the theta harmonic. Further investigation of the relationship between theta oscillations during fine-motor tasks requiring human-like reaching and grasping behaviors may further our understanding of how the hippocampus processes sensorimotor information in behaviors that go beyond traditional tasks involving rodent locomotion through spatial environments.

Disclosures: G.R. Holguin: None. **A.K. Tapia:** None. **A. Vishwanath:** None. **R. Ramamoorthy:** None. **G. Jordan:** None. **S.A. Miron:** None. **E.C. Vigil:** None. **A.L. Webster:** None. **S.L. Cowen:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.03

Topic: E.04. Voluntary Movements

Support: NSERC Discovery Grant 2017-04829

Title: Goal-directed stretch responses are similarly expressed in the dominant and nondominant arms

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Abstract: Humans can flexibly control their movements in different environments. Consider holding a drink in a crowded hallway where a bump on your arm could evoke different corrections depending on the glass being filled and the location of your colleagues. Indeed, many studies have shown that rapid feedback responses following limb displacement, i.e. stretch responses, can be altered to accommodate varying spatial and temporal demands, reward, and the mechanics of the limb and environment. These studies have typically examined stretch responses in the dominant arm. However, behavioral differences in reaching movements between the dominant and nondominant arms have led to the idea that each arm is controlled differently. These differences may extend to rapid feedback responses. Here, we examined goal-directed stretch responses in the nondominant arm and compared them to those in the dominant arm. Twenty healthy adults (11 females and 9 males, 20-26 years old, all right-handed) began each trial by holding a fixed arm posture in a Kinarm exoskeleton robot. Trials were performed in random order with the left and right arms. A goal target was presented either medial or lateral to the initial arm posture at the start of the trial. Step-torque perturbations (±2 Nm) unexpectedly extended (lateral motion) or flexed the elbow (medial motion). The task required a vigorous corrective response when participants were disturbed out of the goal target compared to trials when the arm was disturbed into the goal target by the same perturbation. Thirty blocks of 8 trials (2 arms x 2 perturbations x 2 target locations) were presented in random order. We quantified the vigor of corrective responses by extracting the peak elbow angles in each trial. We recorded the activity of the monoarticular and biarticular elbow and shoulder muscles to assess stretch responses. We found a goal-directed increase in stretch responses that emerged ~60 ms after perturbation onset in both arms and a corresponding reduction in peak elbow displacement when the arms were displaced out of compared to into the goal target by the same perturbation. The goal-directed feedback responses did not differ statistically between the arms, yet correlations in the amplitude of responses revealed similar flexibility in how the nervous system controls the two arms. Collectively, our results highlight that flexible, goal-directed stretch responses are similarly expressed in the dominant and nondominant arms.

Disclosures: P. Maurus: None. **E. Dawson:** None. **I. Kurtzer:** None. **T. Cluff:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.04

Topic: E.04. Voluntary Movements

Support: Imperial College London

Title: Differential reticulospinal control of trapezius in humans during stabilising and movement tasks

Authors: L. THORNLEY[1], C. M. ALEXANDER[3], *P. H. STRUTTON[2];
[1]Surgery and Cancer, [2]Imperial Col. London, London, United Kingdom; [3]Therapies, Imperial Col. Healthcare NHS Trust, London, United Kingdom

Abstract: Trapezius rotates and stabilises the scapula during arm elevation. It moves the glenoid and provides a stable base of support for the arm. It also activates bilaterally during unilateral tasks to stabilise posture during contralateral arm movement. Reticulospinal control supports such activity but little is known about reticulospinal control of trapezius in humans. This study aimed to establish whether reticulospinal drive contributes to trapezius activity in humans and whether control is different during stabilising and movement tasks. With ethical approval and informed consent, 19 healthy participants (63% female; 22.2 ± 1.9 yrs) were recruited. Using the StartReact paradigm, reaction time and amplitude of electromyographic activity (EMG) were recorded bilaterally, from upper (UTr) and lower trapezius (LTr), during 2 tasks under 3 conditions: elevation of the arm (movement task) and the contralateral arm (stabilising task) in response to a visual cue, a visual cue with a quiet sound and a visual cue with a startling sound. Visual Reaction Time (VRT), Visual Auditory Reaction Time (VART), and Visual Startle Reaction Time (VSRT) were measured from visual cue to the rise in EMG activity recorded from UTr and LTr. Amplitude of rectified EMG for 100ms after the reaction time was measured. Reticulospinal gain was calculated ((VRT-VSRT))/((VRT-VART)) and compared across the tasks to investigate differential control. VSRT was shorter than VART and VRT across both tasks in both muscles ($p<0.05$). Amplitude increased with the startling sound compared to the other conditions for both UTr and LTr during the movement task alone ($p<0.05$). Reticulospinal gain for UTr was greater ($p<0.01$) during the stabilising task with no difference between tasks for LTr ($p=0.57$). Modulation of reticulospinal drive to different parts of trapezius has been demonstrated for the first time in humans. Interestingly, results suggest the gain was task specific for upper trapezius, but not for lower trapezius. This is in keeping with other work demonstrating differing functions of distinct parts of trapezius.

	UTr		LTr	
	Movement	Stabilising	Movement	Stabilising
VRT ms (median & IQR)	167 117-198	206 175-232	198 170-214	192 164-205
VART ms (median & IQR)	109 95-132	135 116-173	121 108-156	117 102-141
VSRT ms (median & IQR)	94 87-112	106 98-127	108 98-129	100 89-118
RS Gain (median & IQR)	1.3 1.1-1.4	1.4 1.2-1.9	1.3 1.2-1.4	1.2 1.2-1.4

Disclosures: L. Thornley: None. **C.M. Alexander:** None. **P.H. Strutton:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.05

Topic: E.04. Voluntary Movements

Support: CRCNS (NICT 21701)
CRCNS (NSF-BCS2011716)
JSPS KAKENHI Grant number JP19K04289 & JP22K12775

Title: Juggling skills trained in VR transfer to the real world

Authors: *H. KAMBARA[1], W. CHO[2], H. KIM[4], R. OYA[1], Y. KITAMI[1], M. KOBAYASHI[2], S. SAETIA[2], T. KAGAWA[5], H. TANAKA[6], M. MIYAKOSHI[7], J. R. IVERSEN[9], S. MAKEIG[8], M. SATO[2], N. YOSHIMURA[3];
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Abstract: Motor skill training systems based on virtual reality (VR) technologies are becoming more popular in sports training, entertainment, and rehabilitation. VR technologies enable manipulation of training parameters and feedback on motor performance to make beginners or patients motivated for training. On the other hand, there are many cases in which the training in a VR environment does not lead to the improvement of motor skills in the real environment. It has been suggested that the lower fidelity of VR environments to the real one, and especially the lack of haptic feedback, prevents motor skill transfer from virtual to the real world (Levac et al., J. NeuroEng and Rehab., 2019).Here we developed a VR system enabling ball juggling in the

virtual world. The system is composed of a haptic device and a head-mounted display (HMD). The haptic device, named SPIDAR-W, consists of metal frames carried on the shoulders in front of the body and motors attached to the frame. The motors pull strings attached to ball-shaped grips to generate downward force and users can sense the load force of the ball through the grips held in both hands. In addition, the visual image of balls and the hands are displayed by an HMD to preserve depth cues to assist in sensing the relative position of the balls and the hands.To test whether complex motor skills like juggling trained in a VR environment would transfer to juggling skills in the real world, we asked juggling beginners to practice the 3-ball cascade juggling pattern in the VR system for 20 minutes each time for ten different days. As the result, we observed an increase in the duration of each juggling trial in both the VR and the real environment. The results of this work support the transfer of complex motor skills from the virtual to the real world.

Disclosures: H. Kambara: None. **W. Cho:** None. **H. Kim:** None. **R. Oya:** None. **Y. Kitami:** None. **M. Kobayashi:** None. **S. Saetia:** None. **T. Kagawa:** None. **H. Tanaka:** None. **M. Miyakoshi:** None. **J.R. Iversen:** None. **S. Makeig:** None. **M. Sato:** None. **N. Yoshimura:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.06

Topic: E.04. Voluntary Movements

Support: R15AG067792

Title: Gaze distribution is biased to the dominant limb during continuous bimanual movement control

Authors: *K. KIANI[1], M. PATEL[2], Q. FU[1];
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Abstract: Skilled bimanual coordination is an essential component of activities of daily living. It has been shown that forcing visual attention to be directed to one limb can alter rhythmic bimanual coordination patterns. However, it remains unclear how the Central Nervous System naturally directs visual attention to executing a bimanual movement that has high precision requirements. The objective of this research is to determine the gaze distribution during a bimanual non-rhythmic task in which symmetric or asymmetric motor actions are required. Right-handed young adult subjects (n=10, 5 female) performed a series of bimanual tasks in which each hand must independently and accurately control a cursor with a robotic device to follow the continuous upward movement of a horizontal target line. Two cursors are separated with a visual angle of 20 degrees, and erroneous cursor movement is indicated by the cursor

color turning red from green. The baseline condition of this task represents a symmetric context in which both hands must produce movement with similar kinematics and kinetics to successfully follow the target line. We found that the dominant (right) limb made significantly less error than the nondominant (left) limb ($p < 0.01$). Furthermore, we found that gaze was more frequently directed to the right side when both hands were not making errors ($p < 0.01$). This is consistent with the previous finding that suggests the dominant hemisphere may be driving symmetric bimanual coordination. Furthermore, we also implemented contexts with kinetic and kinematic asymmetry by applying constant force or increased visuomotor gain to one of the limbs, respectively. As expected, the task performance was significantly worse in the early trials (first eight) of the asymmetric contexts as it may be challenged by the inter-limb coupling. Interestingly, subjects were able to adapt to the asymmetry better with the added force than the increased visuomotor gain. Subjects also showed better adaptation when the asymmetry was introduced to the left side than the right side. Most importantly, we found that the gaze distribution was consistently biased to the right side despite the effect of context asymmetry on movement errors. These results suggest that hand dominance is strongly related to the distribution of visual attention during high-precision bimanual coordination

Disclosures: **K. Kiani:** None. **M. Patel:** None. **Q. Fu:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.07

Topic: E.04. Voluntary Movements

Title: Age-related bimanual dexterity impairments depend on dual task type in older adults

Authors: *C. SEAVEY, B. HEINTZ WALTERS;
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Abstract: Introduction. Bimanual dexterity is important for everyday tasks (e.g., tying a shoelace, opening a jar) and dexterity impairments are well-documented in older adults. Attentional deficits, commonly assessed with dual tasks, may contribute to age-related dexterous impairments. Visuospatial dual tasks have shown to impair performance on lower extremity tasks to a greater degree than non-visuospatial tasks though fewer studies have examined the effect of dual task type (i.e., visuospatial and non-visuospatial) on bimanual dexterity in older adults. The purpose of this study was to determine the effect of dual task type on bimanual dexterity in older adults. **Methods.** 23 young (age 19 - 39 yrs; 13 f, 10 m) and 5 older (age 65 - 88 yrs; 3 f, 2 m) healthy, right-handed adults participated. The Grooved Pegboard test and finger tapping tasks are commonly used measures of manual dexterity. Therefore, participants performed a bimanual task by completing the Grooved Pegboard test with the right hand and a finger tapping task by tapping on a touchscreen as quickly as possible with the left index finger. Participants also completed the bimanual task with two types of dual tasks, 1) a visuospatial task

and 2) a non-visuospatial task. Completion time and number of taps per second were recorded to quantify performance for the Grooved Pegboard test and finger tapping task, respectively. **Results.** Grooved Pegboard completion time was greater ($p < .001$) and number of taps was lesser ($p = .002$) for older versus young adults across conditions. Though there was no difference in number of taps when performing the bimanual task with versus without the visuospatial task, number of taps was lesser with versus without the non-visuospatial task in older adults ($p = .016$). There were no differences in Grooved Pegboard completion time across conditions in older adults ($p > .082$). **Conclusions.** Finger tapping performance was impaired when performing only the non-visuospatial task in older adults. This indicates that non-visuospatial tasks impair bimanual dexterity to a greater degree than visuospatial tasks in older adults and contrasts previous findings in the lower extremity. Given there were no differences in Grooved Pegboard performance across conditions, decreased attentional resources may differentially affect preferred and non-preferred manual dexterity. In addition to further recruitment of older adults, future work could investigate if decreased attentional resources impact preferred and non-preferred hand function differently.

Disclosures: C. Seavey: None. **B. Heintz Walters:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.08

Topic: E.04. Voluntary Movements

Title: Through the Looking-Glass: Sense of agency over the illusory hand during mirror therapy.

Authors: *J. KIM, S.-H. YEO, T. PUNT;
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Abstract: During mirror therapy, it is typically considered important for the patient to have ownership and a sense of agency over the illusory limb; that is, they believe the limb they observe in the mirror is their own, and they are the author of its actions. However, measuring these characteristics typically relies on subjective judgments that may be considered unsatisfactory. In contrast, here we aimed to examine ownership and agency over the limb by measuring the kinematic relationship between the two limbs during mirror therapy activity, asking *do participants move their unseen limb in a way that is consistent with the illusory visual information they receive*?
Twenty right-handed unimpaired participants performed 15 s trials of self-paced repetitive aiming movements (between far target and near targets) with a mirror/symmetrical coordination pattern. For the *mirror* condition, vision was directed towards the far target in the mirror. In the *no mirror* condition, the direction of vision was unchanged, but the mirror was replaced with an opaque screen. The movements of both hands were recorded using motion capture apparatus. Analysis sought to examine the consistency of *corrective* movements to the illusive image with

correction angles in each tap.
As we have previously reported, under these circumstances, the unseen hand may undergo substantial positional drift in the course of a 15 s trial (Kim et al., 2019). Here, we plotted the illusory error (generated by the *seen* hand) on each movement, using this to predict the movement trajectory of the unseen hand on the subsequent movement and then comparing this with the actual movement observed. As anticipated, substantial positional drift of the unseen hand was observed as it made corrective movements consistent with the illusory visual information generated by the seen hand. However, at least once (on average) during each *mirror* trial (7% of all movements), we observed unseen hand movements that were inconsistent with illusory information. We interpret these as being indicative of an *illusion break* and diminished ownership and agency over the illusory limb.

Disclosures: J. Kim: None. **S. Yeo:** None. **T. Punt:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.09

Topic: E.04. Voluntary Movements

Support: NSERC Grant 500-503750

Title: Sex differences in the neural underpinnings of bimanual control in adults

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Abstract: While many of the movements we make throughout our day involve just one upper limb, most daily movements require a certain degree of coordination between both upper limbs. Historically, sex differences in eye-hand coordination have been observed. As well, there are demonstrated sex-specific differences in hemisphere symmetry, interhemispheric connectivity, and motor cortex organization. While it has been suggested that these anatomical differences may underlie sex-related differences in performance, sex differences in the functional neural correlates underlying bimanual performance have not been explicitly investigated. Here we tested the hypothesis that the neural activity underlying bimanual movement control differed depending on the sex of an individual. Participants underwent MRI scanning to acquire anatomical and functional brain images. During the functional runs, participants performed unimanual and bimanual coordination tasks using two button boxes. The tasks included pressing the buttons in time to an auditory cue with either just their left or their right hand (unimanual), or using both hands simultaneously (bimanual). The bimanual task was further divided into either an in-phase (mirror/symmetrical) or anti-phase (parallel/asymmetrical) condition. Participants were trained until behavioural task performance was equivalent between men and women. A

generalized psychophysiological interaction (gPPI) analysis was implemented to examine how functional connectivity in each condition was modulated by sex. In support of our hypothesis, women and men demonstrated differences in the neural correlates underlying bimanual movements. During the in-phase condition, women had greater functional connectivity between the right primary sensorimotor cortex and the right thalamus/bilateral caudate ($p\text{-}FDR < 0.01$), regions of the right posterior parietal cortex and the anterior cingulate/bilateral paracingulate gyri ($p\text{-}FDR < 0.05$), and within the cerebellum ($p\text{-}FDR < 0.05$). Meanwhile, men had increased functional connectivity between the right premotor cortex and right supplementary motor cortex ($p\text{-}FDR < 0.05$), as well as between the right supplementary motor cortex and left occipital lobe ($p\text{-}FDR < 0.05$). In the anti-phase bimanual condition, women had greater functional connectivity between the right supplementary motor cortex and the left insular cortex ($p\text{-}FDR < 0.05$). With equivalent performance, we observe sex differences in brain activity associated with bimanual movement control. These findings provide novel insight into how the brain controls such movements in both women and men.

Disclosures: **A. Rogojin:** None. **L.E. Sergio:** None. **D.J. Gorbet:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.10

Topic: E.04. Voluntary Movements

Support: NASA 80NSSC20K1499

Title: Emg-emg wavelet coherence analysis of muscle coupling during bimanual tasks in altered-gravity

Authors: *D. M. KENNEDY[1], O. PINTO NETO[3], M. WEINRICH[1], N. KELLER[1], Y. WANG[1], A. DIAZ-ARTILES[2];
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Abstract: Many activities associated with spaceflight require coordinated activation of involved muscles (e.g., controlling a rover, landing a spacecraft). Recent research has indicated that bimanual control is altered in microgravity (Diaz-Artiles, 2022). The current experiment was designed to determine the neurophysiological effects of gravity on bimanual coordination dynamics. A head-up tilt (HUT)/head-down tilt (HDT) paradigm was used to compare 5 simulated gravity levels (0, 0.25, 0.5, 0.75, 1 g). Right limb-dominant participants (N=12) were required to coordinate patterns of isometric forces in 1:1 in-phase and 1:2 multi-frequency patterns by exerting force with their right and left triceps brachii muscles. Lissajous plots and force templates were provided to guide performance. For each pattern (1:1, 1:2) participants performed three trials at the five gravity levels in an ascending (0-1 g) order, followed by 3 trials

in a descending (1-0 g) order. Muscle activity from the triceps brachii muscles were recorded. EMG-EMG coherence between the two EMG signals was calculated using wavelet coherence. As expected, results indicated significantly higher average coherence for the 1:1 task than the 1:2 task. Results also indicated average coherence was significantly greater at 1 g than 0 g. In addition, the wavelet coherence analysis captured periods of significantly high coherence in the Alpha band (5-13 Hz) at 1 g. Significant coherence in the Alpha band suggests a subcortical influence on muscle interactions. However, the wavelet coherence results demonstrated periods of significant coherence in the beta (13-30 Hz) and gamma (30-60 Hz) bands for the microgravity (0 g) and hypo-gravity (0.25-0.75 g) conditions. Higher coherence in Beta and Gamma bands suggest that the interactions between the involved muscles in altered-gravity are due to cortical influences. The results are consistent with previous research attributing manual control deficits in altered-gravity environments to cognitive and perceptual constraints. EMG-EMG wavelet coherences appears to be a rich source of information for the bimanual control of motor actions in altered-gravity environments.

Disclosures: D.M. Kennedy: None. **O. Pinto Neto:** None. **M. Weinrich:** None. **N. Keller:** None. **Y. Wang:** None. **A. Diaz-Artiles:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.11

Topic: E.04. Voluntary Movements

Support: Banting Research Foundation (D.F.C.)
Natural Sciences and Engineering Research Council of Canada (NSERC RGPIN-2017-06434, D.F.C.)
Natural Sciences and Engineering Research Council of Canada (Undergraduate Student Research Award, ALH, LAG)
Canadian Foundation for Innovation (CFI-JELF 37382, D.F.C.)

Title: High-resolution topographic map of muscle coordination in the frontoparietal cortex in rats using Intracortical microstimulation (ICMS) synced with electromyography (EMG)

Authors: *M. HAFEZI[1,2], L. A. GROCHOWSKI[1], A. L. BERGER[1], B. K. NG[1], A. LANG-HODGE[1], S. R. U[3], A. CIOK[1], D. F. COOKE[1,2];
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Abstract: How does the brain control motor behavior? Intracortical microstimulation (ICMS) has long been used to study the topographic representation of movements evoked from single sites in motor cortex. Although most studies have focused on the representation of a primary joint, we and others have shown that long-train ICMS results in muscle coactivations across

multiple joints that resemble naturalistic movements like feeding, reaching, running and defensive movements. Moreover, GABAergic manipulation of the ICMS-defined defensive domain results in up or down-regulation of that behavior, suggesting that the multi-joint representations revealed by long-train ICMS are not artifactual and do contribute to complex behaviors. Previous kinematic studies of complex ICMS-evoked movements have lacked specificity on the timing, sequence, and identity of activated muscles. Moreover, it has sometimes even been difficult to distinguish which body segments are responsible for observed movements, especially those of the trunk, shoulders, and hips. EMG studies adding temporal and anatomical precision have confirmed links between ICMS and natural behavior but have been limited to only one body segment in low-density maps. Here we combine high-resolution ICMS mapping of the whole-body topography with EMG to create broad muscle coactivation maps of frontoparietal cortex. We applied long-train (500 ms) ICMS to M1 and surrounding fields in anesthetized rats while recording video and EMG from 15 muscles. ICMS site density was moderately high with as many as 136 sites tested in one animal. Because spontaneous movements are common under light anesthesia, a novel closed-loop system controlled the stimulation timing and parameters using EMG feedback. This system can detect spontaneous activity in any of recorded muscles and pause the stimulation sequence to avoid recording contaminated data. EMG-based maps for each muscle were visualized via a custom Voronoi map generator in MATLAB. In real-time our recording system rejects the stimulation artifact that would otherwise obscure weaker signals. We routinely detect EMG evoked by ICMS current as low as 5 μA and see multiple muscles activated by ICMS at a given site at higher currents. We report muscle coactivation during evoked complex movements resembling defensive/aggressive and running/digging behaviors. We determine the topography of sequence, threshold, latency, and co-occurrence of evoked muscle activity. This suite of methodological improvements will enable us and other groups to make large, high-resolution motor maps of cortical muscle coordination and relate it to learning, motor performance, and response to injury.

Disclosures: **M. Hafezi:** None. **L.A. Grochowski:** None. **A.L. Berger:** None. **B.K. Ng:** None. **A. Lang-Hodge:** None. **S.R. U:** None. **A. Ciok:** None. **D.F. Cooke:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.12

Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI Grant Number 20K19629
JSPS KAKENHI Grant Number 22J00911
JSPS KAKENHI Grant Number 21H00967
JSPS KAKENHI Grant Number 22H03946
JP18dm0307005

Title: The left primary motor cortex is a critical hub in bimanual sequential learning

Authors: *Y. H. HAMANO[1,2,3], S. K. SUGAWARA[4,2,5], M. FUKUNAGA[2,5], N. SADATO[2,5,6]; [1]Fac. of Sci. and Engin., Waseda Univ., Shinjuku, Tokyo, Japan; [2]Div. of Cerebral Integration, Natl. Inst. for Physiological Sci., Okazaki, Japan; [3]JSPS Res. Fellow, Chiyoda, Tokyo, Japan; [4]Neural Prosthetics Project, Tokyo Metropolitan Inst. of Med. Sci., Setagaya, Tokyo, Japan; [5]Dept. of Physiological Sci., SOKENDAI, Hayama, Japan; [6]Res. Organization of Sci. and Technol., Ritsumeikan Univ., Kyoto, Japan

Abstract: Bimanual sequential skills are essential for our modern lives, such as typing. However, how the brain learns bimanual sequential skills is mainly unknown. Bimanual sequential skill requires two essential leanings: independently controlling two hands and representing the internal model of motor sequences. The primary motor cortex (M1) and the medial motor-related areas, such as the cingulate motor area (CMA), are involved in bimanual motor control. Our recent neuroimaging study demonstrated that the M1 represents the motor engram of unimanual sequential finger movements. Thus, we hypothesized that the M1 is critical for two learnings underlying bimanual sequential skill as a hub of the motor-control networks. Thirty-five healthy right-handed volunteers practiced a bimanual serial reaction time task in the 7T-MRI scanner to test this hypothesis. The behavioral task included two modes of bimanual coordination: mirror and parallel modes. The mirror mode required the simultaneous movements of the homologous fingers, whereas the parallel mode required the simultaneous movements of the heterologous fingers. We also introduced two types of movements: sequential and random movements. Thus, our behavioral task included four conditions based on a 2-by-2 factorial design. We utilized two learning parameters: repetitive suppression, which measures the prediction error within the predictive coding framework. Another is the sequence-specific increment of the BOLD signal, representing the formation of the internal model.The random parallel conditions evoked a more prominent decrement in the left M1 and the cerebellar vermis than the random mirror conditions. Based on the predictive coding framework, such decreased activation might reflect the reduced prediction error induced by the learning of independent bimanual control. Moreover, psychophysiological interaction analysis seeded at the left M1 showed the learning-related enhancement of the functional connectivity with the anterior cingulate cortex during parallel random conditions compared with random mirror conditions. The left M1 and the cerebellar vermis also showed the increased activities related to parallel mode-specific sequential learning depicted by the contrast between parallel and mirror sequence conditions, indicating the internal model of bimanual sequential movement. These findings concluded that the M1 is involved in both non-sequential and sequence-specific learnings of bimanual sequential skills as a hub of the motor-control networks.

Disclosures: Y.H. Hamano: None. **S.K. Sugawara:** None. **M. Fukunaga:** None. **N. Sadato:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.13

Topic: E.04. Voluntary Movements

Title: The Bimanual Coordination After Stroke Scale - a new behavioural assessment of bimanual coordination after stroke

Authors: *H. JORDAN, B. CHONG, O. NORRIE, C. STINEAR;
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Abstract: Bimanual coordination impairments after stroke can affect a person's ability to perform everyday tasks. There are currently no behavioural assessments that evaluate both bimanual coordination and bimanual task performance after stroke. Here we introduce the Bimanual Coordination After Stroke Scale (BCASS) as a behavioural assessment of coordination during bimanual task performance after stroke. The BCASS evaluates six categories of naturalistic bimanual tasks, and task categories differ depending on movement symmetry and task goal(s). This study aimed to refine the BCASS and assess its validity and reliability in people with chronic stroke. Further study aims included assessing the sensitivity of the BCASS to the effects of aging and stroke, as well as assessing how performance of BCASS tasks was influenced by movement symmetry and goal conceptualisation. This study included 30 younger and 30 older adults without stroke in addition to 30 participants with chronic stroke and unilateral upper limb weakness or altered sensation. All participants performed four BCASS assessments in two sessions and were assessed by two different raters in each session. Within-session interrater reliability, between-sessions intrarater reliability, and between-sessions interrater reliability of the BCASS were evaluated for participants with chronic stroke. Participants with chronic stroke also completed the Box and Block Test, Fugl-Meyer upper-extremity assessment, and ABILHAND assessment to validate the BCASS. Sensitivity of the BCASS was evaluated by comparing the three participant cohorts. Bimanual task categories in the BCASS were compared with one another to evaluate the influence of movement symmetry and goal conceptualisation. Total BCASS scores were sensitive to the effects of stroke but not age. All three reliability measures demonstrated excellent agreement (all ICCs > 0.95). BCASS scores correlated very highly with the unimanual assessments (both $\rho > 0.9$) and highly with the ABILHAND ($\rho = 0.79$). Movement symmetry and task goal(s) influenced BCASS performance as participants performed better for tasks with symmetric compared to asymmetric hand movements ($P < 0.001$), and for tasks with a single common-goal compared to two independent goals ($P < 0.001$). These preliminary results indicate the BCASS is a sensitive, valid, and reliable assessment of coordination during bimanual task performance for people at the chronic stage after stroke. The current study's findings should be evaluated in a larger stroke cohort and external validation of the BCASS is required.

Disclosures: H. Jordan: None. **B. Chong:** None. **O. Norrie:** None. **C. Stinear:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.14

Topic: E.04. Voluntary Movements

Support: NEI Grant EY012135
Washington University Cognitive Computational and Systems Neuroscience Fellowship

Title: Interhemispheric communication supports bimanual coordination: effects of posterior corpus callosum blockade

Authors: *J. KANG[1], E. MOOSHAGIAN[1,2,3], L. H. SNYDER[1];
[1]Neurosci., Washington Univ. Sch. of Med., Saint Louis, MO; [2]Cognitive Sci., Univ. of California San Diego, La Jolla, CA; [3]Systems Neurobio. Labs., The Salk Inst. for Biol. Sci., La Jolla, CA

Abstract: Bimanual coordination is essential to activities such as tying shoelaces or playing a musical instrument. It likely requires communication between areas on each side of the brain. Yet the causal relation between interhemispheric communication and bimanual coordination remains unclear. The Parietal Reach Region (PRR) encodes early planning of contralateral arm movements. To test for a causal link between interhemispheric communication and bimanual coordination, we compared behavioral performance and neural activity before and during reversible blockade of the callosal pathways connecting left and right PRR. We first identified white-matter pathways between left and right PRR using in vivo manganese-enhanced magnetic resonance imaging. We found that axons connecting left and right PRR across the callosum were restricted to the splenium. We then reversibly blocked this pathway using focal lidocaine injections while two animals (rhesus macaques) planned and then executed unimanual movements to a single target or bimanual movements to either a single target or two different targets. We recorded spikes and local field potentials (LFP) in PRR in both hemispheres simultaneously. We observed faster reaction times and less temporal synchrony in movements of the two arms during blockade. This suggests that callosal connections facilitate bimanual coordination so that the faster arm slows down to match the slower arm. Behavioral performance during blockade is consistent with our hypothesis that information carried by callosal pathways connecting left and right PRR supports bimanual coordination. To get an estimate of communication between left and right PRR as a function of task before and during blockade, we measured interhemispheric LFP-LFP coherence. Before blockade, we observed task-dependent levels of interhemispheric LFP-LFP coherence during the planning period primarily in the 20-30 Hz frequency range. Coherence was high when animals planned bimanual movements to a single target and low when animals planned bimanual movements to two different targets. This task- and frequency-dependent modulation of interhemispheric LFP-LFP coherence is consistent with the hypothesis that bimanual coordination relies on interhemispheric PRR communication. During blockade, the difference in LFP-LFP coherence between different bimanual movements was reduced or abolished. This indicates that the communication takes place via the callosum. In conclusion, interhemispheric communication between left and right PRR via the posterior corpus callosum supports sharing of information about the movement plan of each arm in service of bimanual coordination.

Disclosures: J. Kang: None. **E. Mooshagian:** None. **L.H. Snyder:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.15

Topic: E.04. Voluntary Movements

Support: NIH Grant P20GM103449
NIH P41 EB018783

Title: The neural dynamics of real and imagined movement

Authors: E. GABRIELSSON, E. DANIELSON, A. L. BEEBE, M. A. BISHOP, ***H. M. SISTI**; Psychology, Norwich Univ., Northfield, VT

Abstract: Stroke, and related movement disorders such as amyotrophic lateral sclerosis (ALS), result in loss of upper limb function, and hence, severe impairments of bimanual coordination. Motor imagery is an effective clinical intervention for accelerating recovery. Although motor imagery is increasingly used to enhance neurorehabilitation, the cognitive and neurophysiological parameters that inform effective strategies remain elusive. In addition, the nature and extent of interhemispheric coupling that occurs with bimanual coordination remains poorly understood. The aim of the present study is to elucidate the neural dynamics that underlie bimanual coordination during both real and imagined movement. To address this, healthy, young adults (n=13) learned a visuomotor tracking task in a single session using either one or both hands. Briefly, the right dial controls horizontal movement of a cursor and the left dial controls the vertical movement. The objective is to track a moving target on a screen by rotating the left and right dials at the appropriate speed and direction. Each participant was fitted with a 40-channel EEG cap (Compumedics, Neuroscan) before the start of the session. Phase 1 included unimanual control: 5 trials of left hand only (resulting in a vertical line) and 5 trials of right hand only (resulting in a horizontal line). Phase 2 required bimanual control: 20 trials of a 3:1 bimanual pattern followed by 20 trials of a 1:3 pattern. A 3:1 pattern requires 3 rotations of the left hand for every one rotation of the right hand. The 1:3 is the converse pattern. Trials were 10 sec in duration, i.e. elapsed time from target origin to target endpoint; the intertrial interval (ITI) was 5 sec. Each of the trial blocks was followed by a mental imagery condition (MI). Participants were asked to imagine performing the task they had just completed with eyes closed. Mental chronometric data were collected and vividness ratings were assessed by self-report immediately after each trial block. To assess learning across the more complex bimanual trials, a 2 x 2 ANOVA was performed of Trial (first vs. last) and Leading Hand (left vs. right). There was a main effect of trial [$F(1,10)=19.43$, $p<.001$] indicating that learning occurred within a single session. EEG analyses of active vs. rest (ITI) conditions, as well as real vs. imagined conditions, are underway. The results of these data may inform neurorehabilitation strategies for patients recovering from movement disorders of the upper limbs.

Disclosures: E. Gabrielsson: None. **E. Danielson:** None. **A.L. Beebe:** None. **M.A. Bishop:** None. **H.M. Sisti:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.16

Topic: E.04. Voluntary Movements

Support: National Institutes of Health Grant Number R01HD059783
Dorothy Foehr Huck and J. Lloyd Huck Distinguished Chair Endowment Fund

Title: Interlimb differences in multi-degree-of-freedom coordination during cyclic bilateral and unilateral wrist movements

Authors: *K. SELBY[1], G. SRINIVASAN[1], R. L. SAINBURG[2];
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Abstract: The dynamic dominance hypothesis of motor lateralization proposes that in right-handed individuals, the left hemisphere is specialized for intersegmental limb coordination and predictive control, and the right hemisphere is specialized for impedance control. This model predicts a dominant arm advantage for intersegmental coordination which has largely been demonstrated in discrete reaching movements, which we now extend to multi-degree-of-freedom (DOF) rhythmic cyclic movements of a single distal segment. Previous work has shown that when radial-ulnar deviation is performed at high frequencies, there is significantly more non-instructed movement (wrist flexion and extension) in the non-dominant hand. These less-efficient movements imply that dominant arm advantages extend to multiple-DOF movements at a single distal segment. However, that study only assessed unilateral movements and many of the tasks we perform in everyday life require use of both limbs simultaneously. We now ask whether this coordination advantage extends to bilateral movements. Our dynamic dominance hypothesis predicts that interlimb differences in coordination should persist for single segment, multiarticular cyclic movements and that they should persist during bimanual movements. Thirty-two right-handed young adults performed cyclic radial-ulnar deviation. Movements were performed both unilaterally and bilaterally at two frequencies. Participants were instructed to restrict movements to the horizontal plane. Movement outside of the task plane was quantified as frontal plane circumduction. Regardless of instructed frequency, the non-dominant hand displayed significantly more circumduction, with larger differences occurring between hands for the higher frequency. Interestingly, during bilateral performance, circumduction significantly increased in both hands, however interlimb differences persisted. These findings extend previous studies, indicating that these advantages extend to multiarticular coordination at a single and distal segment during rhythmic, non-discrete movements. In addition, bilateral coordination did not extend to the non-instructed plane, in which interlimb differences persisted. Thus, bilateral coordination, often referred to as coupling, appears to be dependent on task-conditions and feedback, and does not extend to aspects of coordination that are not task-related.

Disclosures: **K. Selby:** None. **G. Srinivasan:** None. **R.L. Sainburg:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.17

Topic: E.04. Voluntary Movements

Support: JSPS Grant 21K20293

Title: The effect of reaching duration on arm choice

Authors: *K. HIRAYAMA[1], R. OSU[1], Y. DARMON[2], N. SCHWEIGHOFER[2];
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Abstract: We unconsciously choose which arm to use in everyday life, for example, when picking up a cup. It has been reported that the arm with the higher expected reward value and the minimum expected cost is selected (Schweighofer 2015, Stoloff 2011). Whereas in our previous work, the reward was taken as the target hits, previous theoretical (Sutton and Barto 1998) as well as experimental (Schweighofer et al. 2006; Haith et al 2012, Shadmehr et al, 2010) studies, suggest that the reward value also depends on the time to reward, via hyperbolic or exponential discounting. Here, we, therefore, investigated whether prolonged movement time (MT) modulates the probability of arm choice. Thirteen right-handed neurotypical participants were recruited for this study. Motion sensors were attached to the participant's left and right index fingers. The participants' arm was hidden below a board, on which were projected the targets, as well as cursors showing the position of the left and right indexes. Participants performed arm choice in three conditions, with 88 trials in each. In the control condition, participants chose either their left or right arm to quickly reach a target randomly presented on a circle of 18 cm of radius at one of 11 positions. In the other two conditions, we added velocity-dependent noise (VDN) to either the left or right cursor position during the reach. Because of the VDN, in order to reach the targets, the participants had to reduce their reaching speeds and prolonged the MT in the corresponding arm. We estimated the point of subjective equality (PSE): the virtual point in space at which participants have an equal probability of choosing the right or the left arm for the reach, with a negative PSE indicating a larger right-arm choice probability. The MTs and PSEs with and without VDN conditions were statistically compared. The MTs of the left arm and right arm with VDN were significantly larger in comparison with that of the left arm and the right arm without VDN, respectively ($P < 0.01$) (left arm; VDN MT = 2.0 ± 0.17 sec.; no VDN MT =0.32 ± 0.08 sec., right arm; VDN MT = 2.1 ± 0.16 sec.; no VDN MT = 0.35 ± 0.12 sec.). The PSE of the left arm with VDN was significantly smaller ($P < 0.01$; PSE = -26.1 ± 12.9 deg.) and that of the right arm with VDN significantly larger ($P < 0.01$; PSE = 17.9 ± 12.3 deg.), compared to that without VDN (PSE = -4.5 ± 8.5 deg.). These results suggested that prolonged MTs decreased the arm-choice probability. We are currently studying via modeling whether such effects of MT on arm choice are due to exponential or hyperbolic discounting. In future work, we will test whether

the increase in MT in individuals post-stroke is a cause of the reduced arm non-use in this population.

Disclosures: **K. Hirayama:** None. **R. Osu:** None. **Y. Darmon:** None. **N. Schweighofer:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.18

Topic: E.04. Voluntary Movements

Title: Spatially relevant visual cues reduce the planning load of discrete and rhythmic bimanual movements compared to abstract symbolic visual cues.

Authors: *R. DENYER, L. A. BOYD;
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: When humans perform rhythmic bimanual movements, accuracy improves when both hands move symmetrically in time with one another compared to when both hands move in an asymmetric manner. Furthermore, as movement frequency is increased, asymmetric patterns inevitably transition to symmetric patterns, while transition from symmetric to asymmetric rarely occurs. While the tendency to transition into symmetric patterns has traditionally been thought to be due to constraints inherent to the motor system, other streams of evidence suggest that the way bimanual action is represented by external factors such as task stimuli can shift the way in which action is perceived and confer performance gains. For example, discrete bimanual reaches have a decreased reaction time (RT) and a reduced RT cost for asymmetric reaches when reaches are cued with an imperative stimulus that directly denotes reach location with an LED light in the reaching plane compared with stimuli that denote reach location with abstract symbols. To test whether this effect generalizes from discrete to rhythmic bimanual movements, we recruited 159 participants to perform (1) a bimanual 4-choice RT task (CRTT) and (2) a series of bimanual 4-finger rhythmic tapping tasks. Participants performed 2 versions of a CRTT, one in which action was cued with spatially relevant boxes that represented the location of each task relevant effector (right index, right middle, left middle, left index), and another in which action was cued with 4 words that denoted each bimanual finger combo. The same cueing conditions were used in the bimanual 4-finger rhythmic tapping task, where participants performed symmetric and asymmetric tapping in discrete blocks of 32 taps, with movement frequency starting at 1 hertz (Hz) and increasing by 0.2 Hz after every block up to 3.2 Hz. As predicted, bimanual finger presses had a lower RT ($F1, 158 = 998.8$, $p < 3e\text{-}70$, $\eta p2 = 0.86$) and a reduced RT cost for asymmetric presses ($F1, 158 = 36.2$, $p < 1e\text{-}8$, $\eta p2 = 0.19$) when movement was cued with spatially relevant stimuli. An effect of cue type was also found in the rhythmic task, where symmetric and asymmetric tapping patterns were found to have lower absolute mean error of relative phase ($F1, 158 = 26.6$, $p < 7e\text{-}7$, $\eta p2 = 0.15$) and a higher time until phase transition ($F1, 158 = 51.9$, $p < 2e\text{-}11$, $\eta p2 = 0.25$) when movement timing was cued with spatially relevant

stimuli. Taken together, our results suggest that cognitive-perceptual factors affect planning and execution of discrete and rhythmic bimanual finger movements. We discuss a planned experiment employing repetitive transcranial magnetic stimulation to probe the neural mechanism underpinning this effect.

Disclosures: R. Denyer: None. **L.A. Boyd:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.19

Topic: E.04. Voluntary Movements

Support: German Research Foundation (PA 774/13-1; 13-2; SPP 1772)

Title: Lissajous displays enhance visual and spatial transfer in a continuous multi-frequency task

Authors: Author Block needs to be regenerated

Abstract: Multi-frequency tasks requiring continuous limb motion pose a challenge for the nervous system because both hemispheres have to interact. Accumulating evidence indicates that providing salient integrated visual feedback facilitated multi-frequency performance and transfer. Lissajous templates integrate the spatial position of two limbs into a single point. Experiments indicated that individuals could effectively transfer between bimanual coordination patterns when both upper limbs have to produce different temporal parameters when provided Lissajous feedback. To manipulate the relative frequency of each limbs' movement, participants performed the task with Lissajous displays that differed in their visual orientation or appearance. In the Panzer et al., (2021) experiment, individuals performed left and right hand movements to move a cursor along a Lissajous curve. The flexion/extension of the left hand moved the cursor up/down, while that of the right hand moved the cursor left/right. Individuals performed the task under two visual configurations that were different in their orientation. In the first orientation, the left hand was to move faster than the right (2:1), whereas in the second orientation (90° rotated) the right hand that had to move faster (1:2). In this experiment visual transfer was required. Individuals could effectively tune in a new coordination pattern without additional practice. The objective of the present experiment was to determine if individuals provided a testing environment when keeping the visual orientation stable and instead spatial transfer was required without additional practice by assigning the up/down cursor movement to the right and the left/right cursor movement to the left hand? Dominant right handers (N = 29) were randomly assigned to one of two groups: Same Visual Display (SVD: n = 15; spatial transfer) and Different Visual Display (DVD: n = 14; visual transfer). By changing from the 2:1 to the 1:2 pattern in the SVD group the direction of the cursor movement for the left limb changed from up/down to left/right and for the right limb from left/right to up/down. The order of the coordination patterns 2:1 and 1:2 with Lissajous feedback was counterbalanced. The analysis demonstrated that regardless of whether

visual orientation or the cursor direction changed, individuals could effectively transfer between the coordination patterns. This indicated that Lissajous feedback results in inimitable levels of bimanual coordination across a vast array of coordination requirements and allow individuals to exploit the broad capabilities of the perception-action system and overcome the constraints at the nervous system.

Disclosures: S. Panzer: None. **C. Pfeifer:** None. **C.H. Shea:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.20

Topic: E.04. Voluntary Movements

Title: The investigation of bilateral M1 excitability after training with a bimanual skill

Authors: *Y. WANG[1], M. M. WEINRICH[2], S. BAO[2], Y. LEI[2], D. L. WRIGHT[2], D. M. KENNEDY[2], J. J. BUCHANAN[2];
[1]Dept. of Kinesiology and Sport Mgmt., Texas A&M Univ. - Site 2, College Station, TX; [2]Texas A&M Univ., College Station, TX

Abstract: Motor consolidation after initial training is crucial in refining and stabilizing a trained motor skill. Previous research has often indicated that the change of corticospinal excitability in the primary motor cortex (M1) following training is associated with qualitative changes in motor skills in the retention test. However, little research has investigated the excitability of M1 from both hemispheres after training with a novel bimanual skill. Therefore, the present experiment aims to investigate the characteristics of M1 excitability in both hemispheres after training with a novel bimanual skill. Right-hand dominant individuals (N = 12, age = 22.3) were recruited to perform a bimanual 90^{o} relative phase (RP) pattern by coordinating the movement of their index fingers. The training consisted of 30 trials with a 20-s duration per trial. Augmented visual feedback of the 90^{o} RP pattern was provided for the entire training. Assessment of the performance of the 90^{o} RP pattern occurred with a retention test immediately following training and after a 6-h delay. The intrinsic dynamics (0^{o}, 180^{o}) were assessed at the baseline, immediately after training, and 6-hour delay. Estimates of M1 excitability of the left and right hemispheres using single-pulse transcranial magnetic stimulation (TMS) occurred before and immediately after training. The behavioral results align with previous findings revealing that improved bimanual performance of 90^{o} RP pattern emerges at a 6-hour retention test mediated via consolidation process compared to performance immediately after the training. Further, the formation of a new attractor state at 90^{o} destabilized the intrinsic dynamics (0^{o}, 180^{o}) at the 6-hour retention test. TMS analysis revealed elevated motor evoked potential (MEP) immediately after the training of bimanual 90^{o} RP for both hemispheres, indicating that M1 excitability increased for both hemispheres following training. The current MEP results also align with previous neuroimaging findings that bimanual training activated M1-dependent neural circuits

for both hemispheres. Furthermore, it is possible that increased M1 excitability in both hemispheres is associated with the improved bimanual performance in the retention test after 6-hour delay.

Disclosures: Y. Wang: None. **M.M. Weinrich:** None. **S. Bao:** None. **Y. Lei:** None. **D.L. Wright:** None. **D.M. Kennedy:** None. **J.J. Buchanan:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.21

Topic: E.04. Voluntary Movements

Title: Facilitation of corticospinal excitability in the rectus femoris muscle during motor imagery.

Authors: *K. ISHIKAWA[1], N. KANEKO[1], A. SASAKI[2], K. NAKAZAWA[1];
[1]Univ. of Tokyo, Meguro-ku, Japan; [2]Osaka Univ., Suita-shi, Japan

Abstract: Motor imagery (MI) is known to induce central nervous system activity related to actual movement, e.g., MI increases corticospinal excitability of the muscles related to the imagined movements. In everyday life and in sports, the thigh is a very important part of the body for walking and other activities. However, while many studies have focused on corticospinal excitability in lower leg muscles, such as the tibialis anterior muscle, few studies have focused on the thigh muscles. The purpose of this study was to investigate how corticospinal excitability of the RF muscle would be modulated during MI of single-joint movements of the knee and ankle. Twelve healthy adults participated in this study. The electromyographic signal was recorded from the RF muscle using surface electrodes. Corticospinal excitability was assessed by motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation. The optimal stimulation spot was searched for over the primary motor cortex where the largest MEP could be recorded from the right RF muscle. The stimulus intensity was set at 120% of the motor threshold. MEPs were recorded during rest and four MI conditions. In the rest condition, participants were asked not to imagine anything and not to contract their muscles. In the MI condition, they were asked to imagine knee flexion, knee extension, ankle plantar flexion, and ankle dorsiflexion without muscle contraction. The results showed that MEP amplitudes in the RF muscle were significantly facilitated during MI of the knee extension, ankle plantar flexion, and ankle dorsiflexion, but not knee flexion. Moreover, there was no significant difference in the extent of MEP increase between MI tasks. Overall, our results showed that the corticospinal excitability of the RF muscle was facilitated not only during MI of knee extension, in which the RF muscle is the agonist muscle but also during the other lower leg movement imagery. There may be a neural connection between the muscles of the lower leg and the rectus femoris within the primary motor cortex. The finding that corticospinal excitability was not facilitated during motor imagery of knee flexion suggests that intracortical

inhibition similar to reciprocal inhibition may play a role in the RF muscle, the antagonist muscle of the biceps femoris muscle.

Disclosures: K. Ishikawa: None. **N. Kaneko:** None. **A. Sasaki:** None. **K. Nakazawa:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.22

Topic: E.04. Voluntary Movements

Support: Swiss Excellence Scholarship for Doctoral Research
SNSF Eccellenza Grant (no. 514347)

Title: A tripartite motor control algorithm governing goal-directed antennal grooming in Drosophila

Authors: *P. OZDIL, A. J. IJSPEERT, P. RAMDYA;
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Abstract: The fly, *Drosophila melanogaster*, uses its antennae to perform many ethologically important behaviors including odor-driven search, and wind-based navigation. Flies keep these versatile sensors clean by grooming them with their forelegs. Although neural pathways, including mechanosensory neurons in the antennal Johnston's Organ, that drive grooming have been identified, the overarching control algorithm-how individual body parts and associated neural circuits coordinate to enable successful grooming-remains unknown. Here, we elucidate rules underlying the coordination of *Drosophila* antennal grooming through behavioral experiments, detailed 3D kinematic analyses, and data-driven modeling. First, we will show how antennal grooming consists of the coordination of three body regions-the head, antennae, and forelegs. During antennal grooming, flies lower and rotate their head while rhythmically sweeping their forelegs over one antenna and retracting the other antenna. We use markerless 3D pose estimation approaches to quantify limb, head, and antennal kinematics during either air puff-induced, or optogenetics-induced (i.e., stimulation of Johnston's organs, or antennal descending neurons) grooming. To dissect the relative importance of each of these body part movements, we replay measure 3D kinematics in a physics-based neuromechanical simulation of the fly (NeuroMechFly). This allows us to systematically perturb the movement of individual body parts as well as identify the contribution of biomechanics to observed kinematics. Finally, we present data-driven mathematical and neural network models that recapitulate behavioral dynamics and are used to explore the likely couplings between neural circuits controlling the head, antennae, or limbs.

Disclosures: P. Ozdil: None. **A.J. Ijspeert:** None. **P. Ramdya:** None.

Poster

719. Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 719.23

Topic: E.04. Voluntary Movements

Support: Boehringer Ingelheim Fonds PhD Fellowship
Swiss National Science Foundation Eccellenza Grant #181239

Title: Reverse-engineering Drosophila locomotor control through data-driven modeling

Authors: *S. WANG, P. RAMDYA;
Brain Mind Inst. & Inst. of Bioengineering, EPFL, Lausanne, Switzerland

Abstract: Animals are capable of highly efficient, adaptive, and robust behaviors unmatched by even the most advanced robots. These high-level behaviors comprise motor programs controlled by lower motor centers—the spinal cord in vertebrates, or the ventral nerve cord (VNC) in insects. However, the mechanisms allowing the nerve cord to enable agile body control remain largely obscure. Here, we are investigating these mechanisms by reverse-engineering circuits that control walking and grooming in the fly, *Drosophila melanogaster* (adult females 2–3 days post eclosion). Specifically, we are building neural network models of the VNC to drive the behavior of NeuroMechFly, a neuromechanical *Drosophila* model embedded in a physics simulator. Using modern imitation learning approaches from machine learning, we are optimizing these models to recapitulate recorded fly walking and grooming behaviors at the level of detailed limb kinematics. These behaviors are either spontaneous (wildtype strain) or optogenetically stimulated (MDN-Gal4>UAS-CsChrimson and aJO-Gal4>UAS-CsChrimson strains). Compared to work in the past using neuromechanical animal models to study locomotion, our work benefits from tighter constraints from animal behavior: rather than maximizing high-level behavioral traits such as walking speed and stability, our model learns to execute the exact movements performed by the animal thanks to detailed 3D pose reconstruction. We will describe topological features of our neural network models—particularly inter-leg coupling, recurrence, and sensory feedback—that influence our models' abilities to reproduce animal behavior. Thus far, our modeling results imply that specific neural wiring motifs are more amenable to coordinate walking. We aim to next investigate how descending instructions can be decoded to switch between discrete actions like walking and grooming. We envision that the connection patterns identified by data-driven modeling can be structurally validated using a *Drosophila* VNC electron microscopy (EM) dataset. By building deep artificial neural network models with biologically-plausible topologies, we aim to bridge the gap between detailed modeling of isolated circuits and black-box modeling of the whole motor controller as well as to inspire the development of more efficient artificial controllers for robots and reinforcement learning agents.

Disclosures: S. Wang: None. **P. Ramdya:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.01

Topic: E.04. Voluntary Movements

Support: Independent Research Fund Denmark 0132-00141B

Title: How is perception of movement connected to objective performance and brain signals? - A transcranial magnetic stimulation study

Authors: *I. BRANDT[1], V. SIMONELLI[2], I. SVECOVÁ[1], M. L. ARUP[1], V. LANGE[3], T. GRÜNBAUM[3], M. S. CHRISTENSEN[3];
[1]Dept. of Neuroscience, Univ. of Copenhagen, Copenhagen, Denmark; [2]Sapienza Univ. of Rome, Rome, Italy; [3]Dept. of Communication, Univ. of Copenhagen, Copenhagen, Denmark

Abstract: Objective Which role, if any, does conscious experience of own movement play in motor control? Do we have conscious access to movement-related brain signals? This is an exploratory TMS study with the aim to investigate the relation between subjective angle aim, the objective angle performance, and a measure of the efferent signal, the motor evoked potential (MEP). Probing the content of subjective aspects of movement is a first step in testing its functional role.
Methods Participants (N = 6 (5 F)) perform an angle task with index finger flexion (7x6 min) during TMS and EMG measurement of flexor, extensor, and first dorsal interosseus (FDI). The participant creates a subjective scale of angle (1-9), and for each trial (~4 sec) a tone indicates aim 5 or 7 on this scale. Participants hold either an internal or external focus of attention (FoA). With a linear mixed model (LMM) we investigate the effect of aim, objective angle, FoA, angle at TMS stimulation and background EMG on log(MEP/EMG) of the flexor muscle. We compare 303 possible models that have up to 3-way interactions using Bayes factors (BF).
Results The model comparison favors a LMM with three 2-way interactions of aim, objective angle, and FoA, and shows BF = 5.12 compared with the 2nd best model, a LMM with two 3-way interaction, showing a BF=$2.33*10^{35}$ compared to a full linear model without interactions. The favored model reveals a statistically significant effect of objective angle (Est.=-2.13±0.25, $p<2*10^{-16}$), angle at TMS stimulation (Est.=1.50±0.13, $p<2*10^{-16}$), extensor EMG (Est.=-27.5±2.0, $p<2*10^{-16}$), FDI EMG (Est.=-6.2±1.5, $p<2.2*10^{-5}$), aim and FoA interaction effect (Est.=-0.63±0.10, $p<5.3*10^{-10}$), aim and objective angle interaction effect (Est.=0.86±0.30, p<0.0038), and FoA and objective angle effect (Est.=1.36±0.29, $p<2*10^{-6}$).
Conclusion We see a statistically significant effect of objective angle on MEP, indicating that the angles the participants are performing are reflected in the MEP. However, the lack of effect of aim on MEP indicates that the participants do not have conscious access to this signal. Still, the model comparison favors a model with interaction between aim, objective angle, and FoA on MEP, indicating a complex interaction between these factors.

Disclosures: I. Brandt: None. **V. Simonelli:** None. **I. Svecová:** None. **M.L. Arup:** None. **V. Lange:** None. **T. Grünbaum:** None. **M.S. Christensen:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.02

Topic: E.04. Voluntary Movements

Support: NSERC Grant 418589

Title: From motivation to action: action utility better predicts changes in pre-movement beta-band activity than movement speed

Authors: *E. PIERRIEAU, J.-F. LEPAGE, P.-M. BERNIER;
Univ. de Sherbrooke, Sherbrooke, QC, Canada

Abstract: The amplitude of beta-band activity (13-30 Hz; β) from motor regions has been associated with motor parameters such as velocity. This view comes mainly from studies of Parkinson's disease, in which dopamine depletion is accompanied by an increase in β, correlated with the severity of bradykinesia. However, the existence of a linear association between β and movement velocity is still debated. An alternative explanation is that β reflects the action valuation process, as dopamine is indeed thought to encode action utility, which in turn influences movement velocity. Consequently, the objective of the present study was to dissociate the velocity and utility of a movement, and test their respective influence on β. 31 healthy right-handed participants were asked to reach a target with a peak velocity comprised in a specific range while EEG was recorded. The required velocity was indicated by a gauge: the higher the filling of the gauge, the faster the movement had to be performed, with maximal filling corresponding to the maximal velocity participants could reach. The target could be located at two different positions, so that the maximal peak velocity to reach each target was significantly different. This difference was leveraged to define conditions in which the velocity required to reach the two targets was identical but the relative effort different (i.e., gauges differently filled) and vice-versa. We hypothesized that if β reflects action utility rather than velocity, β should be similar for a given gauge's filling across the two targets, in spite of different velocities. Results showed a significant effect of the gauge's filling, but not of the presented target on β. Furthermore, β did not vary linearly with the level of the gauge as it was significantly decreased both for high and low fillings as compared to a medium filling. Probability density functions of peak velocities revealed that the most chosen velocities were on average closer to the ones required at a medium filling. These preferences were used to model action utility as a function of peak velocity for each target. Modulations of action utility across conditions approximated the ones found in β, and linear mixed effect modeling revealed that action utility but not peak velocity significantly predicted variations of β. These results show that modulations of β with movement velocity are better explained by changes in action utility rather than velocity *per se*. In addition to supporting the association between β and dopaminergic activity, these results bring up the intriguing perspective that manipulating β may influence motor motivation and thus effort exertion.

Disclosures: **E. Pierrieau:** None. **J. Lepage:** None. **P. Bernier:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.03

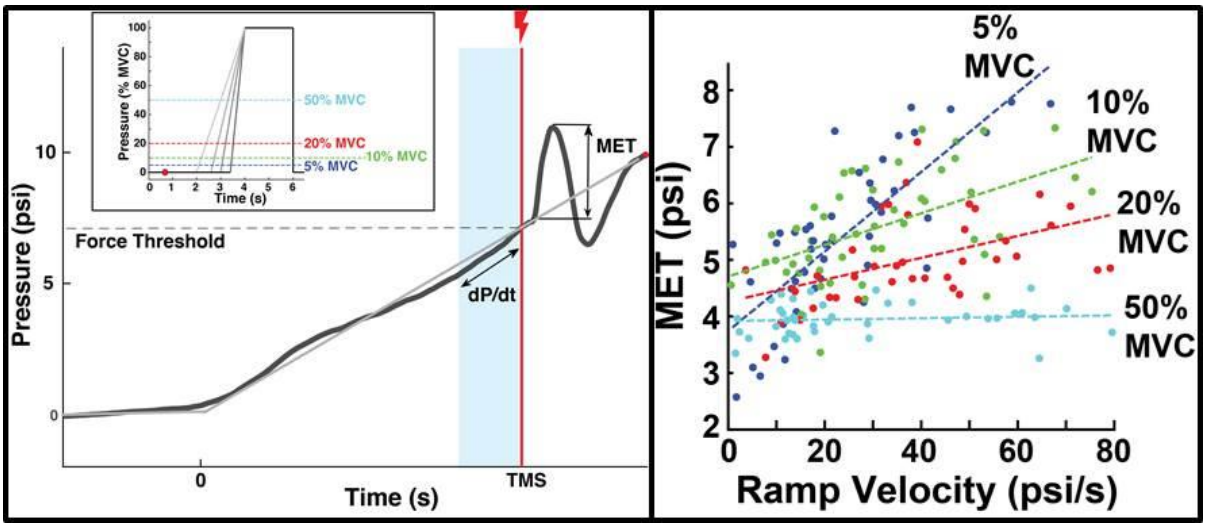
Topic: E.04. Voluntary Movements

Support: NIH Tufts CTSI 3UL1TR002544-04S1
Cinque Foundation
NSF CBET-2117626

Title: Motor Facilitation is Force and Force Rate Dependent

Authors: N. PINKES[1], S. JACOBS-SKOLIK[1], **M. YAROSSI**[1], V. SHARMA[2], E. KEMMERLING[3], E. TUNIK[1], O. SOTO[2];
[1]Northeastern Univ., Boston, MA; [2]Tufts Med. Ctr., Boston, MA; [3]Tufts Univ., Medford, MA

Abstract: Abnormal voluntary activation of motor neurons is a hallmark of numerous neurological diseases, including amyotrophic lateral sclerosis (ALS). Voluntary activation is associated with an increase in the excitability (facilitation) of the cortical and spinal motoneurons participating in the task. Transcranial magnetic stimulation provides a non-invasive means to probe facilitation of motor outputs, however most attempts to date have done so only under static isometric contractions, likely missing effects of activation dynamics. Our goal was to characterize the relationship between facilitation of corticospinal drive (measured as the amplitude of the TMS-induced motor evoked twitch, MET) and two key features of isometric force production: the instantaneous force level and the rate of change in force level. Eleven healthy young individuals participated following IRB approved informed consent. Participants were seated in front of a LCD with each arm-hand supported by an armrest. The right hand gripped a standard sphygmomanometer bulb connected to a pressure transducer sampled at 2000Hz. Participants traced 4 ramp-and-hold shaped pressure trajectories (Fig. 1, left). TMS to the contralateral motor cortex was triggered at 5, 10, 20, and 50% of MVC for each ramp condition. Participants completed 10 trials per ramp velocity - trigger threshold pair, pseudorandomized across 4 blocks. Pressure velocity (dP/dt) at the time of stimulation was calculated as the mean velocity in a 100 ms window prior to TMS. MET amplitude was quantified from the twitch in response to TMS. For each pressure level, a linear regression was fit to determine the slope of the relationship between MET amplitude and dP/dt at the time of stimulation (force-dependent facilitation, FdF). FdF was found to be strongest at lower force levels and decays as the force level increases (Fig. 1, right). This measure may provide a 'stress test' to corticospinal facilitation that may serve as a sensitive way to measure failure of facilitation in neurological diseases such as ALS.



Disclosures: **N. Pinkes:** None. **S. Jacobs-Skolik:** None. **M. Yarossi:** None. **V. Sharma:** None. **E. Kemmerling:** None. **E. Tunik:** None. **O. Soto:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.04

Topic: E.04. Voluntary Movements

Support: NIH R01DC019498

Title: The neural representation of probabilistic phonotactics for sequential speech production

Authors: ***S. DURAIVEL**[1], S. RAHIMPOUR[9], K. BARTH[2], D. G. SOUTHWELL[3], S. R. SINHA[4], N. LAD[5], M. VESTAL[6], E. M. THOMPSON[6], A. H. FRIEDMAN[5], J. VIVENTI[7], G. B. COGAN[8];
[1]Biomed. Engineering, Neurosurgery, Neurol., [2]Biomed. Engin., [3]Biomed. Engineering, Neurosurgery, Neurology, Neurobiology, Duke Comprehensive Epilepsy Ctr., [4]Neurol. and Duke Comprehensive Epilepsy Ctr., [5]Neurosurg., [6]Neurosurg. and Duke Comprehensive Epilepsy Ctr., [7]Biomed. Engineering, Neurosurgery, Neurobiology, and Duke Comprehensive Epilepsy Ctr., [8]Neurosurgery, Neurology, Duke Comprehensive Epilepsy Center, Ctr. for Cognitive Neurosci., Duke Univ., Durham, NC; [9]Dept. of Neurosurgery, Clin. Neurosci. Ctr., Univ. of Utah, Salt Lake City, UT

Abstract: The neural basis of speech production involves multi-level speech planning that converts abstract semantic representations to motor programs for speech articulation. A crucial step in this speech planning is the transformation of internal lexical (words) representations into phoneme sequences (phonological encoding, e.g., ‘cat’, /*k*/→/*a*/→/*t*/). While recent work using

intracranial recordings has identified that the speech motor cortex (SMC) encodes articulatory features of phonemic units during speech articulation, the speech planning mechanisms that transform phonological sequences to phoneme articulation are not well established. We sought to investigate this speech transformation by using a speech task that explicitly isolates planning from articulation stages and can track speech sequences independently of overt semantic information: a nonword delayed repetition task. We hypothesized that if phonological encoding is part of the speech planning process, information about the statistical relationship between phonemes (phonotactics) should be present during a delay/planning period. This phonological encoding during speech planning would thereby support subsequent sequential phoneme articulation. To test this hypothesis, we performed cortical recordings from 22 epilepsy patients (11 female, mean age - 27.4) implanted with intracranial-electroencephalographic electrodes in a pre-operative clinical monitoring setting. After a delay, patients repeated auditorily presented nonwords that had parametrically varying phonotactic probabilities. Our results show a significant increase in high-gamma power (HG: 70 - 150 Hz; $p < 0.05$; one-sided permutation test) in electrodes from a wide range of areas including the premotor cortex and SMC both during articulation and in the preceding delay period. To characterize phonological encoding, we developed a time-resolved multivariate decoding strategy to predict the phonotactics (BLICK score) from HG using electrodes in premotor and SMC. Our results revealed significant BLICK prediction during the delay period as measured by R-squared values ($p < 0.05$, F-statistic test). In addition, our temporal-generalization maps identified diffuse but stable decoding contours during the delay, suggesting a neural architecture that maintains and plans information for sequences for speech articulation. These results highlight the presence of phonological encoding information during a delay/planning period for speech articulation. Our results also demonstrate the utility of intracranial recordings for revealing separate planning and articulation components for speech production.

Disclosures: S. Duraivel: None. **S. Rahimpour:** None. **K. Barth:** None. **D.G. Southwell:** None. **S.R. Sinha:** None. **N. Lad:** None. **M. Vestal:** None. **E.M. Thompson:** None. **A.H. Friedman:** None. **J. Viventi:** None. **G.B. Cogan:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.05

Topic: E.04. Voluntary Movements

Support: John Templeton Foundation #61283
Fetzer Institute, Fetzer Memorial Trust #4189

Title: Decoding action selection from preceding neural activity

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Abstract: The readiness potential (RP) is a slow negative deflection in the electroencephalographic (EEG) activity of the brain prior to a voluntary motor movement. Previous research has interpreted the RP as indicating that decisions are made unconsciously, without the participant's conscious awareness. However, no EEG studies have examined whether neural activity can be used to predict the outcome of a decision before conscious awareness. The goal of this research project is to use machine learning algorithms and EEG to investigate whether we can predict the outcome of a spontaneous decision from underlying brain activity. More specifically, we are examining whether the RP can give insight into the outcome of the decision, prior to the participant's awareness of the decision. We are attempting to determine whether the participant made a right or left-hand button press under three conditions: an instructed condition in which the participant is told at the start of the trial which hand to use, an early decision condition in which the participant makes their own decision about which hand to use at the start of the trial, and a late decision condition in which the participant intentionally delays making their decision until just before their response. These conditions allow us to create a proxy for the participant's awareness of the decision. In all three conditions, the participants perform a computer task where they watch a rotating clock on the screen and input their responses (left or right) into a button box after one full rotation. Machine learning and EEG is then used to predict how early and how accurately we can decode the outcome of the decision. More specifically, this enables us to investigate decisions' decoding accuracies with respect to participants' awareness. If cortical activity preceding awareness encodes the decision's outcome, then this would support the hypothesis that the brain is making decisions unconsciously, while the conscious self simply witnesses them. On the other hand, if the decision's outcome on late-decision trials cannot be predicted using preceding cortical activity, then this would not support the hypothesis that spontaneous decisions-to-move are made unconsciously in advance. Our current results suggest that decoding accuracy increases only after the participant is aware of their decision and has decided which button they will press.

Disclosures: **A. Whitmarsh:** None. **L. Jeay-Bizot:** None. **U. Maoz:** None. **A. Schurger:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.06

Topic: E.04. Voluntary Movements

Support: NSERC

Title: Exploring the effects of cerebellar intermittent theta burst stimulation on error feedback and motor planning cortical activity during motor adaptation

Authors: *L. KAETHLER, K. E. BROWN, R. STAINES;
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Abstract: Motor adaptation is marked by neurophysiological changes in the primary motor cortex; however, other regions of the motor network (i.e cerebellum and non-primary motor areas) also contribute to this process. Enhancing cerebellar activity has been shown to increase the rate of motor adaptation, though it is unclear what mechanisms of motor control are influenced by the cerebellum to promote adaptation. The aim of the current study was to gain insight into activity in the sensorimotor cortex during adaptation and to understand how sensory feedback integration and motor planning processes are affected by enhancing cerebellar activity. We hypothesized that enhancing cerebellar activity using intermittent theta burst stimulation (iTBS) would modulate sensorimotor cortical activity to increase excitability. This was measured by changes in the pre movement alpha (α: 8-12 Hz) and beta (ß: 13-30 Hz) band activity and the movement related cortical potential (MRP), as well as in the post movement α and ß band activity, reflective of changes in the pre-movement motor planning and post-movement sensory and error feedback. To test this, 34 healthy young participants completed a practice block of training on a visuomotor task, where they used a joystick to move a cursor to one of 8 target locations equidistant from a central starting point, before receiving either active or sham cerebellar iTBS. Following iTBS participants returned to the task to complete 400 trials of the visuomotor task, with a 45º rotation to the cursor movement. Angular error at peak velocity was the primary behavioural measure. Pre- and post- movement α and ß band activity and MRP measured in the sensorimotor cortex were the neurophysiological measures. α and ß band activity was measured as a change in power from baseline to the pre- or post-movement time windows. Trials were epoched with the movement onset at time 0 for MRPs and premovement α and ß measures and to the cessation of movement for the post-movement measures. Measures were compared between groups in the motor adaptation phase of training and at the end of training once the rotation had been learned. Analysis of the behavioural data confirmed that cerebellar iTBS significantly improved the rate of adaptation. Preliminary analyses of the neurophysiological data showed cerebellar iTBS increased motor cortical excitability, as seen in the premovement ß event related desynchronization (ERD), during motor planning across the training session. Results from this study will help to deepen our understanding of the cerebellar role in motor control and how increasing cerebellar activity can promote faster motor adaptation.

Disclosures: L. Kaethler: None. **K.E. Brown:** None. **R. Staines:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.07

Topic: E.04. Voluntary Movements

Support: NIH R01 NS101013-01
NIH R01 EB026429

NIH U24 NS109103
NIH U01 NS108916
NIH P41 EB018783
McDonnell Center for Systems Neuroscience
Foundazione Neurone

Title: A motor reaction-time task evokes band-limited high gamma coherence between task-responsive sensory-motor cortical areas

Authors: *S. ANAND[1], H. CHO[3], M. ADAMEK[4], H. BURTON[5], P. BRUNNER[6], E. C. LEUTHARDT[2], D. MORAN[2];
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Abstract: Synchronous neuronal oscillations are ubiquitous in the mammalian brain and may affect cognition and behavior. These oscillations occur across an extended spectral range, with unique roles purportedly served by different frequency bands. For example, electrical activity in the canonical low gamma band (30-50 Hz) is thought to arise from inhibitory interneurons acting on cortical pyramidal cells. Low-gamma coherence has been extensively studied in numerous sensory-motor contexts.
The canonical high-gamma band (70-170 Hz) is largely considered a broadband signal whose electrical activity reflects various consequences of neuronal spiking (like afterpotentials and hyperpolarization) though high-frequency oscillations are also present. Therefore, there has not been as much focus on high gamma coherence.
We studied cortical-cortical coherence in relation to presentation of sensory cues and subsequent motor response. Our objective was to relate stimulus-evoked activity and task response to identify potential roles of coherence. We also investigated the relationship between coherence and power across frequency bands. Participants were presented with a visual, auditory, or tactile stimulus, prompting a quick button press with their thumb. We calculated coherence between electrodes that recorded an increased high gamma power, a reliable index for population-level cortical activity in response to auditory stimulation or motor activity. We analyzed electrocorticography data from four participants who had at least two motor and auditory responsive electrodes.
In all cases, high gamma activity recorded from button-press-responsive electrodes showed increased coherence during the button press compared to baseline. There was no equivalent, consistent increase in high gamma coherence between auditory stimulus-responsive areas during auditory stimulus presentation. Coherence during the button press was independent from power across trials in all analyzed frequency bands.

Disclosures: S. Anand: None. **H. Cho:** None. **M. Adamek:** None. **H. Burton:** None. **P. Brunner:** None. **E.C. Leuthardt:** None. **D. Moran:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.08

Topic: E.04. Voluntary Movements

Title: Interhemispheric inhibition during selective stopping: Evidence from M1-M1 dual coil transcranial magnetic stimulation

Authors: *C. G. WADSLEY, J. CIRILLO, A. NIEUWENHUYS, W. D. BYBLOW;
The Univ. of Auckland, Auckland, New Zealand

Abstract: Response inhibition is essential for terminating inappropriate actions. Selective stopping occurs when only part of a multi-effector action needs to be terminated. A substantial delay is often observed in the response of the non-stopped effector when a concurrent effector is successfully stopped (partial-stop trial). This 'stopping-interference' is believed to result from fast-acting and nonselective response inhibition. Stopping-interference is reduced with proactive cueing. This reduction may be partly due to increased activity of intracortical gamma-aminobutyric acid (GABA)-mediated inhibitory networks within the primary motor cortex (M1). This study aimed to elucidate the role of M1-M1 interhemispheric interactions during selective stopping with and without proactive cueing. We hypothesised that stopping-interference would be reduced as stopping certainty increased, owing to dynamic modulation of facilitatory and inhibitory M1-M1 interactions. Twenty-three healthy human participants performed an anticipatory response inhibition paradigm. Cues signalling the likelihood of a partial-stop trial occurring were given at trial onset (i.e., 0%, 33%, 66% chance of stopping). Electromyography (EMG) was collected from the task-relevant first dorsal interosseous (FDI) muscle bilaterally and a task-irrelevant muscle (left abductor pollicis brevis). Transcranial magnetic stimulation (TMS) was used to assess corticomotor excitability (CME), interhemispheric inhibition (IHI) and interhemispheric facilitation (IHF) in left FDI at rest and during the task. Evidence was quantified using Bayes factors (BF) in favour of the alternative hypotheses. Behaviourally, Go-trial response times were longer and stopping-interference was less as stopping certainty increased (both BF > 100). EMG signatures of response inhibition latency indicated that selective stopping was faster with increased stopping certainty (BF > 100). There was a nonselective release of IHI from rest to in-task contexts (BF > 100), independent of CME modulation (BF = 0.13). IHF was not observed across response contexts (BF = 0.08). An effector-specific CME (BF = 8.13) but not IHF or IHI (both BF < 1) reduction was observed when the left FDI was cued to stop. The results demonstrate that stopping-interference can be abolished in proactive selective stopping contexts. The context-dependent IHI finding corroborates a previously identified role of GABA-B receptor-mediated inhibition within M1. Interhemispheric channels are involved in setting inhibitory tone across response contexts but do not appear capable of dynamically modulating inhibition on a trial-by-trial basis.

Disclosures: C.G. Wadsley: None. **J. Cirillo:** None. **A. Nieuwenhuys:** None. **W.D. Byblow:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.09

Topic: E.04. Voluntary Movements

Support: Canadian Institutes of Health Research
Canada Foundation for Innovation
Faculty of Medicine and Dentistry, University of Alberta

Title: Effect of cervical transcutaneous spinal cord stimulation on sensorimotor cortical oscillations during goal-directed arm reaching movements

Authors: *B. PARHIZI[1,2], T. S. BARSS[1,2,3], A. DINEROS[4], G. SIVADASAN[4], V. K. MUSHAHWAR[1,2,3];
[1]Neurosci. and Mental Hlth. Institute, Univ. of Alberta, Edmonton, AB, Canada; [2]Sensory Motor Adaptive Rehabil. Technol. (SMART) Network, Univ. of Alberta, Edmonton, AB, Canada; [3]Div. of Physical Med. and Rehabilitation, Dept. of Medicine, Univ. of Alberta, Edmonton, AB, Canada; [4]Dept. of Electrical and Computer Engineering, Fac. of Engineering, Univ. of Alberta, Edmonton, AB, Canada

Abstract: Introduction: Transcutaneous spinal cord stimulation (tSCS) is a neuromodulatory technique to activate spinal cord circuitry non-invasively, and has the potential to improve upper-limb function after spinal cord injury. Various studies attempted to capture the cortical and spinal mechanisms underlying the effects of tSCS by measuring H-reflexes, motor evoked potentials and spinally evoked potentials. The goal of this project was to identify the influence of tSCS on sensorimotor cortical activity during goal-directed arm reaching movements, which included both unimanual and bimanual movements. **Methods:** The underlying mechanisms of tSCS during goal-directed reaching movements were investigated in three (3) neurologically-intact (NI) study participants. Cortical activity was recorded via electroencephalographic electrodes while the participants performed multiple movements using a KINARM exoskeleton. The movements included: 1) unimanual visually-guided reaching (VGR) where the participants moved their virtual hand to peripheral targets surrounding a central location; 2) uncooperative bimanual VGR in which each arm performed similar center-out reaching movements to peripheral targets simultaneously; 3) cooperative bimanual reaching movements where the participants moved a ball placed on a horizontal bar to peripheral targets through cooperative movement of the two arms, each holding one end of the bar. The same tasks were repeated in the presence of cervical tSCS. Beta band (13-30Hz) cortical activity associated with sensorimotor processes was computed using spectral power for CP3, C3, and FC3 electrodes. Interhemispheric connectivity between right and left motor cortex and primary somatosensory cortex were evaluated as well. **Results:** Our preliminary results indicate that regardless of the movement type, spectral power increases when tSCS is delivered to the cervical region of the spinal cord, pointing to the synchronous neural firing at pre-motor, primary motor, and primary somatosensory regions. Interestingly, we observed increased right-left sensorimotor cortical connectivity in the tSCS condition across all movement types. **Significance:** This study

demonstrates the effect of tSCS on cortical oscillations during unimanual and bimanual arm movements. While previous studies used transcranial magnetic stimulation to explore corticospinal excitability during tSCS, to the best of our knowledge, the present preliminary findings are the first to demonstrate a measurable effect of tSCS using both cortical activity and connectivity. This understanding is critical for guiding the future use of tSCS in neurological conditions.

Disclosures: B. Parhizi: None. **T.S. Barss:** None. **A. Dineros:** None. **G. Sivadasan:** None. **V.K. Mushahwar:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.10

Topic: E.04. Voluntary Movements

Support: DEVCOM Army Research Laboratory (ARL) Research Associateship Program (RAP).

Title: Human brain correlates of strong anticipation in motor coordination between dyads

Authors: *Z. ZHOU[1,2], J. O. GARCIA[2,1], R. SRINIVASAN[1,2];
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Abstract: Interpersonal motor coordination happens all the time in our daily activities. As individuals interact with each other in coordinated movements two types of coordination dynamics of mutual adaptation have been observed in previous studies. Weak anticipation is the result of local adjustments to motor behavior by one individual by perception of the other individual. Weak anticipation often will give rise to leader-follower dynamics, where one individual sets a pace and the other individual continuously adapts to the variability of the other individual. Strong anticipation reflects the ability of individuals to learn the long-range statistics of their environment in order to predict future events. In the motor system, strong anticipation is grounded in the observation that repetitive rhythmic motor behaviors such as tapping exhibit long-range-correlations or complexity. The purpose of the present study is to examine whether motor coordination between dyads reflects weak or strong anticipation. We investigated two finger tapping coordination tasks, synchronization and syncopation between dyads, by means of hyperscanning with simultaneous behavioral, EEG, and fNIRs recordings. Participants were paired into dyads and the experiment was performed in two separated indoor cubicles (labeled L and R) with sound isolation. There were 4 experimental conditions repeated under conditions of synchronization and syncopation: 1) Uncoupled tapping. The two members of the dyads tapped independently on their own following a pacing metronome. 2) Unidirectional coordination (L-> R). Subject L received the pacing metronome, then tapped independently while Subject R tried to

synchronize or syncopate with the real-time tapping sequence by subject L. 3) Unidirectional coordination (R->L). Same as condition 2, with roles reversed. 4) Bidirectional coordination (L<-> R). Subject L and R both received tapping feedback (shown on their screens) from the other, and tried to synchronize or syncopate with each other. Tapping intervals for each individual fluctuated in and out of synchronization with their partner in the coupled conditions. Across all participants, synchronization was higher in coupled than in uncoupled conditions. Behavioral correlation was highest in bidirectional coupling when neither subject was in the role of leader or follower and instead both subjects exhibited strong anticipation and synchronization exhibited no lags. Higher behavioral correlation was associated with higher EEG power in the higher delta and lower theta range (2 - 4 Hz) on the left posterior parietal cortex which may play a vital role in coordinating movement by visual feedback.

Disclosures: Z. Zhou: None. **J.O. Garcia:** None. **R. Srinivasan:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.11

Topic: E.04. Voluntary Movements

Support: Sir Henry Dale Fellowship, funded by the Wellcome Trust and the Royal Society (102584/Z/13/Z)

Title: Determining the test-retest reliability of controllable pulse parameter TMS (cTMS) metrics

Authors: *P. CAMBALOVA, K. THOMPSON, I. GRIGORAS, E. C. EDMOND, C. STAGG; Univ. of Oxford, Oxford, United Kingdom

Abstract: Transcranial magnetic stimulation (TMS), a form of non-invasive brain stimulation, enables us to study the neurophysiology of the primary motor cortex (M1) by recording muscle activity induced by TMS pulses. Controllable pulse parameter TMS (cTMS) is revolutionary as it is the first TMS device that enables the modulation of pulse duration, which may allow the selective activation of neurons based on their size (Rapp et al., 2022), including distinct populations such as excitatory and inhibitory neurons. Therefore, cTMS may facilitate breakthroughs in M1 neurophysiology, but its test-retest reliability is yet to be determined. Here, we investigated cTMS test-retest reliability using a within-subject design, where young healthy participants (aged 18-35) completed two identical visits between one week and one month apart. On each visit, participants had cTMS at three pulse durations (30, 60, and 120 μs) and completed two motor tasks, thought to be dependent on levels of M1 inhibition. For each pulse duration, we acquired input-output (IO) curves, which describe muscle response changes with pulse intensity. We then calculated the IO curve slopes as a measure of corticospinal excitability. Interim analysis shows increasing pulse duration results in steeper IO curve slopes, confirming previous

findings (D'Ostilio et al., 2016; Peterchev et al., 2013), and suggesting differential activation of cortical circuits by modulating the duration of pulses. For each pulse duration, we found high relative standard errors of the measurement (SEM%) and low intraclass correlation coefficients (ICC) of IO curve slopes, indicating poor test-retest reliability. Simple reaction times showed both low SEM% and high ICC, therefore indicating good test-retest reliability. There were no significant correlations between the IO curve slope and task performance. The current small sample size ($n = 8$) limits our ability to draw conclusions about the test-retest reliability of cTMS metrics or the neuronal circuits activated by pulses of different durations, but data collection is still ongoing. Furthermore, we will also look at different IO curve parameters, which may show different test-retest reliability. If proven reliable, cTMS has the potential to inform about patterns of neuronal dysfunction in neurological disorders.

Disclosures: P. Cambalova: None. **K. Thompson:** None. **I. Grigoras:** None. **E.C. Edmond:** None. **C. Stagg:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.12

Topic: E.04. Voluntary Movements

Support: Marie Sklodowska-Curie Individual Fellowship (H2020-MSCA-IF Grant 798957)
Be-for-ERC funding

Title: Cortical markers of inhibitory deficits in Parkinson's disease: a TMS-EEG study

Authors: *E. CASULA[1], V. PEZZOPANE[2], A. RONCAIOLI[3], I. BORGHI[2], S. AJAO[4], L. ROCCHI[5], L. BRUSA[7], J. C. ROTHWELL[6], G. KOCH[8];
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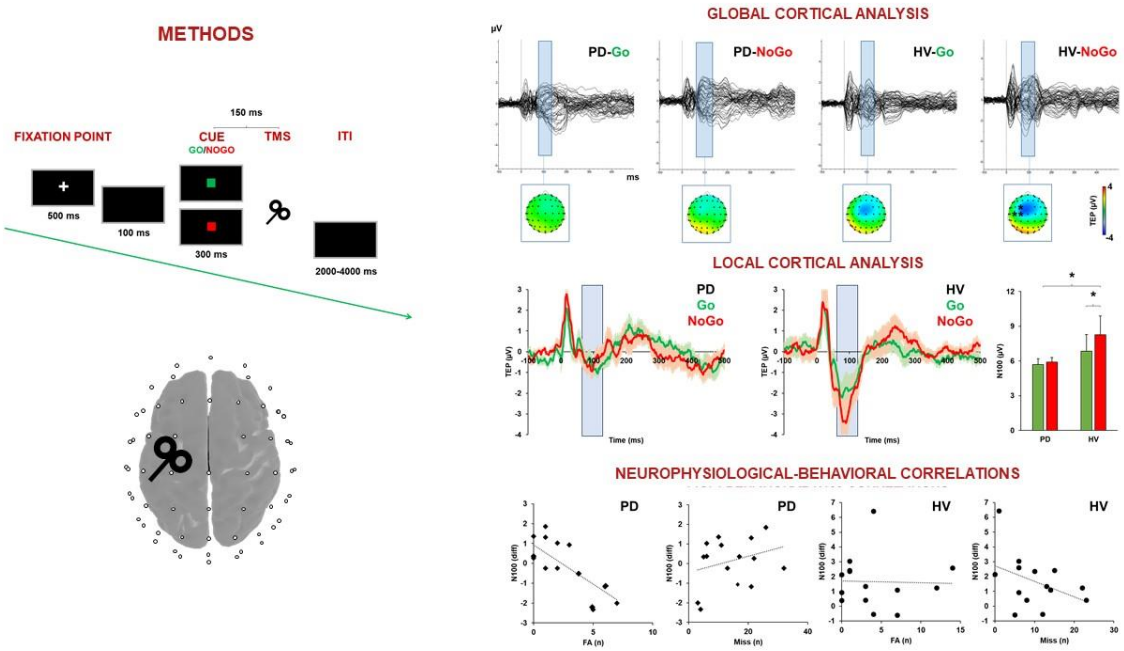
Abstract: Abnormal functioning of inhibitory processes in Parkinson's disease (PD) has been investigated and also linked to major clinical manifestations of the disease. The combination of transcranial magnetic stimulation and electroencephalography (TMS-EEG) allow to non-invasively investigate cortical dynamics [1]. Here, we used TMS-EEG during the execution of a Go/No-Go task to investigate inhibitory processes in PD patients.20 PD patients in ON condition underwent an EEG recording during TMS of the most affected primary motor cortex (M1), while perforimng in a Go/NoGo task. A total of 140 TMS pulses were delivered after 150 ms from the task cue (70 in a Go condition, 70 in a NoGo condition). 20 age-matched healthy volunteers were recruited as a control group.In the NoGo trials, HV showed a higher TMS-evoked N100, compared to the Go condition ($p<0.05$). PD patients showed a generally smaller N100, which

was not modulated by the task condition. The number of false alarms in PD patients was inversely correlated with the TMS-evoked N100 ($p<0.05$).Our results showed the presence of a deficit in the motor inhibitory mechanism required in the task for PD patients. This is highlighted from the lack of modulation of the TMS-evoked N100, which is known to be higher during the engagement of an inhibitory mechanism [2,3], as we observed in the HV group. Importantly, we observed higher rates of FAs in PD patients were inversely related with the TMS-evoked N100 amplitude. Our study highlights the sensitivity of the TMS-EEG technique in detecting abnormal neuronal mechanisms.



Disclosures: **E. Casula:** None. **V. Pezzopane:** None. **A. Roncaioli:** None. **I. Borghi:** None. **S. Ajao:** None. **L. Rocchi:** None. **L. Brusa:** None. **J.C. Rothwell:** None. **G. Koch:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.13

Topic: E.04. Voluntary Movements

Support: NIH 1R01 AR069176-01

Title: Estradiol does not modulate cortical silent period in primary motor cortex

Authors: ***Y.-C. CHUNG**[1], L. MOHAMED[2], S. SOEDIRDJO[1], L. A. RODRIGUEZ, Jr.[1,2], H. KIM[1], C. HUTCHERSON[1], B. PIECEWICZ[1], K. MCGOVERN[1], C. KUMALA[2], N.

PERIKALA[1], L. ROGERS[3], Y. DHAHER[1];
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Abstract: BACKGROUND AND AIM: Animal models show that estradiol (E2) receptors are present in the central nervous system, including the cortex (Kritzer, 2002). In humans, direct evidence is lacking, but hormone concentrations have been linked to brain conditions like seizure, cognitive function and emotional states (Toffoletto, Lanzenberger, Gingnell, Sundström-Poromaa, & Comasco, 2014; Velíšková & DeSantis, 2013). The link between E2 and cortical motor function is unclear. Our preliminary data shows that during low level isometric muscle contractions, E2 increases the intracortical inhibition likely mediated by $GABA_A$ activation. In this study, we aim to explore the likelihood that the E2 effect is specific to $GABA_A$ activation by assessing the cortical silent period (CSP) post TMS. We hypothesize that the CSP will change with different E2 levels.**METHODS:**Seven young females with normal menstrual cycle were tested at menses and peak E2, confirmed by the serum E2 level. A single pulse TMS paradigm was used to test the CSP of the tibialis anterior muscle while participants generated 10% of maximal ankle torque (active condition). The stimulation intensity was the minimal intensity producing peak-to-peak motor evoked potential (MEP) amplitudes of 0.5-1.5 mV. The absolute CSP duration was determined as the duration between MEP offset to the time point when the muscle activity returned to the prestimulation level. Repeated-measures ANOVA was used to compare the absolute CSP duration between two E2 levels. The difference of stimulation intensity between the two E2 levels, expressed as the percentage of the active MEP threshold, was included as covariants. The active MEP threshold (AMT) was defined as the minimal intensity eliciting MEPs distinguishable above background muscle activity.**RESULTS:**The stimulation intensity did not differ significantly between the two E2 levels, both in % maximal machine output (p=0.57), or % AMT (p=0.47). No significant E2 level effect (p=0.31) was observed on the absolute CSP duration.**CONCLUSIONS:**The preliminary result suggests that the $GABA_B$R-mediated cortical silent period is not modulated by estradiol. Along with our previous finding of increased $GABA_A$R-mediated intracortical inhibition by high estradiol level, estrodial may modulate cortical inhibition by acting on ionotropic $GABA_A$ receptor, not metabotropic $GABA_B$receptor.

Disclosures: Y. Chung: None. **L. Mohamed:** None. **S. Soedirdjo:** None. **L.A. Rodriguez:** None. **H. Kim:** None. **C. Hutcherson:** None. **B. Piecewicz:** None. **K. McGovern:** None. **C. Kumala:** None. **N. Perikala:** None. **L. Rogers:** None. **Y. Dhaher:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.14

Topic: E.04. Voluntary Movements

Support: NIH 1R01 AR069176-01

Title: Estradiol increases intra-cortical inhibition in primary motor cortex

Authors: *S. SOEDIRDJO[1], **Y.-C. CHUNG**[1], L. A. RODRIGUEZ, II[1,3], H. KIM[1], C. HUTCHERSON[1], B. PIECEWICZ[1], K. MCGOVERN[1], C. KUMALA[4], N. PERIKALA[2], L. ROGERS[5], Y. DHAHER[1];
[1]Dept. of Physical Med. and Rehabil., [2]Sch. of Med., Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [3]Dept. of Biomed. Engin., [4]Dept. of Biol. Sci., Univ. of Texas at Dallas, Dallas, TX; [5]Northwestern Univ., Chicago, IL

Abstract: BACKGROUND Animal models show that estradiol (E2) receptors are present in the central nervous system, including the cortex (Kritzer, 2002). The link between E2 and the motor function of the brain is unclear. Our earlier examination indicated that the aggregate motor excitability can be influenced by hormonal fluctuations in young healthy women (Rogers & Dhaher, 2017), E2 plays an "amplifying" agent of repetitive transcranial magnetic stimulation (rTMS) mediated cortical inhibition. It is not clear if this effect was colored by the combined inhibitory state of the rTMS stimulus used in that paradigm. Thus, we aim to unfold this aggregate effect by interrogating the isolated role of E2 on the inhibitory and facilitatory intra-cortical interneuron circuits. We hypothesize that both intra-cortical inhibition and facilitation will change with different E2 levels. METHODS Fifteen young eumenorrheic women were tested at menses and peak E2. A TMS paired-pulse paradigm was used to test the excitability of inhibitory intra-cortical interneurons of the tibialis anterior muscle while participants generated 10% of maximal ankle torque. The conditioning stimulus (CS) intensity was 90% of the active motor evoked potential (MEP) threshold. The test stimulus (TS) intensity was the minimal intensity producing peak-to-peak MEP amplitudes of 0.5-1.5 mV. The inter-stimulus intervals (ISI) included 2, 3, 4, 5, 6, 7, 10, 15, 20, 25 and 30 ms. The degree of inhibition produced by the CS on the TS at each ISI was calculated as the ratio of the conditioned MEP to the average unconditioned MEP amplitude. For short-interval intra-cortical inhibition (SICI) analysis, repeated measures ANOVA was used to compare the normalized MEP amplitude across 2- to 6-ms ISIs between two E2 levels. For intra-cortical facilitation (ICF), repeated measures ANOVA was used to compare the normalized MEP amplitude across 7- to 30-ms ISIs between two E2 levels. RESULTS For both SICI and ICF, no significant E2 level effect or ISI effect was observed. There was a significant E2 level by ISI interaction only on SICI ($p<0.05$). Post-hoc pairwise comparisons with Bonferroni correction indicated that the normalized conditioned MEP amplitudes measured at 6-ms ISI (0.81 ± 0.15 vs 1.03 ± 0.22; $p=0.02$, $n=10$) was significantly smaller at peak E2 than at menses. CONCLUSIONS The preliminary result supports our hypothesis that the GABAAR-mediated intra-cortical inhibition is enhanced by high estradiol level, potentially via a genomic pathway resulting in increased GABAAR mRNA expression (Herbison & Fenelon, 1995). Estradiol may influence neuromuscular control via modulating intra-cortical inhibition.

Disclosures: S. Soedirdjo: None. **Y. Chung:** None. **L.A. Rodriguez:** None. **H. Kim:** None. **C. Hutcherson:** None. **B. Piecewicz:** None. **K. McGovern:** None. **C. Kumala:** None. **N. Perikala:** None. **L. Rogers:** None. **Y. Dhaher:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.15

Topic: E.04. Voluntary Movements

Title: Remote ischemic conditioning increases cortical activation during multijoint isometric visuomotor tracking tasks in people with chronic stroke.

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Abstract: Introduction: This novel study measured the changes in cortical activation after a single session of remote ischemic conditioning (RIC) applied to the leg in people with stroke. We posited that stroke survivors would increase cortical activation during a multijoint isometric visuomotor task post-RIC intervention.**Methods**: Twelve chronic stroke survivors (mean age 54.57±13.95, 9 females) completed a visuomotor task with EEG recordings before and after RIC (225mmHg) and Sham (25mmHg) interventions. RIC and Sham sessions were presented in random order, spaced at least 4 days apart. During each intervention, a blood pressure cuff placed on the paretic thigh was used to perform five cycles of cuff inflation and deflation, each lasting 5 mins. The visuomotor task consisted of a combination of isometric elbow flexion/extension, and shoulder abduction/adduction to trace an 'infinity' target in two dimensions. During the task, EEG signals were recorded using 64 active electrodes set in a conventional 10-20 international system. The signals were sampled at 1000Hz, bandpass filtered (0.3 and 200Hz), notch filtered (60Hz), and amplified 10,000X. Processing consisted of filtering, downsampling, artifact reduction, re-referencing to a common reference, and calculating the Laplacian. EEG power in the beta band (13-26Hz) was obtained for the baseline period (defined as 5-1s before the movement onset) and for the task period (3 infinity patterns over 56s duration). Eighteen trials were obtained (a total of 54 'infinity' traces) and data were divided into single circle segments for ensemble analysis. Percent reduction in beta band power compared to baseline (beta event related desynchronization (beta ERD)) was used to estimate cortical activation for each circle segment. The change in cortical activation before and after the intervention for RIC and Sham were compared. **Results**: Beta ERD increased nearly 10% with RIC compared to Sham in the contralesional hemisphere. A two factor repeated measures ANOVA (intervention: RIC vs. Sham and time: before vs. after) showed an interaction effect in the contralesional hemisphere ($F(1,11) = 7.99$, $p = 0.016$) in which beta ERD during RIC increased more than Sham. Bonferroni-adjusted pairs comparisons indicated that beta ERD Post RIC was 5.8% higher than Pre RIC ($p = 0.028$) with no detected difference in beta ERD for Pre and Post Sham ($p = 0.57$). **Conclusion**: RIC increases cortical activation associated with multijoint isometric upper limb motor tasks in the contralesional hemisphere of people with stroke. As an aid to other therapies or as a stand-alone therapy, RIC might prime the cortex to enhance neurorehabilitation therapy post-stroke.

Disclosures: **P. Balasubramanian:** None. **E. Klevenow:** None. **A.S. Hyngstrom:** None. **M.J. Durand:** None. **B.D. Schmit:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.16

Topic: E.04. Voluntary Movements

Support: DFG (German Research Foundation) – Project-ID 431549029 – SFB 1451

Title: Phase-based source connectivity states in EEG

Authors: *S. DAUN[1], N. ROSJAT[2], M. HOMMELSEN[2], G. FINK[2];
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Abstract: Using functional magnetic resonance imaging (fMRI), the human brain connectivity at rest has been shown to be clustered in several resting state (RS) networks (e.g. default mode network). Similarly, in electroencephalography (EEG) amplitude related activity patterns, so called microstates, have been shown on the level of electrodes. However, it is less clear whether these patterns are caused by the alternating activity of a few underlying networks (comparable to the networks defined by fMRI) or by changes in connectivity within the network structure. EEG was acquired on five consecutive days in 23 individuals. On each day, participants performed 5 minutes of RS, followed by a simple motor task consisting of short periods of button presses (index finger) with long waiting periods in between (=Waiting), followed by another 5 minutes of RS. The recorded EEG was cut into epochs of 1 min (for RS) and 2 s around movement onset (for Waiting) and transformed to source space using dynamic statistical parametric maps (dSPM) onto a template structural MRI. The obtained source activity was assigned to 68 source labels of the *aparc* parcellation. The corresponding time courses were then extracted and transformed into phase-space. Single-trial connectivity metrics were computed to define temporal connectivity between all labels. Dynamic graphs, i.e. time-varying networks, were defined by thersholding the obtained dynamic pairwise connectivity. Several connectivity measures, i.e. PLI, weighted PLI, PLV and corrected imaginary part of phase locking value, were computed for a comparison of their performance on source space. The Waiting task was used as a control condition that is used for validation of source reconstruction and connectivity measures. Our results show that the PLV has inflated connectivity from neighboring regions and is therefore not a useful measure for our research question. Weighted PLI failed to show increased motor activity in the Waiting Task, which, however, is to be expected from previous results. PLI and ciPLV provided reliable results both without and with baseline correction. In addition, a reappearing pattern of connectivity in the resting state was visible in the dynamic graphs of individual subjects based on the ciPLV, which may be indicative of underlying resting state networks.

Disclosures: **S. Daun:** None. **N. Rosjat:** None. **M. Hommelsen:** None. **G. Fink:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.17

Topic: E.04. Voluntary Movements

Support: ERC

Title: An alternative cortico-subcortical loop for movement control via the pontine reticular formation

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Abstract: The cortico-basal ganglia-thalamocortical loop has been known to be involved in movement control. Disturbance of the basal ganglia activity results in characteristic, unilateral rotation. Similar to basal ganglia the pontine reticular formation (PRF) also sends inhibitory terminals to the intralaminar thalamic nuclei (IL). Activation of the GABAergic/glycinergic PRF-IL pathway in the thalamus induces a complete behavioral arrest. In this study we examine the cortical impact on the glycinergic (GlyT2+) PRF neurons. We study the effect of unilateral optogenetic activation of PRF inhibitory cells (PRF/GlyT2+) and on locomotor behavior. Conditional anterograde viral tracing, from the frontal cortex (M2 and cingulate) of RBP4-Cre/Glyt2-eGFP double transgenic mice revealed that mid-caliber dendrites and spines of the PRF/GlyT2+ cells are the major targets of the cortical L5 inputs. In *in vitro* slice preparation, the photoactivation of the L5 fibers faithfully produced purely glutamatergic synaptic responses on PRF/GlyT2+ neurons. *In vivo* juxtacellular recording showed that photoactivation of the cortical L5 cells evoked short-latency APs with high probability in the PRF/GlyT2+ cells. Spontaneous rhythmic activity of PRF/Glyt2+ neurons was strongly linked to the slow cortical oscillation. Photoactivation of PRF/Glyt2+ neurons lead to significantly decreased firing rate of the IL cells. At the behavioral level activation of the PRF/Glyt2+ cells resulted in unilateral rotation and in movement initiation. We propose that synchronous frontal cortical activity conveys behavioral signals to PRF. PRF/GlyT2+ cells. These neurons transfer the cortical input as inhibitory signals to the IL, before they return to the cortex via the thalamocortical pathway. The concept of network organization and the evoked behavioral response is similar to but independent of the cortico-basal ganglia loop.

Disclosures: **E. Bősz:** None. **V. Plattner:** None. **M.A. Diana:** None. **L. Acsády:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.18

Topic: E.04. Voluntary Movements

Support: 1939987/National Science Foundation
1940202/National Science Foundation
1940162/National Science Foundation
1939999/National Science Foundation
1939992/National Science Foundation

Title: Stability of Motor Cortex Decoders during Learning

Authors: *M. BHATTACHARYA[1], S. MEAMARDOOST[1], E. HWANG[2], T. KOMIYAMA[3], R. GUNAWAN[4];
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Abstract: The motor cortex of the brain is a key driver of voluntary movements. The motor cortex undergoes significant plasticity while learning a motor skill, a process that is crucial for achieving reproducible and efficient motor response. Our work focuses on the interplay between the motor cortex and its decoder, specifically whether the decoder rewires concurrently with the motor cortex during learning, and the interaction, if any, between the two. To this end, we analyzed data from simultaneous measurements of neuronal activity via two-photon Calcium fluorescence imaging and lever displacement in a reward-driven lever-press task experiment in mice ($n=7$) [1]. Calcium fluorescence data were deconvolved to produce spiking activity, while lever displacement data were smoothened and differentiated to give lever velocity. We built motor cortex decoders using Long-Short Term Memory (LSTM) which predict lever velocity (output) from spiking activity (input). The decoders were trained either independently for each learning session or sequentially using transfer learning. In the latter, the loss function includes not only the root mean square error between actual and predicted velocity, but also the difference of weights to the previous session decoder based on 'Elastic Weight Consolidation' concept [2].We noted that decoders from transfer learning become more correlated over time and gradually converge. Also, transfer learning decoders perform better than those trained using data from each respective session. Notably, the ultimate transfer learning decoder is a good predictor of lever velocity in the entire learning period (R^2 >0.8). By sensitivity analysis, we identified the existence of a subset of neurons whose activity effectively encode lever velocity, and decoders based on such neurons give high accuracy of prediction for the entire learning period. These neurons form a highly interconnected hub in the connectome, and this hub undergo significant rewiring during learning. Taken together, our results suggest that decoders of motor cortex remain relatively stable during motor-skill learning, and that such decoders rely on a core set of interconnected neurons. References1. Peters, A. J., Chen, S. X. & Komiyama, T. Emergence of reproducible spatiotemporal activity during motor learning. Nature 510, 263-267 (2014). 2.

Kirkpatrick, J. *et al.* Overcoming catastrophic forgetting in neural networks. *Proceedings of the National Academy of Sciences* 114, 3521-3526 (2017).

Disclosures: M. Bhattacharya: None. **S. Meamardoost:** None. **E. Hwang:** None. **T. Komiyama:** None. **R. Gunawan:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.19

Topic: E.04. Voluntary Movements

Title: Comparative sulcal-cytoarchitectonic organization of motor areas in the human and chimpanzee medial paracentral cortex

Authors: *K. LOH[1], J. NOVEK[1], Y. ZHOU[1], C. SHERWOOD[2], W. HOPKINS[3], M. PETRIDES[1];
[1]Montreal Neurolog. Institute, McGill Univ., Montreal, QC, Canada; [2]George Washington Univ., Washington, DC; [3]Keeling Ctr. for Comparative Med. and Res., The Univ. of Texas MD Anderson Cancer Ctr., Bastrop, TX

Abstract: Found at the posterior part of the medial frontal cortex, the human and chimpanzee paracentral cortex contains two cytoarchitectonically distinct motor areas: 1) the medial part of primary motor area 4, where the primary lower-limb motor representation lies; and 2) medial area 6, which forms the posterior part of the supplementary motor cortex. Currently, the precise boundaries of areas 4 and 6 in the human and chimpanzee medial paracentral cortex, and their relation to local sulcal features requires further exploration. Addressing this knowledge gap will establish important sulcal landmarks for locating medial paracentral motor areas 4 and 6 across human and chimpanzee brains. In both species, two sulci are present in the medial paracentral region: the *paracentral fossa*, which is situated anterior to the central sulcus, and the *paracentral sulcus* that lies anterior to the *paracentral fossa*. Post-mortem chimpanzee (n=2) and human (n=1) paracentral brain blocks containing the *paracentral fossa* and *paracentral sulcus* were sectioned optimally (i.e. cut perpendicularly to the main direction of the sulci; Novek et al. 2022). The sections were then Nissl-stained to study their underlying cellular organisation in relation to the two sulci of interest. The criteria used to identify cytoarchitectonic areas 4 and 6 were comparable across the two species: area 4 is an agranular cortical area defined by the presence of the giant pyramidal Betz cells in the deeper part of layer V; area 6 is also an agranular cortical area that can be distinguished from area 4 by the absence of the giant Betz cells.In the brains examined in both species, area 4 extended from the medial part of the central sulcus to the anterior portion of the *paracentral sulcus*, and surrounded the *paracentral fossa*. Thus, the *paracentral fossa* appeared as an axial sulcus for medial area 4. By contrast, the *paracentral sulcus* appeared to be a limiting sulcus between medial area 6 anteriorly and area 4 posteriorly. This result indicates, for the first time, that the *paracentral fossa* and the *paracentral*

sulcus are sulcal landmarks for locating paracentral medial areas 4 and 6 across human and chimpanzee brains. Ongoing research will confirm these observations in more brains, and examine further relations between sulci and cytoarchitectonic areas in more anterior parts of the human and chimpanzee medial frontal cortex.

Disclosures: K. Loh: None. **J. Novek:** None. **Y. Zhou:** None. **C. Sherwood:** None. **W. Hopkins:** None. **M. Petrides:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.20

Topic: E.04. Voluntary Movements

Support: UNAM-DGAPA PAPIIT IN201121
CONACyT Ciencia Básica A1-S-8686. CONACyT
Scholarship from CONACyT for Paola Rodríguez Moreno (CV 934973)

Title: Anatomic and Functional organization of cortico-spinal and cortico-rubral neurons in the rat

Authors: *P. RODRIGUEZ-MORENO[1], A. SANCHEZ-LOEZA[2], J. LOZA-VAQUEIRO[1], R. OLIVARES-MORENO[1], V. LOPEZ-VIRGEN[1], G. ROJAS-PILONI[1], M. LOPEZ-HIDALGO[3]; [1]Inst. De Neurobiologia (INB), UNAM, Inst. De Neurobiologia (INB), UNAM, Santiago De Queretaro, Mexico; [2]Dept. de bioingenieria y ciencia, Inst. Tecnologico de Monterrey y de Estudios Superiores de Monterrey, Santiago De Queretaro, Mexico; [3]ENES, UNAM, Escuela Nacional de Estudios Superiores Unidad Juriquilla (ENES), Santiago De Queretaro, Mexico

Abstract: Layer 5 (L5) neurons of the motor cortex participate in the coordination of the activity of subcortical systems related to muscle control, playing a fundamental role in the coordination of movements and postures. L5 neurons connect with several subcortical structures like the red nucleus, pons, striatum, and spinal cord, by means of the pyramidal system, contributing to various phases of the movement such as the planning, execution, and termination of movements. Here, we characterized corticorubral (CS) and corticospinal (CS) pathways to identify their specific role during voluntary movements in physiological conditions. First, the distribution of L5 CR and CS neurons within the cortex was determined using retrograde tracers Flourogold and BDA. We found that only 10% ± 6 neurons with double tracer and their distribution along cortical depth is very similar between the two populations. However, a difference in the distribution in the medio-lateral and anteroposterior axis has been found: CR neurons are denser in the anterior and medial region corresponding to the motor cortex area, while the CS neurons are more abundant in the posterior and lateral regions, corresponding to somatosensory areas (S1 and S2).
Next, the neuronal activity of CR and CS neurons was identified before and during the execution

of a voluntary movement. The results indicate that CR and CS neurons are differentially modulated during the preparation and execution of movements.

Disclosures: P. Rodriguez-Moreno: None. **A. Sanchez-Loeza:** None. **J. Loza-Vaqueiro:** None. **R. Olivares-Moreno:** None. **V. Lopez-Virgen:** None. **G. Rojas-Piloni:** None. **M. Lopez-Hidalgo:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.21

Topic: E.04. Voluntary Movements

Support: Cutberto Dorado
Nydia Hernández
Ericka de los Ríos
Martín García Servin
Christian Josué Delgado Guzmán
Edgar Bolaños Aquino
Beca CONACyT-CVU1094565

Title: Participation of the corticospinal and corticorubral projections in the performance of a movement.

Authors: *J. LOZA VAQUEIRO[1], P. RODRIGUEZ MORENO[2], R. OLIVARES-MORENO[3], G. ROJAS-PILONI[4];
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Abstract: The sensorimotor (somatosensory and motor cortices), has a different role modulating voluntary movements, regulating the sensory afferences and organizing the motor information into the subcortical structures related with motor control. It is largely unknown if the different roles of sensorimotor cortex are carried out by distinct subtypes of pyramidal Tract Neurons (PTN) Here, we analyzed the functional role of two classes of PTNs projecting to the spinal cord (corticospinal tract neurons) and red nucleus (corticorubral tract neurons). The purpose of this study it's to characterize how these tracts participate in a voluntary movement, and to identify if they had different roles in the phases of a movement. Thus, we compared selective optogenetic inhibition of sensorimotor cortex corticospinal (CST) or corticorubral (CR) neurons during lever pressing movements to analyze movement performance in rats trained in an operant conditioned task.During the training phase movement trajectories gradually display less variability and

become more stereotyped. However, the photoinhibition of CST and CR neurons differentially modify the cinematic parameters: duration, area under the curve and velocity of the movement trajectories, suggesting that both class of PTNs has different roles for sensorimotor integration.

Disclosures: J. Loza Vaqueiro: None. **P. Rodriguez Moreno:** None. **R. Olivares-Moreno:** None. **G. Rojas-Piloni:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.22

Topic: E.04. Voluntary Movements

Support: CONACYT Ciencia Básica A1-S-8686
UNAM-DGAPA-PAPIME PE205821
UNAM-DGAPA PAPIIT IN20112

Title: Functional organization of cortical projections to the red and pontine nuclei.

Authors: *V. LOPEZ-VIRGEN[1], M. MACIAS[2], P. RODRIGUEZ-MORENO[2], R. OLIVARES-MORENO[2], V. DE LAFUENTE[2], L. CONCHA[2], G. ROJAS-PILONI[2]; [1]Inst. de Neurobiologia, UNAM, Inst. De Neurobiologia, UNAM, Queretaro, Mexico; [2]Inst. de Neurobiologia, UNAM, Inst. De Neurobiología, UNAM, Queretaro, Mexico

Abstract: Pyramidal tract neurons (PTNs) are fundamental elements for motor control. However, it is largely unknown if PTNs are segregated into different subtypes executing in parallel specific computations important for movement performance. Using anatomical, electrophysiological and optogenetics tools, we analyzed PTNs from motor cortex projecting to red and pontine midbrain nuclei, which are important hubs connecting cerebral cortex and cerebellum playing a critical role in the regulation of movement. We reveal that vast majority of M1 neurons projecting to the red and pontine nuclei constitutes different populations. Corticopontine neurons have higher conduction velocities and morphologically, a most homogeneous dendritic and spine distributions along cortical layers. Optogenetically inhibiting either kind projection, differentially affects forelimb movement onset and execution in a lever press task, but only the activity of corticopontine neurons is significantly correlated with trial-by-trial variations in reaction time. The results indicate that cortical neurons projecting to the red and pontine nuclei constitute distinct functional and anatomical pathways and they contribute differently to sensorimotor integration, suggesting that layer 5 output neurons are functionally compartmentalized generating, in parallel, different downstream coding.

Disclosures: V. Lopez-Virgen: None. **M. Macias:** None. **P. Rodriguez-Moreno:** None. **R. Olivares-Moreno:** None. **V. de LaFuente:** None. **L. Concha:** None. **G. Rojas-Piloni:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.23

Topic: E.04. Voluntary Movements

Support: NSF SBE 2104666
NSF BCS 1849169

Title: Dissociable top-down and bottom-up effects in temporal and effector preparation

Authors: *M. MENCELOGLU, D. ROY, S. YI, J. GAO, J.-H. SONG;
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Abstract: Preparing the timing of a given movement and the effector to execute the movement is important to optimize motor behavior. We studied temporal and effector preparation driven by top-down cueing or bottom-up priming. We orthogonally manipulated the cue-to-target delay (short vs. long) and response hand (left vs. right). We presented temporal and effector cues, which could be informative (100% predictive of cue-to-target interval or response hand) or uninformative (50%), followed by a short or long delay, followed by an arrow target. Participants (N=16) were asked to indicate the direction of the target arrow (left vs. right) using their corresponding hand while we recorded scalp electroencephalography (EEG). We intermixed trial types which allowed us to examine priming effects driven by short-term repetitions or switches of target timing and response hand, independently from cueing effects. Analyses focused on response time (RT), event-related potentials (ERPs), and their correlations. Temporal cueing (informative compared with uninformative) as well as temporal priming (repeated compared with switched timing) speeded responses indicating that top-down and bottom-up biases in temporal preparation have effects in the same direction. While effector cueing had a strong speeding effect, effector priming had a small delaying effect on responses, indicating that top-down and bottom-up biases in effector preparation have opposing effects. The negative going slow-wave ERP component indexing anticipatory processes (the Contingent Negative Variation, "CNV"), was modulated by the temporal and effector manipulations. In particular, both temporal cueing and temporal priming were associated with a more negative CNV amplitude. Further, effector cueing, but not effector priming, was associated with a more negative CNV amplitude. Lastly, the magnitude of the CNV effects (amplitude differences in cueing and priming conditions) were closely associated with the corresponding RT effects (RT differences in cueing and priming conditions), solidifying the CNV's role in temporal and effector preparation. Overall, these findings signify a dissociation between temporal and effector preparation regarding the involvement of top-down and bottom-up biases and reveal that the CNV is a common ERP marker for temporal and effector preparation.

Disclosures: M. Menceloglu: None. **D. Roy:** None. **S. Yi:** None. **J. Gao:** None. **J. Song:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.24

Topic: E.04. Voluntary Movements

Support: Robert and Janice McNair Foundation
Pew Scholars Program
NS112312
NS113110
McKnight Foundation
Simons Collaboration on the Global Brain

Title: Behavioral measurements of motor readiness in mice.

Authors: *E. MANGIN, J. CHEN, J. LIN, N. LI;
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Abstract: Many goal-directed movements occur too quickly for online correction. The brain prepares voluntary movements before execution. Classic experiments suggest the existence of a "state of readiness" which permits rapid and precise execution of prepared movements once entered. In human and nonhuman primate studies using delayed response tasks, subjects are faster to initiate movements if given time to prepare, and the resulting movements are more accurate. However, behavioral measurements of motor preparation are lacking in mice, an increasingly popular model system ideal for manipulations and circuit dissections of motor preparation.

Standard measures of readiness are post-hoc: signatures of motor preparation are measured in executed movements. We reasoned that motor preparation might be reflected online in the body posture. We examined non-body-restrained mice in an autonomous behavior system in which animals voluntarily engaged in two different delayed response tasks: a directional licking task involving the tongue and a reaching task involving the forepaw. In these tasks, animals planned their upcoming movement during a delay epoch (1.3s) and had to correctly lick or reach an instructed target after an auditory Go cue to receive a water reward. These behaviors were captured with high-speed videography and body features were tracked using DeepLabCut. We observed a reaction time (RT) savings with preparation time, replicating classic findings. On occasional probe trials in which the Go cue arrived before the end of the delay epoch, mice were slower to initiate movement. RT decreased with increased delay duration before reaching a plateau. Tracking of the tongue and forelimb showed that movement trajectories were more precise with increased preparation time.

We found that the degree of readiness was reflected in the body features. In the licking task, mice oriented their jaws and noses toward the instructed lick target during the delay epoch, well before movement onset. The upcoming lick direction could be reliably predicted from the jaw position. In the forelimb task, mice positioned their forepaws in anticipation of the reach. Postural changes were most pronounced in task-relevant effectors. Posture changes occurred gradually with a timecourse that tracked the RT saving as a function of preparation time,

suggesting a direct relationship to the degree of readiness. RT could be predicted from the degree of postural changes even at the level of single trials.
Together, these results indicate that the task-relevant body feature readout is a viable real-time readout of motor preparation in mice which can be exploited in future studies.

Disclosures: E. Mangin: None. **J. Chen:** None. **J. Lin:** None. **N. Li:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.25

Topic: E.04. Voluntary Movements

Support: John Templeton Foundation #61283
Fetzer Institute #4189

Title: Metacognitive access to motor intention relies on midfrontal theta and parietal beta oscillations, not the readiness potential

Authors: *J. C. GAVENAS[1], A. SCHURGER[1,2], U. MAOZ[1,3,4];
[1]Brain Inst., Chapman Univ., IRVINE, CA; [2]NeuroSpin, INSERM, Orsay, France; [3]UCLA, Los Angeles, CA; [4]Caltech, Pasadena, CA

Abstract: Being aware of one's aims and intentions is crucial for goal-directed behavior, but it is not clear how such awareness is realized in the brain. Spontaneous self-initiated actions are preceded by an EEG component termed the Readiness Potential (RP), a gradual shift in midfrontal brain activity, which has been claimed to reflect unconscious motor preparation. Studies that interrupt participants with probes before movement have linked the RP to latent awareness of motor preparation, in the sense that participants will report that they were preparing to move if asked. In particular, Parés-Pujolràs and colleagues (2019) found that when participants reported preparation, probes were preceded by a negative EEG deflection resembling the RP. However, prior studies do not account for the processes by which participants assess their state of motor preparation, which we argue has caused misleading results. We hypothesized that probe-based reports correspond to metacognitive decisions over the action-generation process, which would resolve several puzzling findings in prior studies. In line with this view, we ran a new experiment wherein participants inhibited movement in response to probes and only then reported whether they were preparing to move. After removing cases where participants failed to inhibit their movements and therefore wouldn't have had time to process the probe, the contingency between reported preparation and the RP disappeared, suggesting that prior results were due to confounds. By computationally modeling the action-generation and metacognitive processes, we found that dual-stage metacognition over a stochastic accumulator could account for our findings while several other plausible models could not. Further analyses in the time-frequency domain revealed that whether or not participants reported preparation was

primarily reflected in post-probe midfrontal theta and parietal beta power, analogous to findings in the metacognition literature. Our results provide evidence that reports of motor preparation should be thought of as metacognition over a dynamical process, and suggest that metacognitive mechanisms may be important for awareness of intentions in general.

Disclosures: J.C. Gavenas: None. **A. Schurger:** None. **U. Maoz:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.26

Topic: E.04. Voluntary Movements

Support: John Templeton Foundation #61283
Fetzer Memorial Trust #4189

Title: Dissociating action execution from consciousness of action execution - a closed-loop TMS-EMG study

Authors: *A. WONG[1], T. LAN[2], D.-A. WU[4], A. SCHURGER[5], U. MAOZ[3];
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[4]Caltech, Pasadena, CA; [5]Brain Inst., INSERM U992 / Neurospin / Cea-Saclay, Orange, CA

Abstract: We typically experience a sense of agency (i.e., consciousness over action control) over active, voluntarily executed actions (e.g., when you move your own finger), but not for passive, externally executed movements (e.g., when a robot or another person moves your finger). But what would happen to your sense of agency if your voluntarily executed actions would be carried out passively, just as you geared up to execute the action?
We investigated this question with a series of 3 experiments, showing that action execution and consciousness of action execution can be dissociated. In all experiments, we asked participants to make a voluntary finger movement with their dominant hand while undergoing different types of TMS (transcranial magnetic stimulation). In Experiment 1 (n=25), participants were stimulated on the primary motor cortex (M1) in a region that would lead to a visible finger movement. In Experiment 2 (n=12), participants were stimulated with sham TMS in the same region as Experiment 1, with no visible finger movement due to the nature of the sham TMS. In Experiment 3 (n=15), participants were stimulated directly on the forearm of their dominant hand, similarly leading to a visible finger movement. Critically, on 25% of trials in all three experiments, the TMS was directly triggered when electromyography (EMG) of the relevant finger indicated an imminent voluntary action, creating a closed-loop setup.
Interestingly, when asked to identify the initiator of the action, participants Experiments 1 and 2 tended to report that it was not only they—but rather the computer or both they and the computer—who initiated the finger movement, much more often than those in Experiment 2 (i.e., sham TMS). This pattern of results demonstrates that the sense of agency and consciousness

of action execution can be dissociated from each other, and that the dissociation does not rely on disruption to M1. Instead, our results are in line with the sense of agency being constructed by multi-sensory cue integration, with especially large weighting to proprioceptive and tactile cues in the domain of action control.

Disclosures: **A. Wong:** None. **T. Lan:** None. **D. Wu:** None. **A. Schurger:** None. **U. Maoz:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.27

Topic: E.04. Voluntary Movements

Support: John Templeton Foundation #61283
Fetzer Institute, Fetzer Memorial Trust #4189

Title: Studying the onset of the readiness potential using a spiking-network model

Authors: J. GAVENAS[1], U. RUTISHAUSER[2], A. SCHURGER[1], ***U. MAOZ**[1];
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Abstract: The assumption that humans are in control of their behavior is a pillar of our social order. Moreover, our experience of controlling our own behavior—and in particular of voluntarily initiating action—is among the most fundamental of human experiences. Yet, throughout human history, we had to rely on individuals to subjectively report about their action initiation processes. This changed with the discovery of the readiness potential (RP; Kornhuber & Deecke, 1965)—a deepening negativity leading up to movement onset, recorded by EEG mainly above the supplementary motor area of the brain (SMA). Measuring the RP enabled neuroscientists to objectively track the neural preparation of voluntary action. And many viewed the onset of the RP as also reflecting the onset of an unconscious decision to move (Libet, 1985). More recently, stochastic accumulator models of self-initiated action have posited that the RP (and possibly other, similar components) corresponds to a diffusion-to-threshold process, where the threshold crossing leads to movement onset (Schurger et al., 2012). Interestingly, similar pre-movement ramping was also found in the firing rates of individual neurons in the SMA (Fried et al., 2011). However, autocorrelation timescales of individual neurons are too low for a single-neuron diffusion process to account for this ramping (Cavanagh et al., 2016). This implies that stochastic accumulation can only occur at the network level. But what network features could give rise to these gradual changes in firing rates is poorly understood.
We simulated networks of spiking neurons (N=400) with clustered architectures (previously shown to exhibit slow fluctuations; Litwin-Kumar & Doiron, 2012). We found that slow synaptic dynamics stabilized fluctuations and resulted in pre-threshold ramping, while fast synapses did

not. The average activity of such networks further exhibited a gradual negative shift reminiscent of the RP. In addition, by including a combination of slow and fast synapses, threshold-crossing times closely matches those found empirically. Our results thus provide evidence that RP onset is a result of spontaneous fluctuations across the network rather than specific state transitions that reflect unconscious control of an upcoming movement.

Disclosures: **J. Gavenas:** None. **U. Rutishauser:** None. **A. Schurger:** None. **U. Maoz:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.28

Topic: E.04. Voluntary Movements

Support: John Templeton Foundation #61283
Fetzer Memorial Trust #4189

Title: Disentangling the neural correlates of intention and foresight

Authors: ***E. CHEN**[1], T. DOMINIK[1], I. GAVISH[2], M. BRILLHART[1], G. YAFFE[3], U. MAOZ[1];
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Abstract: Imagine a scenario in which a military officer must make a difficult decision. She must choose whether to bomb an enemy target at the cost of killing civilians in the process. In this scenario, it is likely that the officer foresees civilian casualties as a possible consequence of her action but does not actually intend such a consequence. This hypothetical moral dilemma is a paradigmatic illustration of the double-effect principle. This doctrine posits that it is sometimes morally permissible to cause harm so long as the harm is merely a *side effect* (or "double effect") of bringing about some greater good, rather than a *means* to an end (McIntyre, 2019). Importantly, the doctrine presupposes that the distinction between intention and foresight is real, in the sense that one can foresee an outcome without intending it. The double effect principle has been controversial in religion, philosophy, medicine, and the law. Specifically within criminal law, a guilty verdict may rest on the distinction between intention and foresight. However, no reliable method exists to distinguish the two. Here, neuroscience may offer an empirical solution: this study aims to disentangle the neural correlates of intention and foresight by using electroencephalography (EEG) to differentiate their associated brain states.
The experimental design for this project has undergone several iterations. In all versions, we manipulated varying degrees of intention and foresight in different decision-making scenarios. We used a 2×2×2 design: (intending, not intending) an outcome × (foreseeing, not foreseeing) an outcome × outcome (occurs, does not occur). In our first paradigm (n=4), we found that subjects displayed neural signatures of differing amplitudes when responding to intended and foreseen consequences of their decisions in comparison to intended but unforeseen consequences.

However, we failed to see any meaningful difference between the conditions in which the consequences were not intended. In our second paradigm (n=8, with n=4 including EEG), we found that intention and foresight can indeed be disentangled in some subjects, but only if the subject finds the task at hand to be sufficiently engaging. Our third and current paradigm aims to resolve the aforementioned issues with the previous designs.

Disclosures: E. Chen: None. **T. Dominik:** None. **I. Gavish:** None. **M. Brillhart:** None. **G. Yaffe:** None. **U. Maoz:** None.

Poster

720. Movement Planning and Execution

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 720.29

Topic: E.05. Brain-Machine Interface

Support: Swedish Research Council Grant 2017-00892
Region Västerbotten (Strategic funding VLL-358901; Project No. 7002795, Cuttinge Edge funding RV966109, ALF funding RV 967112
Swedish Research Council for Sport Science (Grant Nos. P2020-0035, P2021-0061; FO2021-0011)
Umeå University School of Sport Science; IH 5.2–25-2021
The Umeå University Foundation for Medical Research
King Gustaf V and Queen Victoria's Foundation of Freemasons
Kempe foundation scholarship, Spring 2020

Title: An electroencephalography-based approach to evaluate movement-related anxiety in physically active adults and following anterior cruciate ligament injury

Authors: *A. GRINBERG[1], A. STRONG[1], J. STRANDBERG[2], J. SELLING[1], D. G. LIEBERMANN[3], M. BJÖRKLUND[1], C. K. HÄGER[1];
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Abstract: Background: Psychophysiological consequences often persist following musculoskeletal trauma and can result in vastly decreased quality of life. Re-injury anxiety is particularly common among individuals following anterior cruciate ligament (ACL) injury. Existing assessments of re-injury anxiety are, however, restricted to subjective suboptimal questionnaires, which may result in under-reporting and thus poorer injury management. We propose a novel approach to objectively quantify arousal response to movement-related anxiety. A new experimental paradigm was implemented to induce and record a conditioned electrophysiological response to a sudden perturbation, experienced to be potentially injurious. Objective: To explore the feasibility of detecting anxiety-associated electrocortical response and to evaluate its discriminative ability between asymptomatic individuals and those who had

experienced an ACL injury. Methods: Physically-active asymptomatic persons and individuals post-ACL reconstruction stood blindfolded on a perturbation platform capable of generating high-acceleration translations (1.5 m/s2). Auditory stimuli were repeatedly presented in four-second intervals, as either low- or high-frequency tones. Half of the high-frequency tones were followed 1.5 seconds later by a destabilizing perturbation in one of eight randomized directions. The two tone conditions were thus termed 'Neutral' and 'Anxiety', as the high-frequency tone was intended to invoke an arousal response in anticipation of a potential perturbation. Event-related potentials (ERP) were computed for nine electrodes by averaging 100 Neutral and 100 Anxiety trials. Significant ERP components were identified using functional data analysis. Paired difference-waves' amplitudes (Neutral - Anxiety) were compared between groups. Results: ERP correlates of anxiety were detected for both groups in frontal and central midline locations, with an observable contingent negative variation (CNV) from 500 ms post-stimulus in Anxiety compared with Neutral trials. This ERP component is reflective of a threat-induced arousal response, associated with attention and expectancy of an anxiety-relevant event. Preliminary data indicate no group differences in CNV amplitudes. Conclusions: Objective evaluation of an arousal response to movement-related anxiety was found to be feasible, resulting in a threat-induced CNV. Further investigation will elucidate the discriminative power of such an approach to differentiate between individuals with high and low re-injury anxiety, as well as potential associations with existing patient-reported outcome measures.

Disclosures: A. Grinberg: None. **A. Strong:** None. **J. Strandberg:** None. **J. Selling:** None. **D.G. Liebermann:** None. **M. Björklund:** None. **C.K. Häger:** None.

Poster

721. Neuroprosthetics and Brain Computer Interfaces: Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 721.01

Topic: E.05. Brain-Machine Interface

Support: NIH NINDS R01NS105691
NIH NINDS R01NS115707
NIH NINDS T32 NS08674932
NSF CAREER 1943906

Title: Biomimetic stimulation trains in sensory cortices improves neural responses over engineered stimulus trains

Authors: *C. HUGHES, T. D. KOZAI;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Intracortical microstimulation (ICMS) of the sensory cortices is an emerging tool to restore sensation to people with neurological injuries or disease. Current brain-computer interfaces (BCIs) apply ICMS in sensory cortices with engineered stimulus trains, which mimic

sensory input directly. Biomimetic stimulus trains, which mimic neuronal activity evoked by sensory input, may improve the utility of ICMS over engineered trains. However, studying neural responses to ICMS in humans is limited. To address this gap, we are using simultaneous ICMS and two-photon imaging in the visual and somatosensory cortices of anesthetized GCaMP6s mice. Here, we built principled biomimetic amplitude (B1), frequency (B2), and comodulated trains (B3) as well as fixed (engineered) parameter trains. All biomimetic trains consisted of a 200-ms "onset" and "offset" period where the amplitude and/or frequency were elevated. These trains were delivered for short durations (1-s on, 4-s off) or long durations (30-s on, 15-s off). Preliminary analyses indicate that biomimetic amplitude modulation (B1 and B3) produces neural population activity that entrains strongly to the stimulus profile for both short and long trains, with an onset and an offset peak of equal size. Biomimetic frequency modulation alone (B2) produces population activity that closely resembles activation with fixed trains, with an initial onset peak followed by decreases in activation (adaptation) to 92±4% (B2, mean±std) and 75±8% (fixed) of the max amplitude at the end of the short trains (n=9) and 21±17% and 14±9% at the end of the long trains (n=7). Adaptation of neural responses can decrease intensity of evoked sensation over time which limits the utility of ICMS. Ideal observer analysis applied to the recorded calcium response to long ICMS trains demonstrated that the strong transients elicited by B1 and B3 allow for faster detection of stimulus onset (0.06±0.09 s vs. B2 and 0.02±0.07 s vs. fixed). Additionally, stimulus offset was determined with high confidence for B1 (90% success for 28 trains) but was difficult to determine for B2 (0%) and fixed trains (14%) due to adaptation, which made the end of single trains barely separable from noise. We expect then that biomimetic amplitude modulation increases the speed and confidence of sensory detection and better maintains sensitivity to changes in sensation vs. engineered approaches. These preliminary findings suggest that biomimetic amplitude modulation can produce strong onset and offset responses which can have utility for BCI applications, where timing and confidence of sensory input are critical for improved performance.

Disclosures: C. Hughes: None. **T.D. Kozai:** None.

Poster

721. Neuroprosthetics and Brain Computer Interfaces: Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 721.02

Topic: E.05. Brain-Machine Interface

Support: EU Horizon 2020 programme Marie Skłodowska-Curie grant agreement No 86142 (enTRAIN Vision)
EU Horizon 2020 programme grant agreement Nà. 88160 No. 88160 (GrapheneCore3)

Title: Graphene-based implants for reading and writing neuronal visual activity with functional ultrasound imaging on rodents

Authors: *J. M. ZHANG[1], R. GOULET[1], V. NGUYEN[1], J. DÉGARDIN[1], F. DUVAN[2], E. MASVIDAL-CODINA[2], A. GUIMERÀ-BRUNET[3], F. ARCIZET[1], G. GAUVAIN[1], J. A. GARRIDO[2], R. C. WYKES[4], S. PICAUD[1];
[1]Inst. de la Vision, Paris, France; [2]Inst. Català de Nanociència i Nanotecnologia, Barcelona, Spain; [3]Microelectronics Inst. of Barcelona - Spanish Natl. Res. Council, Barcelona, Spain; [4]UCL Inst. of Neurol., London, United Kingdom

Abstract: Brain-computer interfaces (BCIs) can help in clinical diagnosis or treatments to "read from" (record) and "write to" (electrically stimulate) neurons. Graphene could address challenges current devices are facing such as lack of spatial resolution. For instance, graphene solution-gated flexible field-effect transistors (gSGFETs) show high transconductance beneficial for low-noise amplification of recorded signals. Reduced graphene oxide (rGO) microelectrodes display high charge injection capacity encouraging enough for efficient electrical stimulation. We demonstrate here the potential of graphene-based electrodes for either recording cortical spreading depressions (CSDs) at infraslow frequencies or stimulating retinal neurons in rodents, with the use of functional ultrasound imaging (fUSi) to quantify the cerebral neural activity.
CSDs were recorded simultaneously with fUSi and gSGFET placed on the visual cortex in a model of pharmaco-induced epileptic rat. The high correlations in visual cortex and hippocampus ($p>0.0030$ and $p>0.0036$ respectively, $n=4$) between cerebral blood volume (CBV) variation and electrophysiological signals account for the complementary coupling of both technologies.
Cortical CBV changes were measured with fUSi in response to monopolar electrical stimulation of rGO electrodes inserted in the subretinal space of wild type rats. Global linear modelling (GLM) of the CBV highlights a significant fit with the stimulation pattern in the superior colliculus suggesting successful information transmission to this subcortical visual area.
Additionally, we investigated the *in vivo* biocompatibility of rGO electrodes using post-mortem immunolabelling. Quantification of microglial cells revealed a non-significant inflammation of the retina compared to control eyes.
These results provide great confidence in the graphene technology for the elaboration of future-generation BCIs for neural responses reading or specific stimulation of localized areas.

Disclosures: J.M. Zhang: None. **R. Goulet:** None. **V. Nguyen:** None. **J. Dégardin:** None. **F. Duvan:** None. **E. Masvidal-Codina:** None. **A. Guimerà-Brunet:** None. **F. Arcizet:** None. **G. Gauvain:** None. **J.A. Garrido:** None. **R.C. Wykes:** None. **S. Picaud:** None.

Poster

721. Neuroprosthetics and Brain Computer Interfaces: Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 721.03

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01EY030569

Title: Photothermal activation of retinal ganglion cells in rodents toward minimally-invasive restoration of vision

Authors: *J. NIE[1], K. EOM[2], H. ALGHOSAIN[1], J. LEE[1,3];
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Abstract: Non-genetic approaches to vision restoration require implantable devices to activate retinal neurons either electrically or optically. Electrical retinal implants are currently the only approved option to restore vision in blindness caused by photoreceptor degeneration. Clinical studies with these retinal implants, however, revealed limitations: visual acuity still worse than legal blindness, and complex implant surgery. In contrast, optical stimulation has a potential for a higher resolution of artificial vision with a less invasive process. Here, we demonstrate a retinal ganglion cell (RGC) - targeting photothermal stimulation approach to vision restoration. This approach activates temperature-dependent ion channels on the neural membrane via surface plasmon resonance of gold nanorods. To induce highly localized and transient photothermal effects on RGCs, GCaMP3 mice were intravitreally injected with Thy-1 antibody-conjugated gold nanorods of 980-nm resonance wavelength (Thy-1-AuNRs). We combined a near-infrared (NIR) laser scanning system and wide-field fluorescence Ca^{2+} imaging microscope to stimulate and record activities of multiple RGCs on live retinal explants of mice. Results show that, compared to retinas without AuNRs, the retinas with Thy-1-AuNRs elicited significant Ca^{2+} responses of RGCs over 3 % dF/F (n = 12, $p < 0.05$) to the scanning NIR laser pulses (200 x 200 μm square-pattern). Higher laser power resulted in larger amplitudes of Ca^{2+} responses. To determine which laser pulse width is optimal, we repeated the experiment for various pulse widths. Moreover, we observed that the RGCs responses were activated by different wavelengths (780-nm and 980-nm) of NIR when using nanorods of different aspect ratios (4.8 and 3.5). This demonstration and optimization support the promising potential of the photothermal approach to restoring vision in blindness.

Disclosures: **J. Nie:** None. **K. Eom:** None. **H. AlGhosain:** None. **J. Lee:** None.

Poster

721. Neuroprosthetics and Brain Computer Interfaces: Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 721.04

Topic: E.05. Brain-Machine Interface

Support: NeuroNex Technology Hub: MINT (NSF 1707316)
University of Michigan

Title: Intraretinal Stimulation with High Density Carbon Fiber Microelectrodes

Authors: *D. HAJI GHAFFARI, E. DELLA VALLE, P. R. PATEL, J. RICHIE, C. A. CHESTEK, J. D. WEILAND;
Univ. of Michigan, Univ. of Michigan, Ann Arbor, MI

Abstract: Retinal prostheses restore rudimentary vision in patients blinded by photoreceptor degenerative diseases such as retinitis pigmentosa and dry age-related macular degeneration. However, the best visual acuity for artificial vision is 20/400 (legal blindness = 20/200), which limits shape and letter recognition abilities in prostheses users. Studies show that current approaches of retinal stimulation (epiretinal, subretinal, and suprachoroidal) with surface electrodes do not activate the retina with high precision due to large electrode-retina distances, spreading of electric field, and off-target stimulation. We used intraretinal carbon fiber electrodes for stimulation *in vitro*, to increase the specificity of stimulation. High density carbon fiber arrays (HDCF) were fabricated and the tips were coated with a platinum iridium alloy (PtIr). Intravitreal injection of an adeno-associated virus (AAV) vector (pGP-AAV-CAG-jGCaMP7f-WPRE) was done 3-4 weeks before experiments to induce expression of the calcium indicator jGCaMP7f in healthy mouse retinal ganglion cells (RGCs). Retinas were dissected and mounted on a transparent chamber with RGCs facing down to allow for calcium imaging. HDCFs were inserted from the subretinal side and the electrode tip was placed at either 20 or 70 µm above the RGC layer. Electrical stimulation consisted of biphasic charge balanced pulses with 0.5 or 1 ms duration per phase, and delivered at 120 Hz frequency. Our results show that intraretinal stimulation activates RGCs with 80-90% lower current thresholds compared to epiretinal stimulation. Average activation thresholds at 20 µm RGC-electrode distance (3.42 µA and 2.28 µA) were 63% and 55% lower than 70 µm distance (9.28 µA and 5.14 µA) with 0.5 ms and 1 ms pulse widths respectively (p=0.006, p=0.02). At 70 µm distance, the average activation threshold was 45% less with 0.5 ms pulse width compared to 1 ms pulse width (p= 0.0025), but this difference was not significant at 20 µm RGC-electrode distance (n = 7). RGC activation area (area of an ellipse fitted to active pixels) increased with higher current amplitudes and smaller electrode-RGC distances. In general, activation areas were smaller and more focal with intraretinal stimulation compared to epiretinal stimulation in a similar setup, which may be an indication of indirect RGC activation. Together, our preliminary data demonstrates the potential of intraretinal stimulation for high resolution activation of RGCs.

Disclosures: D. Haji Ghaffari: None. **E. Della Valle:** None. **P.R. Patel:** None. **J. Richie:** None. **C.A. Chestek:** None. **J.D. Weiland:** None.

Poster

721. Neuroprosthetics and Brain Computer Interfaces: Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 721.05

Topic: E.05. Brain-Machine Interface

Support: NIH grant NS099700
DoD grant W81XWH-19-1-0057

Title: Micro-scale magnetic stimulation of primary visual cortex for evoking visual percepts

Authors: J. TANNER[1], ***B. GREGER**[1,2], J. S. PEZARIS[3], S. RYU[3], S. LEE[3], S. FRIED[3]; [1]Arizona State Univ., Arizona State Univ., Tempe, AZ; [2]Barrow Neurolog. Inst., Phoenix, AZ; [3]Massachusetts Gen. Hosp., Boston, MA

Abstract: Electric stimulation of primary visual cortex reliably elicits visual percepts in both nonhuman primates and humans (Brindley & Lewin 1968, Schmidt et. al 1996, Bradley et. al 2005, Davis et. al 2012, Chen et. al 2020). Unfortunately, the ability to produce more complex spatial objects, e.g., letters, has been less consistent, possibly due to the inability to focally confine elicited neural activity from individual electrodes. This technology has begun to be translated into a functional visual prosthesis (Salas et. al 2022). Magnetic stimulation from implantable microcoils may be an attractive alternative to conventional electrodes as its inherent dipole field helps to better confine activation in a manner similar to that from a stereotrode (Moleirinho, et al., 2021). Much recent in vitro and in vivo testing in rodent confirms the viability of the microcoil approach. (Tanaka et. al 2019, Lee & Fried 2022). Here, we present preliminary results from acute magnetic micro-stimulation experiments in a behaving nonhuman primate. We used custom, single-turn microcoils that are approximately the same physical dimensions as traditional recording electrodes. The nonhuman primate was trained to report the presence or absence of a visual stimulus initially with small flashes of visible light on a CRT monitor, lifting one hand (left) to indicate its presence and the other (right) to indicate its absence. Prior to the start of magnetic stimulation experiments, a traditional recording micro-electrode was inserted into primary visual cortex through a craniotomy chamber and lowered until multi-unit activity was observed; the microcoil was then lowered to the same depth. Stimulation current was delivered through the coil in lieu of a photic stimulus on the CRT in a subset of trials, and the monkey reported whether a visual percept (phosphene) was detected; stimulus amplitudes were randomly varied across trials. A logistic fit revealed a 75% detection threshold of 16 mA providing preliminary evidence that magnetic micro-stimulation can indeed be used to elicit visual percepts in a non-human primate. Further, the thresholds here were more than one order of magnitude lower than those required to generate electrophysiological responses in anesthetized rodents. In future work, we plan to optimize micro-stimulation parameters, to determine the best depth of the micro-coil placement relative to cortical layers, and to correlate perception with evoked activity in higher cortical areas.

Disclosures: J. Tanner: None. **B. Greger:** None. **J.S. Pezaris:** None. **S. Ryu:** None. **S. Lee:** None. **S. Fried:** None.

Poster

721. Neuroprosthetics and Brain Computer Interfaces: Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 721.06

Topic: E.05. Brain-Machine Interface

Support: NIH NCI Grant 5R21CA226726-02

Title: Towards a bionic breast: Characterizing the spatial acuity of the human breast

Authors: *E. E. FITZGERALD, K. H. LONG, A. FAWAZ, S. T. LINDAU, S. J. BENSMAIA; Univ. of Chicago, Chicago, IL

Abstract: In the US alone, 100,000 women undergo mastectomy each year to prevent or treat breast cancer. Mastectomies typically result in a reduction or total loss of sensation in the breast and nipple-areolar complex (NAC). As part of an ongoing effort to develop a prosthetic to restore breast sensation, we set out to characterize the tactile acuity of the breast. This is part of a larger undertaking to better understand breast sensation and its neural basis. We evaluated the spatial acuity of the lateral breast and compared it to its counterpart on the back and hand. To this end, we developed a new method for evaluating spatial acuity on the breast, adapting current methods for assessing spatial acuity in the hand. Then, we determined the spatial threshold (ST) for each of these body locations. We found that the spatial acuity for the breast was lower than that of the back, and both thorax locations (the back and breast) had lower spatial acuity than the hand. Furthermore, breast ST's increased with bust size, consistent with the documented inverse relationship between body size and spatial acuity.

Disclosures: E.E. Fitzgerald: None. **K.H. Long:** None. **A. Fawaz:** None. **S.T. Lindau:** None. **S.J. Bensmaia:** None.

Poster

721. Neuroprosthetics and Brain Computer Interfaces: Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 721.07

Topic: E.05. Brain-Machine Interface

Support: JPMJCR18A5
JPMJPR1506
JPMJER1801
JPMJMS2012
JP26560467
JP17H06032
JP20K16466

Title: Imagery-based control of feedback images using electrocorticograms from visual areas

Authors: *R. FUKUMA[1,2,3], T. YANAGISAWA[1,2,3,4], S. NISHIMOTO[5,6], H. SUGANO[7], K. TAMURA[8], S. YAMAMOTO[1], Y. IIMURA[7], Y. FUJITA[1], S. OSHINO[1], N. TANI[1], N. KOIDE-MAJIMA[5,6], Y. KAMITANI[3,9], H. KISHIMA[1,4];
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Abstract: Visual stimuli evoke cortical activity in visual cortex, which is also affected by visual imagery. We hypothesized that a subject could intentionally control feedback image of a closed-loop (real-time) brain-computer interface (BCI) using visual imagery so that the feedback image contained intended meaning. Subjects were shown with six 10-min movies as visual stimuli under recording of electrocorticograms (ECoG) from occipital or temporal lobes. The stimuli movies consisted of short video clips (median duration: 16 s) cropped out from films and contained a variety of semantic content such as humans, animals, and landscapes. Still images were extracted from the movies every 1 s to be annotated by cloud-workers; the nouns, verbs and adjectives in the annotations for each image were converted to 1,000-dimensional vectors using a word2vec model and averaged to create a semantic vector for the image. From high-γ powers of the ECoGs, the semantic vectors were inferred using ridge regression and nested cross-validation. Decoding accuracy of the semantic vectors was evaluated by the accuracy of identifying image categories from the inferred vector; for this analysis, 50 images were selected for each category of “human face”, “landscape”, and “word” from the 3,600 annotated images based on the highest correlation coefficients between the semantic vector and vector for each category. Finally, subjects participated in a feedback task using the trained ridge regression model. Semantic vectors were inferred every 250 ms from the subject’s real-time cortical activity to determine feedback images from the annotated images based on the highest correlation coefficient. The subjects were instructed to control the feedback image by visual imagery so that it contained meaning of instruction given aurally (“human face”, “landscape”, or “word”). The controllability of the feedback image was evaluated using the correlation coefficient between the inferred semantic vector and vectors for the three instructions. The averaged accuracy of identifying the category of the 50 images against another category was 70.5%. In the feedback task, all four subjects could control the inferred semantic vector according to the instructions with a significant accuracy of 41.7-50.0% (chance level: 33.3%). The results of this study show for the first time that subjects can use visual imagery to intentionally control feedback images so that they contain the instructed meaning. This new type of the BCI based on visual imagery could be useful for patients with amyotrophic lateral sclerosis in future.

Disclosures: R. Fukuma: None. **T. Yanagisawa:** None. **S. Nishimoto:** None. **H. Sugano:** None. **K. Tamura:** None. **S. Yamamoto:** None. **Y. Iimura:** None. **Y. Fujita:** None. **S. Oshino:** None. **N. Tani:** None. **N. Koide-Majima:** None. **Y. Kamitani:** None. **H. Kishima:** None.

Poster

721. Neuroprosthetics and Brain Computer Interfaces: Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 721.08

Topic: E.05. Brain-Machine Interface

Support: BLAUSTEIN GRANT AWARD

Title: Mechanical activation of sensory afferents in vascularized denervated muscle targets for proprioceptive feedback in neuroprosthetic limbs

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Abstract: After amputation, nerves that normally innervate peripheral skeletal muscles are transected, resulting in a loss of motor function. A common approach to restore motor function is to perform a muscle reinnervation surgery, whereby the transected nerve is provided a new muscle target to reinnervate. For example, vascularized denervated muscle targets (VDMTs) are a novel type of muscle reinnervation surgery in which motor nerves are rerouted to nearby vascularized muscle grafts. After the VDMT is reinnervated by motor axons, it produces robust electromyography signals which serve as a control source for advanced prosthetic limbs. While reinnervated muscles are proven to be ideal interfaces for prosthesis control, it is largely unexplored whether the interface could be bidirectional; that is, whether reinnervated muscles could provide sensory feedback from the prosthesis to the user. For example, in an intact limb, proprioceptive sensation is mediated by muscle stretch. Proprioceptive neurons, known as muscle spindle afferents, wrap tangentially around muscle fibers and act as stretch sensors. Contraction of an agonist muscle (e.g., bicep) causes a stretch of its antagonist pair (e.g., tricep). The degree of muscle stretch is encoded by spindle afferents and used by the brain to determine the extent the joint has moved, and subsequently the limb position in space. VDMTs are a promising approach to restore proprioceptive feedback because spindle afferents natively innervate muscle. In muscle reinnervation surgeries, the 'motor' nerves that are typically rerouted to target muscles are in fact a mix of motor *and* sensory fibers. Our goal is to demonstrate that sensory afferents, specifically proprioceptive afferents, also reinnervate VDMTs like their motor counterparts, and that they can be activated via mechanical stretching of the muscle graft. To that end, male Lewis rats underwent a VDMT surgery in which a denervated soleus muscle was neurotized with the residual end of a transected tibial nerve. At least six months post-reinnervation, soleus VDMTs were stretched at varying lengths (1.5 mm, 3 mm, 4.5 mm, 6 mm). Afferent signals were simultaneously recorded from the dorsal root ganglion, the region where afferent cell bodies coalesce. We found mechanical stretch of VDMTs evokes an increase in proprioceptive afferent firing rate in the L4-dorsal root ganglion compared to baseline. We present direct evidence that proprioceptive afferent fibers successfully reinnervate VDMTs. These results constitute the first proof of concept that VDMTs can be used to provide proprioceptive feedback for neuroprosthesis applications.

Disclosures: K. Quinn: None. **M. Iskarous:** None. **C. Glass:** None. **A. Lowe:** None. **S. Tuffaha:** None. **N. Thakor:** None.

Poster

721. Neuroprosthetics and Brain Computer Interfaces: Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 721.09

Topic: E.05. Brain-Machine Interface

Support: DARPA Grant NC66001-15-C-4041
T32 Training Grant TRN228211

Title: First implementation of a high channel count, bidirectional somatosensory neuroprosthetic system with wireless communication

Authors: *S. R. CADY[1,3], J. M. LAMBRECHT[1,3], K. T. DSOUZA[1,3], J. L. DUNNING[1,3], J. R. ANDERSON[3,4,2], K. J. MALONE[3,4,2], E. L. GRACZYK[1,3], D. J. TYLER[1,3];
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Abstract: Peripheral nerve stimulation using Flat Interface Nerve Electrode (FINE) and composite FINE (CFINE) cuffs can restore tactile sensation to individuals with limb loss. Our lab has worked with five upper extremity amputee participants across ten years with implanted percutaneous stimulation systems. However, the upkeep of the percutaneous leads, the high wire count, and the burden of using an external stimulator may deter prosthesis users from adopting the system at home. Thus, our team developed a high channel count peripheral nerve stimulation and myoelectric recording device with wireless communication: the Implanted Somatosensory Electrical Neurostimulation and Sensing (iSens) system. The purpose of this study was to compare sensory percepts resulting from the iSens and percutaneous systems, assess the iSens system's wireless signal strength, and evaluate the separability of intramuscular EMG channels. One participant with a transradial amputation and percutaneous implant enrolled in the study. The percutaneous system, consisting of three 8-channel FINEs, was explanted, and the iSens system was implanted. The iSens system included four 16-channel CFINEs on the median, ulnar, and radial nerves and four Tetra Intramuscular EMG recording electrodes in residual muscles. An implanted neural controller (INC) regulated stimulation and recording while providing Bluetooth Low Energy (BLE) communication to an external "Hub" device. Cathode-first, charge balanced stimulation was applied at each electrode contact at threshold perception. The participant described perceived sensation qualities using his own terms and circled each sensory location on a tablet. Sensory locations and quality, threshold charge values, and tissue impedances were monitored across lab visits and compared to results from the participant's percutaneous system. Intramuscular EMG channel cross correlation was compared to previously reported values from surface EMG. BLE Received Signal Strength Indicator (RSSI) values were recorded as the Hub was shifted to several orientations near the participant's residual limb and waist. Stimulating through both systems provided unique percept locations and qualities along the phantom limb. Intramuscular EMG recording resulted in low crosstalk between channels compared to surface EMG, which may support high degree-of-freedom control of prostheses. BLE RSSI values varied based on the orientation of the Hub relative to the INC. Results from this work suggest that the iSens system provides stable sensory percepts and separable EMG recording channels that can be adopted more readily at home in a bidirectional neuroprosthetic system.

Disclosures: **S.R. Cady:** None. **J.M. Lambrecht:** None. **K.T. Dsouza:** None. **J.L. Dunning:** None. **J.R. Anderson:** None. **K.J. Malone:** None. **E.L. Graczyk:** None. **D.J. Tyler:** None.

Poster

721. Neuroprosthetics and Brain Computer Interfaces: Sensory Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 721.10

Topic: E.05. Brain-Machine Interface

Support: NIH Grant UH3NS095557

Title: The Wireless Floating Microelectrode Array: Updates on Research Usage and Performance

Authors: *M. J. BAK[1], N. A. ALBA[1], B. BAK[1], S. SUH[2], G. DEMICHELE[3], S. F. COGAN[4], P. R. TROYK[2];
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Abstract: The Wireless Floating Microelectrode Array (WFMA) is an implantable 16-channel microelectrode array based upon the Microprobes for Life Science Floating Microelectrode Array (FMA) in which the wired percutaneous connector is replaced with a miniature integrated-circuit inductive telemetry unit resulting in a true wireless free-floating intracortical implant. Multiple WMFAs can be implanted as a group with a system capacity of up to 127 randomly addressable devices, for a potential neuronal interface comprised of 2,032 electrodes. Using activated iridium oxide stimulating electrodes, the current version of the WFMA allows for intracortical stimulation over a wide range of charge capacity, typically up to 60nC/phase. An advantage of the WFMA system is that a very large number of intracortical electrodes can be placed over a broad cortical geographic area. As part of pre-clinical testing for an on-going clinical trial for an intra-cortical visual prosthesis, WFMAs were tested in-vitro as well as in large animal tests to investigate the device reliability, the functional flexibility, and the tissue response. Results from 4, 13, and 26-week implantations in canine occipital lobe showed that neuronal survivability surrounding each of the 16 WFMA electrodes was uncharacteristically high, with H&E, as well as NeuN, stains showing minimal to no decrease in local cell and neuron density as compared to controls. Results from a 24-hour intense (4nC, 8nC, 12nC, and 16nC/phase) continuous stimulation showed minimal inflammatory effects as evaluated by pathological examination. Related to device reliability, results from a 26-day continuous in-vitro (PBS) durability testing at the maximum device stimulus level (80uA, 200uS, 16nC/Phase), for a total of 3.888×10^8pulses, showed insignificant changes in the AIROF electrode driving voltage (Vdrive), electrode polarization, and access resistance. Similarly, in rat sciatic nerve implantations, the WFMA neuronal interface remained functional over the lifetime of the animal (typically 12 – 18 months), with stable stimulation thresholds. In recent work, 25 WFMAs were implanted in the occipital lobe of a human volunteer as part of clinical trial to investigate an

intracortical visual prostheses. Preliminary data from this study show stable electrode characteristics, and stable perceptual thresholds, with the nature of the percepts being complex (lines, movements, shapes) as opposed to simple phosphenes. These are being investigated for use as building blocks of artificial vision. Emerging versions of the WFMA will include neural recording as well as stimulation with the same device.

Disclosures: **M.J. Bak:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Microprobes for Life Science, Inc. **N.A. Alba:** A. Employment/Salary (full or part-time):; Microprobes for Life Science, Inc. **B. Bak:** A. Employment/Salary (full or part-time):; Microprobes for Life Science, Inc.. **S. Suh:** None. **G. DeMichele:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sigenics, Inc.. **S.F. Cogan:** None. **P.R. Troyk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sigenics, Inc..

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.01

Topic: E.06. Posture and Gait

Title: Similarity between training and testing contexts is more important for generalization of motor memories than the amount of sensorimotor adaptation in locomotion

Authors: *K. FJELD, Y. AUCIE, G. TORRES-OVIEDO;
Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Generalization is the ability to carryover motor learning from trained to untrained situations and it is a critical aspect for rehabilitation. In sensorimotor adaptation paradigms, generalization from a training context (where a motor memory is learned) to a testing context (an alternate context where said motor memory is tested), can be enhanced by either augmenting the magnitude of adaptation or by increasing the similarity between the training and testing contexts. However, little is known about which one of these factors is more important for generalization. To address this question, we assessed the generalization of adapted locomotor patterns to unassisted level overground walking following two adaptation conditions: flat split-belt walking vs. incline split-belt walking on a treadmill, which moves the legs at different speeds. This was done because incline split-belt walking is known to augment the amount of sensorimotor adaptation while decreasing the contextual similarity between the training context (i.e., incline walking) and the testing context (i.e., overground walking). We hypothesized that the amount of sensorimotor adaptation would be more important for generalization than contextual similarity. Thus, we anticipated greater generalization of adapted movements (i.e., aftereffects) following incline, compared to flat, split-belt walking. To test this, sixteen healthy young adults were

adapted on either the flat (n=8) or incline (n=8) split-belt conditions. We compared the generalization of adapted movements (i.e., step length asymmetry) from these two adaptation conditions by quantifying 1) the aftereffects overground (i.e., testing context) and 2) the remaining aftereffects on the treadmill (training context) following overground walking. Contrary to our expectations, we found that the generalization of flat split-belt walking was larger than that of incline split-belt walking. This was indicated by the significantly larger aftereffects overground ($p=0.016$) and smaller remaining aftereffects on the treadmill ($p=0.001$) when participants were adapted flat compared to those who adapted incline. Therefore, our results indicate that the similarity between the training and the testing contexts is more important for generalization than the amount of adaptation. This suggests that training strategies which maximize contextual similarity to unassisted walking may lead to better outcomes when learning or re-learning motor skills.

Disclosures: K. Fjeld: None. **Y. Aucie:** None. **G. Torres-Oviedo:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.02

Topic: E.06. Posture and Gait

Support: University of Pittsburgh Momentum Fund 3455

Title: Novel automaticity index combining cortical activation and performance in dual tasks reveals an age-related decline in gait automaticity

Authors: *S. LIU[1,4], A. L. ROSSO[2], E. M. BAILLARGEON[2], A. M. WEINSTEIN[3], G. TORRES-OVIEDO[1,4];
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Abstract: Gait automaticity refers to the ability to walk without recruiting attentional networks typically mediated through the prefrontal cortex (PFC). A common assessment of gait automaticity is to examine PFC activation via near-infrared spectroscopy (fNIRS) during dual-task (DT) walking, such as walking while performing a cognitive task. However, interpreting changes in PFC activity during a DT without considering task performance is limited. For example, a larger PFC activation could be interpreted as better gait automaticity when accompanied by better DT performance or as worse gait automaticity when accompanied by worse DT performance. Thus, we propose a novel analytical approach that combines changes in PFC activity with changes in DT (i.e., cognitive and motor) performance to quantify gait automaticity (automaticity index). We hypothesize that the automaticity index would better quantify the age and cognitive ability-related decline in gait automaticity compared to PFC measurements. Furthermore, the index will reflect an individual's attentional cost to complete a

DT such that a higher index is needed in a harder task that requires more attentional and less automatic control. To test this, 69 participants (+65 y/o) completed DTs with two levels of difficulty while PFC activation was recorded with fNIRS. The two DTs consisted of reciting every other letter of the alphabet (cognitive task) while either walking over an even (even-ABC task) or uneven surface (uneven-ABC task). Motor performance was measured by gait speed, and cognitive performance was measured by the rate of correct letters generated. We found that the automaticity index for uneven-ABC showed a significant positive correlation with age (ρ=0.242, p=0.046) that was not observed when using PFC activity alone (ρ=0.233, p=0.054). The index also had a stronger correlation to general cognitive ability, quantified with Mini-Mental State Examination scores (even-ABC: ρ=-0.492, p<0.001; uneven-ABC: ρ=-0.378, p=0.001), compared to PFC activation (even-ABC: ρ=-0.307, p=0.010; uneven-ABC: ρ =-0.134, p=0.271). Lastly, the index value increased as the task became harder (from even-ABC to uneven-ABC) for 78% of the participants compared to 55% in PFC activation. In sum, the proposed automaticity index addresses a major gap in the current approach by providing a unified measure of gait automaticity that considers both brain activation and performance, and it better correlates with aging and cognitive function than PFC activity alone. The new approach opens exciting possibilities to assess subject-specific deficits and intervention-induced improvements in gait automaticity.

Disclosures: S. Liu: None. **A.L. Rosso:** None. **E.M. Baillargeon:** None. **A.M. Weinstein:** None. **G. Torres-Oviedo:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.03

Topic: E.06. Posture and Gait

Support: NSF-GRFP1747452
NIH 5T32GM081760-12
NSF 1847891

Title: Characterization of the neuromuscular dynamics during adaptation and generalization of split-belt walking patterns

Authors: *D. MARISCAL[1,2], K. FJELD[1], G. TORRES-OVIEDO[1];
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Abstract: Humans can adapt their walking patterns to compensate for changes in environmental demands and generalize learned movements from one situation to another. One way to study the adaptation is by exposing participants to split-belt walking, in which the legs are forced to move at different speeds. We can study generalization by contrasting the adaptation effects (i.e.,

aftereffects) that participants exhibit in the same context in which they adapt their walking (split-belt treadmill) vs. another context (overground walking). An extensive body of work has characterized the adaptation and generalization of movements, such as step length asymmetry. However, less is known about what happens at the neuromuscular level. Therefore, we propose to quantify the adaptation and de-adaptation of muscle activation patterns across multiple muscles at every step.
Previous work has shown that at least two processes are needed to describe the adaptation and de-adaptation of kinematics. Hence, we hypothesize that at least two processes with distinct dynamics underly the changes in neuromuscular patterns during locomotor adaptation and de-adaptation. Specifically, we hypothesize that a fast reactive process will recruit a neuromuscular pattern to maintain balance at every transition between walking environments, whereas a slow adaptive process will forge a contextual pattern meeting the specific demands of the novel split environment. To test this hypothesis, we tracked the evolution of muscle activity across 14 leg muscles in 7 young adults who experienced split-belt adaptation and where de-adaptation was measured either on the treadmill (n=4) or overground walking (n=3).
Our preliminary analysis shows the hypothesized dynamics for the reactive and contextual patterns. Namely, during the adaptation, the reactive component emerges quickly upon introducing the split-belt perturbation but is rapidly mitigated as individuals adapt their gait, whereas the contextual pattern slowly develops during the adaptation period. During de-adaptation, people tested on the treadmill recruited rapidly the reactive pattern in the negative direction, as if they experienced the oppositive split-belt perturbation, whereas the contextual pattern was slowly disengaged. Conversely, people tested overground during de-adaptation only recruited the reactive pattern. Taken together, our results suggest that reactive and contextual patterns contribute to the evolution of neuromuscular patterns during split-belt walking, but only reactive ones generalize to walking without the training device, explaining the smaller movement aftereffects reported when walking overground.

Disclosures: **D. Mariscal:** None. **K. Fjeld:** None. **G. Torres-Oviedo:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.04

Topic: E.06. Posture and Gait

Support: NSF Career Award 1847891
NSF-GRFP

Title: The human sensitivity to speed asymmetries does not obey Weber's law

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Abstract: Sensation has a central role in the planning, execution, and adaptation of our movements. Weber's law posits that animals' sensitivity to a change in sensory stimulus scales proportionally to the intensity of the background sensory information. For example, one can detect a small change in lumens in the dark, but this sensory change needs to be large for detecting it under the bright sunlight. This sensitivity scaling has been observed across multiple sensory modalities. We asked if the same principle is observed when detecting speed asymmetries between the legs during walking. This information could explain the distinct locomotor adaptations in response to asymmetric leg motions at different walking speeds. We hypothesized that the human sensitivity to speed asymmetries would be scaled according to Weber's law. To test this hypothesis, we assessed the sensitivity of speed asymmetries in young adults (n=14) who walked at two different mean walking speeds: slow (1.05 m/s) and fast (1.4 m/s). According to Weber's law, we expected people would be more sensitive to speed asymmetries when walking slow than fast; such that people would maintain the same sensitivity when expressed as a function of Weber Fraction (i.e., speed asymmetries as a proportion of walking speed). We estimated each participant's sensitivity to speed asymmetries with a series of 2-alternative-forced choice tasks (2AFC) presented in a pseudorandom sequence while walking slow or walking fast. In each 2AFC task, participants were presented with speed asymmetries of a given magnitude and they indicated within a limited time (8sec) which leg moved slower. We fitted a logistic regression indicating the probability of people's responses as a function of perturbation size. Contrary to our hypothesis, we found that people were more sensitive to speed asymmetries when walking fast than what was predicted by Weber's law. This was indicated by a significantly higher slope for the fast than the slow logistic regressions when expressed as a function of Weber Fraction ($p=0.03$) and a similar slope for the two walking speeds when the logistic regressions were expressed as a function of perturbation size ($p=0.953$). Our results suggest that the intensity of the sensory stimulus in walking is not the primary factor governing the sensitivity to speed asymmetries (as predicted by Weber's law). Perhaps other aspects, such as habitual walking speeds, determine people's sensitivity to speed asymmetries, which will be addressed in future studies characterizing changes in said sensitivity at preferred vs. unusual walking speeds.

Disclosures: **M. Gonzalez-Rubio:** None. **P.A. Iturralde:** None. **G. Torres-Oviedo:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.05

Topic: E.06. Posture and Gait

Support: Wings for Life - Spinal Cord Research Foundation (WFL-US-07/19:199)
The Yerger NeuroRobotics Research Fund, Jackson MS
Wilson Research Foundation, Jackson MS

Title: Characterizing the pulse duration of transcutaneous spinal stimulation for evoking the lumbosacral posterior root reflexes

Authors: *E. A. GORDINEER[1], D. S. STOKIC[2], M. J. KRENN[3,2,4];
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Abstract: Transcutaneous spinal stimulation (TSS) is a promising neuromodulation approach for movement recovery and control of spasticity after spinal cord injury. Previous studies have applied different frequencies and intensities of TSS, however, the pulse duration has not been explored. We addressed two questions: Q1) do pulses of different durations preferentially depolarize posterior roots versus anterior roots, and Q2) how does pulse duration affect the motor threshold of posterior root reflexes in different lower limb muscles. We recruited 12 healthy participants. TSS was applied by surface electrodes with the cathode (5x5 cm) over T11/12 spinal processes and the anode (15x10 cm) over the abdominal wall. Short-latency responses were recorded in supine from 16 lower limb muscles. For Q1, pulse durations of 50 and 1000 us were used in a paired-pulse paradigm (inter-stimulus intervals 25, 50, 100, 200, 400 ms). For Q2, eight pulse durations (50, 100, 200, 300, 500, 700, 1000, 2000 us) were used to generate the input-output curve in each muscle from which we determined threshold, strength-duration curve, rheobase (minimal current of infinitely long pulse), and chronaxie (minimum pulse duration at twice the rheobase) according to the Weiss-Lapicque formula. For Q1, the paired-pulse suppression indicated the reflex origin of short-latency responses in the majority of muscles, suggesting the preferential activation of posterior roots, which did not differ between 50 and 1000 us pulse durations. As to Q2, the average motor thresholds ranged from 346 (SD, 112) mA at 50 us to 56 (22) mA at 2000 us across all muscles. The corresponding rheobase and chronaxie were 45 (3) mA and 374 (45) us across muscles with no difference between the four bilaterally recorded muscles or proximal and distal muscles. In conclusion, a wide range of TSS pulse durations can depolarize posterior roots to evoke short-latency reflexes in the lower limb muscles. Chronaxie, an indicator of the most energy-efficient pulse for TSS, is about 2.5 times shorter than the commonly used 1000 us pulse, suggesting that shorter TSS pulses can successfully depolarize posterior roots of the lumbosacral cord which falls in the range of currently available stimulator devices used in clinical practice.

Disclosures: E.A. Gordineer: None. **D.S. Stokic:** None. **M.J. Krenn:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.06

Topic: E.06. Posture and Gait

Support: Wings for Life - Spinal Cord Research Foundation (WFL-US-07/19:199)
The Yerger NeuroRobotics Research Fund, Jackson, MS
Wilson Research Foundation, Jackson, MS

Title: Capacity of the spinal network for neuromodulation during robot-guided stepping in humans with SCI

Authors: *M. KRENN[1,3,4], E. A. GORDINEER[2,1], D. S. STOKIC[3], K. E. TANSEY[3,1,5]; [1]Dept. of Neurosurg., [2]Grad. Program in Neurosci., Univ. of Mississippi Med. Ctr., Jackson, MS; [3]Ctr. for Neurosci. and Neurolog. Recovery, Methodist Rehabil. Ctr., Jackson, MS; [4]Dept. of Neurosurg., Massachusetts Gen. Hosp., Boston, MA; [5]Spinal Cord Injury Med. and Res. Services, VA Med. Ctr., Jackson, MS

Abstract: The lumbosacral network has become a target for neuromodulation interventions to augment stepping or reduce spasticity after spinal cord injury (SCI) in humans. Recent studies presented evidence that transcutaneous spinal stimulation (TSS) can modify the spinal motor output. Despite reported heterogeneity of outcomes, however, commonalities among individual responses to neuromodulation have not been addressed, which was the objective of this investigation.Nine chronic motor-incomplete SCI individuals were studied during robot-guided stepping without and with TSS applied at random frequencies (1-100 Hz) at constant sub-motor threshold intensity and body-weight support. The hip and knee robotic torques needed to maintain the pre-defined stepping trajectory and EMG in eight bilateral leg muscles were recorded and analyzed between TSS and no TSS conditions.
Overall, we found heterogeneous changes in robotic torques during TSS across individuals. However, agglomerative clustering of robotic torques identified four distinct groups. On one end of the spectrum, robotic torques monotonically increased with increasing stimulation frequencies, which coincided with a decrease in EMG, mainly due to the reduction of clonus in the lower leg muscles. On the other end, we found an inverted u-shape change in torque over the mid-frequency range along with an increase in EMG, reflecting the augmentation of gait-related physiological or pathophysiological output.
We conclude that TSS during robot-guided stepping reveals distinct groups of motor profiles in individuals with chronic motor-incomplete SCI. This suggests the need for better neurophysiological characterization of SCI before applying TSS as a therapeutic intervention for improving gait. Here, we will present a framework to characterize neurophysiological profiles during stepping.

Disclosures: M. Krenn: None. **E.A. Gordineer:** None. **D.S. Stokic:** None. **K.E. Tansey:** F. Consulting Fees (e.g., advisory boards); ONWARD Medical BV (Eindhoven, Netherlands)..

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.07

Topic: E.06. Posture and Gait

Title: Vestibular-evoked frequency responses for balance control in the proximal upper limb

Authors: *P. HA, M. I. B. DEBENHAM, G. OOSTLANDER-ENNS, M. KENNEFICK, B. H. DALTON;
Univ. of British Columbia, Okanagan Campus, Kelowna, BC, Canada

Abstract: The vestibular system encodes for head motion and provides information relevant for assessment of self-motion, gaze stabilization and balance control. During an arm-supported postural task, the body remains upright through the summation of appropriate balance responses within the musculature of the upper and lower limbs. Even though the upper limbs are used to maintain standing balance during daily activities (e.g., holding a railing, cane, or crutch), limited details exist regarding the vestibular control of balance of the upper limb during arm-supported tasks. Therefore, the purpose of this study was to characterize vestibular-evoked balance responses in the triceps brachii (TB). Eight right-hand dominant participants, which included five females (22±3 years) and three males (32±11 years), were exposed to binaural, bipolar stochastic (0-25 Hz; root mean square = ~1 mA) electrical vestibular stimulation (EVS) while holding an earth-fixed handle with the right hand and vision occluded. All participants were subjected to 100-s trials of EVS with the head rotated in yaw facing over the left shoulder (nose perpendicular to the toes). The relationship between the EVS signal and the rectified, electromyography (EMG) from the TB as well as the left (LMG) and right (RMG) medial gastrocnemius were quantified using cumulant density and coherence. The EVS-EMG relationships were considered different than 0 when values exceeded 95% confidence limits. The polarity of short- and medium-latency peak amplitudes as well as peal-to-peak amplitudes (EVS-RMG EMG: 0.062±0.045, EVS-LMG EMG: 0.050±0.047, and EVS-TB EMG: 0.105±0.083)were not different between the muscles tested (p>0.05). The EMG activity of all muscles cohered to the EVS signal over the 0-25Hz bandwidth (p<0.05). However, there was greater EVS-TB coherence compared to EVS-RMG (≤15Hz) and EVS-LMG (≤17Hz) over multiple frequencies (p<0.05). As reflected by a significant EVS-EMG coherence over a 0-25Hz frequency range, vestibular-evoked balance responses in the TB span a similar operational bandwidth as the plantar flexors, during arm-supported balance. Thus, vestibular-driven signals controlling the upper limb should likely be considered when modeling whole-body balance control for populations requiring assistive mobility devices.

Disclosures: P. Ha: None. **M.I.B. Debenham:** None. **G. Oostlander-Enns:** None. **M. Kennefick:** None. **B.H. Dalton:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.08

Topic: E.06. Posture and Gait

Title: Normobaric hypoxia reduces Achilles tendon reflex inhibition during quiet stance

Authors: *M. DEBENHAM[1], C. D. BRUCE[1], C. J. MCNEIL[2], B. H. DALTON[3];
[1]Univ. of British Columbia, Okanagan campus, Kelowna, BC, Canada; [2]The Univ. of British Columbia, Kelowna, BC, Canada; [3]UBC Sch. of Hlth. and Exercise Sci., Univ. of British Columbia, Kelowna, BC, Canada

Abstract: Normobaric hypoxia reduces Achilles tendon reflex inhibition during quiet stance
AuthorsM. I. B. DEBENHAM[1], C. D. BRUCE, C. J. MCNEIL, B. H. DALTONUniv. of British Columbia Okanagan, Kelowna, Canada
DisclosuresM. I. B. Debenham: None. **C. D. Bruce:** None. **C. J. McNeil:** None. **B. H. Dalton:** None.
AbstractHypoxia impairs standing balance such that postural sway is increased compared to normoxia, but the underlying factors are unclear. Hypoxia also disrupts proprioception, which may contribute to observed increases in sway. One mechanoreceptor contributing to proprioception is the Golgi tendon organ (GTO), which is located within the musculo-tendinous junction. The GTO senses tension and sends inhibitory signals to the agonist motor neuron pool. These inhibitory signals (when assessed via musculo-tendinous stimulation, MTstim) may be important for balance control, as their amplitude changes with different postural orientations (decreases with standing vs seated or lying prone). However, it is unknown if these inhibitory reflexes are altered in hypoxia. Thus, the purpose was to determine how normobaric hypoxia influences lower limb musculo-tendinous inhibitory reflexes during quiet standing. It was hypothesized that the musculo-tendinous inhibitory reflex area would decrease during normobaric hypoxia compared to normoxia. Participants (n = 8; 6 males, 2 females) stood quietly, with their feet together, and completed three blocks of MTstim at baseline (BL; 0.21 fraction of inspired oxygen, F_IO_2), and at ~2 (H2) and ~4 (H4) hours of normobaric hypoxia (0.11 F_IO_2) in an environmental chamber. Each block consisted of two, 50 MTstim trials (random inter-stimulus interval between 1-4 s) lasting ~2-3 min. The MTstim was delivered to the left Achilles tendon at the musculo-tendinous junction and reflexes were recorded with surface electromyography from the ipsilateral medial gastrocnemius. Oxyhemoglobin saturation, measured by finger pulse oximetry, was ~22 and ~20% lower at H2 and H4 compared to BL, respectively ($p<0.05$). Similarly, the musculo-tendinous inhibitory reflex area was reduced at H2 and H4 by ~57 and ~38% compared to BL, respectively ($p<0.05$). Overall, normobaric hypoxia impaired MTstim-evoked responses, which indicates less GTO-mediated inhibition onto the left medial gastrocnemius. The reduced inhibition is likely a factor in the increased sway previously reported with acute exposure to hypoxia.

Disclosures: M. Debenham: None. **C.D. Bruce:** None. **C.J. McNeil:** None. **B.H. Dalton:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.09

Topic: E.06. Posture and Gait

Support: NSERC

Title: Sport-related concussion and the effects on reactive balance control following upper limb perturbations under varying attentional demands

Authors: *M. TROTMAN[1], J. DIERIJCK[1], J. SMIRL[2], M. KENNEFICK[1], P. VAN DONKELAAR[1], B. H. DALTON[1];
[1]Univ. of British Columbia, Kelowna, BC, Canada; [2]Univ. of Calgary, Calgary, AB, Canada

Abstract: Sport-related concussions can influence an athlete's performance as well as everyday function. Acute concussion negatively influences postural control, but most findings focus on quiet standing balance. While studies of quiet standing balance are informative, they do not challenge the postural control system and may not reflect the postural demands of contact sports. To simulate the movements and perturbations one may experience during a game more closely, we implemented the use of an endpoint KINARM robot with the capabilities of applying forces to the hand. Thus, exploiting a paradigm whereby voluntary reaching can be integrated with reactive balance control. The purpose here was to explore how a previous history of concussion influences reactive balance control following external arm perturbations while standing under varying attentional demands. Male athletes with either no concussions (n=16; age: 19.3 ± 1.6 years) or two or more concussions (n=16; age: 19.5 ± 1.8 years) were recruited. Participants used their dominant hand to generate reaching movements to visual targets, during which the movements could receive randomized force perturbations. The reaching movements were performed either on their own or in conjunction with a secondary simple reaction time button press task with the non-dominant hand in response to an auditory cue. Responses were assessed by measuring centre of pressure (COP), hand movement reaction time and kinematics, and secondary task reaction time. Data were analyzed using a 2 (concussion history) × 2 (single vs dual task) × 2 (perturbation condition) mixed model analysis of variance. Overall, reactive balance, reaching responses, and secondary task reaction time were worse during the dual task conditions compared to single task. In the anteroposterior direction, larger peak COP displacements and velocities were found in participants with a history of concussion (1.3±0.5cm and 9.5±3.2cm/s, respectively) compared to those with no previous concussions (1.0±0.5cm and 6.7±3.1cm/s, respectively) ($p<0.03$). Larger peak mediolateral COP displacements and velocities were also found in those with a history of concussion (2.2±0.6cm and 21.2±7.3cm/s, respectively) than those with no concussions (1.7±0.9cm and 14.9±7.3cm/s, respectively) ($p<0.02$). There were minimal differences in hand kinematics between groups, with only a slower reaching reaction time in the concussion history group (347.1±29.4ms) than no concussion group (331.3±23.5ms) ($p=0.03$). Thus, a history of concussion negatively alters reactive balance control, and a disruption in the ability to properly allocate attentional resources may underlie these effects.

Disclosures: M. Trotman: None. **J. Dierijck:** None. **J. Smirl:** None. **M. Kennefick:** None. **P. van Donkelaar:** None. **B.H. Dalton:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.10

Topic: E.06. Posture and Gait

Support: NSERC grant 2017-06632
CFI grant 30979

Title: Vestibular control of balance is down regulated prior to a discrete upper limb reaching task

Authors: *Q. MALONE[1], C. J. DAKIN[3], M. KENNEFICK[4], P. VAN DONKELAAR[2], C. J. MCNEIL[4], B. H. DALTON[5];
[2]Univ. of British Colombia: Okanagan, [1]Univ. of British Colombia, Kelowna, BC, Canada; [3]Dept. of Kinesiology and Hlth. Sci., Utah State Univ., Logan, UT; [5]UBC Sch. of Hlth. and Exercise Sci., [4]Univ. of British Columbia, Kelowna, BC, Canada

Abstract: Optimal feedback control (OFC) theory posits that task-irrelevant sensory feedback is down regulated to allow for more relevant feedback sources to inform movements. Previous work using electrical vestibular stimulation (EVS) has demonstrated that vestibular-driven postural activity is suppressed during the transition from quiet standing to walking, potentially lending evidence to OFC. However, it is unclear if a task less relevant to balance control, such as an upper limb reaching task, would elicit similar results. Thus, the goal of this study was to determine if vestibular control of balance is down regulated during the transition from quiet standing to the execution of a discrete upper limb reaching task. Eight participants stood with their feet together, parallel, and without shoes, facing forward on a force plate, which measured whole-body ground reaction forces (GRFs). The participants held a manipulandum with their right hand while the elbow was flexed to 90° and their left arm relaxed at their side. Participants started each trial with the manipulandum positioned over a red circle (1cm radius) that marked the home position. After a short, random foreperiod (1000-3000ms), the circle turned green and participants responded by moving the manipulandum in the sagittal and transverse planes to a series of white, 0.5cm target circles, which turned green when reached. Each participant completed a total of 270 trials. Before and during movements, stochastic (0-25Hz, ~1mA root mean squared), binaural, and bipolar EVS was applied. Coherence between the applied EVS signal and the measured mediolateral GRF was calculated for each participant. Paired Student's t-tests were then used to assess if mean coherence between 0-25Hz for 1000ms to 600ms before movement onset was significantly different than mean coherence between 200ms before movement onset and 200ms after movement onset. Coherence from 1000ms to 600ms before movement onset (*M*: 0.017, *SD*: 0.008) was significantly greater than coherence from 200ms before movement onset to 200ms after movement onset (*M*: 0.003, *SD*: 0.002) (t_7=5.78, $p<0.001$). Therefore, similar to findings concerning the transition from quiet standing to walking, vestibular contributions to standing balance control appear to be down regulated prior to reaching with an upper limb.

Disclosures: Q. Malone: None. **C.J. Dakin:** None. **M. Kennefick:** None. **P. van Donkelaar:** None. **C.J. McNeil:** None. **B.H. Dalton:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.11

Topic: E.06. Posture and Gait

Support: Natural Sciences and Engineering Council of Canada
The Stober Foundation Health Fund

Title: Flexibility of vestibulomyogenic reflexes: modified time and frequency characteristics to maintain balance while standing with lower limbs crossed

Authors: *P. V. COPELAND, P. HA, M. I. B. DEBENHAM, C. J. MCNEIL, B. H. DALTON; Univ. of British Columbia, Okanagan Campus, Kelowna, BC, Canada

Abstract: While standing, the central nervous system (CNS) must integrate vestibular cues of head motion with other sensorimotor signals to elicit appropriate muscle responses to maintain upright posture. These vestibular cues are contextualized based on head-on-feet posture, as well as the consequence of a muscle's action. Yet, it is unknown if the CNS can transform vestibular-driven signals into appropriate balance responses when a perturbation is directed mediolaterally and the consequence of a muscle's action is reversed (i.e., feet crossed). The aim of this study was to explore how crossing the feet alters vestibular-evoked balance responses in the lower limb. Eight, healthy participants (30±8 years; four females) completed six, 90-s trials of stochastic electrical vestibular stimulation (EVS; 0-25 Hz, ±4 mA) while standing on a force plate and facing forward. Electromyography (EMG) was sampled from the left (LMG) and right medial gastrocnemius (RMG) in three foot positions (feet together, left-crossed-over-right, and right-crossed-over-left). Vestibular-evoked responses were created using the known EVS input and EMG and mediolateral force outputs to investigate muscle and whole-body responses, respectively. The responses were characterized using cumulant density and coherence estimates. With feet crossed, the polarity of the vestibular-evoked balance response was inverted for both medial gastrocnemii ($p \leq 0.01$), whereas the polarity of the whole-body vestibular-evoked balance response was similar across foot positions. In the context of feet crossed, the medial gastrocnemius medium-latency peak amplitude timing was not different than feet together when crossed in front ($p=0.08$ and $p=0.20$). However, the medial gastrocnemius positioned in the back exhibited a slowed medium-latency peak amplitude by ~60 and 45 ms to 174 and 161 ms ($p<0.001$) for LMG and RMG, respectively. The front leg displayed lower EVS-EMG coherence than feet together over most of the 0-25 Hz operational bandwidth for both gastrocnemii. For the back leg, coherence was reduced at ~2-4 and 4 Hz but increased at some frequencies between ~6-20 and 8-20 Hz for LMG and RMG, respectively, compared to feet together. No time or frequency differences were detected for whole-body vestibular-evoked balance responses between foot positions. When a vestibular perturbation is directed mediolaterally, the CNS adapts to provide appropriate postural adjustments in line with the functional consequence of the muscle's action to maintain balance.

Disclosures: **P.V. Copeland:** None. **P. Ha:** None. **M.I.B. Debenham:** None. **C.J. McNeil:** None. **B.H. Dalton:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.12

Topic: E.06. Posture and Gait

Support: NIH Grant RO1NS115487

Title: Kinematic and neuromuscular responses of the neck and trunk during imitative horseback riding movements in children with cerebral palsy

Authors: *S. YAN[1,2], S. PARK[1,2], R. KEEFER[1], W. DEE[1], A.-M. ROJAS[1,2], W. Z. RYMER[1,2], M. WU[1,2,3];
[1]Northwestern Univ., Shirley Ryan AbilityLab, Chicago, IL; [2]Northwestern Univ., Dept. of Physical Med. and Rehabil., Chicago, IL; [3]Univ. of Illinois at Chicago, Dept. of Biomed. Engin., Chicago, IL

Abstract: Postural control is one of the factors restricting physical activities of children with cerebral palsy (CP). Hippotherapy has been used for improving postural control, gait speed, and gross motor function in children with CP. However, it is unclear whether different intensities/speeds of horseback riding movement would cause different postural responses in children with CP. Also, the optimal intensity/speed of horseback riding movement remains unclear. The purpose of this study was to examine kinematic and neuromuscular responses of the neck and trunk during sitting with different perturbation intensities and frequencies in children with CP. We hypothesized that horseback riding movements with greater intensity and lower frequency would result in greater trunk movements and muscle activities. In this study, a robotic toy horse was pulled forward and backward (anterior-posterior, AP) with external perturbation force repeatedly, which mimicked horseback riding movements. Twelve children with CP (age = 7.3 ± 2.8 years) who sat on the toy horse and kept an upright position completed two sessions. In session 1, four perturbation intensity levels (10%, 15%, 20%, and 25% of body weight (BW)) with a frequency of 1Hz were applied to the horse. Subjects exhibited the greatest pelvic range of motion (ROM) in the AP direction, the greatest sagittal ROM of neck, trunk, and pelvic angle, and the greatest muscle activities of the trunk flexor, neck flexor and extensor when perturbation intensities of 20% and 25% were applied ($p < 0.05$, $N = 12$). In session 2, six perturbation frequency levels (0.5Hz, 1Hz, 1.5Hz, 2Hz, 2.5Hz, and 3Hz) with the same perturbation intensity (20%) were applied. Subjects showed the greatest pelvis ROM in the AP direction and the greatest sagittal ROM of the neck, trunk, and pelvic angle when perturbation frequencies of 0.5Hz, 1Hz, and 1.5Hz were applied ($p < 0.05$, $N = 12$). Muscle activities of the trunk extensor differed among frequency levels ($p = 0.02$, $N = 7$). In conclusion, effects of horseback riding movements on postural responses may be intensity and frequency dependent. The medium to

high force intensity and low force frequency can be applied in future hippotherapy interventions in children with cerebral palsy.

Disclosures: S. Yan: None. **S. Park:** None. **R. Keefer:** None. **W. Dee:** None. **A. Rojas:** None. **W.Z. Rymer:** None. **M. Wu:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.13

Topic: E.06. Posture and Gait

Support: NIH Grant 5R01HD083314

Title: Intermittent adaptation to pelvis perturbation during walking enhances retention and generalization of improved weight transfer in people with spinal cord injury

Authors: *S. PARK[1], S. YAN[3], W. DEE[1], R. KEEFER[1], W. Z. RYMER[2], M. WU[4]; [2]Shirley Ryan AbilityLab, [1]Shirley Ryan AbilityLab, Chicago, IL; [3]Home, Northwestern Univ., Evanston, IL; [4]Shirley Ryan Abilitylab- Chicago, Shirley Ryan Abilitylab- Chicago, Chicago, IL

Abstract: Many individuals with spinal cord injury (SCI) walk with restrained mediolateral weight transfer due to the impaired ability to maintain balance during walking. Continuous motor adaptation to external pelvis perturbation while walking was demonstrated to facilitate motor learning of improved weight transfer in people with SCI. However, the influence of intermittent adaptation to perturbation-induced new walking patterns on locomotor learning in individuals with SCI remains unknown. To address this, fifteen individuals with chronic incomplete SCI visited the lab once to complete two experimental conditions. Each condition included a) treadmill walking with either intermittent or continuous adaptation to externally perturbed walking patterns and b) overground walking before, immediately after, and 10 min after treadmill walking. During the treadmill walking, an external pulling force was applied to the pelvis toward the lateral side during the early-to-mid stance phase of the leg to perturb mediolateral weight transfer. The intermittent condition induced longer retention of improved weight transfer and enhanced muscle activation of hip abductor after the removal of pelvis perturbation load during treadmill walking ($P < 0.02$), whereas the continuous condition did not ($P = 0.50$). During overground walking, participants also showed improved weight transfer 10 min after treadmill walking for the intermittent condition ($P = 0.04$), but not for the continuous condition ($P = 0.76$). In conclusion, intermittent motor adaptation to pelvis perturbation load during walking practice may enhance preservation of improved weight transfer and generalization of motor learning in people with spinal cord injury.

Disclosures: S. Park: None. **S. Yan:** None. **W. Dee:** None. **R. Keefer:** None. **W.Z. Rymer:** None. **M. Wu:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.14

Topic: E.06. Posture and Gait

Support: CBIR19IRG033

Title: Enhance Anticipatory and Compensatory Postural Responses to Improve Balance in People with TBI

Authors: *K. K. KARUNAKARAN, O. A. IBIRONKE, K. J. NOLAN, R. PILKAR; Kessler Fndn., West Orange, NJ

Abstract: Anticipatory postural adjustments (APA) and compensatory postural adjustments (CPA) are neuromuscular responses generated to stabilize the body and achieve balance during dynamic standing. Traumatic brain injury (TBI) results in impaired functioning of the visual, vestibular, and somatosensory inputs or their integration thus affecting the body-position awareness in relation to self or the environment. The deficits in sensory function or integration can limit the ability to perceive perturbations and thus affect APA and CPA. Therefore, training the APA and CPA to perturbations may lead to improved balance function and a reduced risk of falls. The objective of the investigation was to evaluate the efficacy of Perturbation-based Training with visual cues (PBTvc) – a feedback-based balance intervention that specifically targets the execution of the APA and CPA strategies. The efficacy of the intervention is evaluated using biomechanical (Center of Pressure (COP), silver index [quantitative measure of fall risk]), and functional (Timed-up and Go (TUG), Berg Balance Scale (BBS)), Falls Efficacy Scale – Int'l (FES-I)) outcomes. Preliminary data are presented for two participants with chronic non-penetrating TBI and two age-matched healthy controls (HC). Participants with TBI were trained using PBTvc for 16 sessions (4 sessions/week for 4 weeks) using a customized interface (Neurocom Clinical Research System and Matlab). Data were collected before and after PBTvc training for the TBI and compared with HC. The results from this study demonstrated improved biomechanical (improved silver index and COP changes) and functional (improved time in TUG, improved BBS and FES-I scores) outcomes after training.

Disclosures: K.K. Karunakaran: None. **O.A. Ibironke:** None. **K.J. Nolan:** None. **R. Pilkar:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.15

Topic: E.06. Posture and Gait

Title: Corticomuscular coherence of dynamic balance during walking at three difficulty levels in healthy young adults

Authors: *A. ABUD DA SILVA COSTA[1], R. MORAES[2], L. BAKKER[3], R. DEN OTTER[4], T. HORTOBAGYI[4];
[1]Sch. of Physical Educ. and Sport of Ribeirao Preto, Univ. de São Paulo, Ribeirão Preto, Brazil; [2]Sch. of Physical Educ. and Sport of Ribeirao Preto, Univ. of Sao Paulo, Ribeirao Preto, Brazil; [3]Human Movement Sci., Univ. Med. Ctr. Groningen, Univ. of Groningen, Groningen, Netherlands; [4]Ctr. for Human Movement Sci., Univ. of Groningen Med. Ctr., Groningen, Netherlands

Abstract: Dynamic balance during walking (DBDW) relies on the coordination of several muscles controlled by specific neural circuits, which can be task difficulty-dependent. A detailed understanding of the processes involved in the central and peripheral control of DBDW would help to characterize neuromotor integrity and guide interventions to improve DBDW in aging and neurological conditions. Corticomuscular coherence (CMC) is a neurophysiological marker of the strength of the descending neural drive from the motor cortex to muscles active in DBDW. So far, CMC has been used to characterize corticospinal involvement in locomotor tasks but not in relation to DBDW difficulty. Here, we determined CMC between EEG and lower extremity muscle activity at three difficulty levels of DBDW. Healthy young adults (n=6, age: 22y) walked at a self-selected pace on the floor (Floor), a 6-cm wide tape affixed to the floor (Tape), and on a wooden beam (Beam; width: 6cm, height: 5cm; length: 13m). We recorded 32 channels of EEG and surface EMG of the Tibialis Anterior (TA), Peroneus Longus, Gastrocnemius Medial (GM), Rectus Femoris (RF), Biceps Femoris, Gluteus Medius, Adductor Magnus bilaterally. DBDW was quantified as the normalized distance traveled over the trials by the maximum possible distance (25 trials, 13m/trial=325m=1.0). CMC was determined between Cz and the 7 muscles of the right leg in a 350-ms window during stance and swing phases of gait at 8-12 (alpha), 13-30 (beta), and 31-45Hz (gamma band). In the stance phase, alpha band CMS was higher on the Floor vs Tape in TA (Floor: 0.42±0.33; Tape: 0.14±0.12) and vs Beam in RF (Floor: 0.40±0.47; Beam: 0.24±0.50) and GM (Floor: 0.41±0.37; Beam: 0.25±0.53, all $p<0.05$). In the swing phase, beta band CMC was greater on the Floor vs Beam in RF (Floor: 0.82±0.96; Beam: 0.27±0.28). DBDW performance did not correlate with CMC. These exploratory analyses revealed muscle and band-specific modulations in CMC in relation to DBDW difficulty. The poster will include results from the complete data set.

Disclosures: A. Abud da Silva Costa: None. **R. Moraes:** None. **L. Bakker:** None. **R. den Otter:** None. **T. Hortobagyi:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.16

Topic: E.06. Posture and Gait

Support: NSF DBI2015317

Title: Behavioral Investigation of the I5 Buccal Mass Muscle in Aplysia californica Feeding

Authors: *S. SUN[1,2], M. J. BENNINGTON[1], J. P. GILL[3], H. J. CHIEL[3,4,5], V. A. WEBSTER-WOOD[1,2,6];
[1]Mechanical Engin., [2]Biomed. Engin., Carnegie Mellon Univ., Pittsburgh, PA; [3]Biol., [4]Neurosciences, [5]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH; [6]McGowan Inst. for Regenerative Med., Pittsburgh, PA

Abstract: The multifunctional feeding behaviors demonstrated by the buccal mass in *Aplysia californica* are controlled by the coordinated activation and physical interactions of the buccal mass intrinsic muscles [1-4]. To properly describe and model these behaviors, it is necessary to understand the contributions of each muscle within the buccal mass. One of these muscles, I5, alternatively referred to as the accessory radular closer (ARC), was originally described as assisting in the closing of the radular halves during ingestive behaviors [1]. In reduced preparations, stimulation of I5 brought together the radular halves [1]. However, further investigation in a more intact buccal mass preparation demonstrated that the ability of the I5 to close the grasper was context-dependent [5]. Specifically, I5 stimulation resulted in a higher degree of radular closing when the radula was fully open (as it would be at peak protraction during feeding behaviors) than when it was in a resting position [5]. However, these prior investigations of I5 have been in reduced *ex vivo* preparations, and I5's contributions to *in vivo* feeding behavior have not been investigated.
To investigate the contributions of I5 to feeding behaviors, *in vivo* lesion experiments were performed in adult *Aplysia*. Experimental methods were adapted from prior investigations on the roles of I2 [6], I7, and the subradular fibers [2]. Briefly, feeding experiments were performed in *Aplysia* before and after true and sham *in vivo* bilateral lesions of I5, allowing animals to serve as their own controls. In these experiments, video recordings of bites and unloaded swallows and force recordings of swallows on unbreakable seaweed [4] were collected. Performance metrics related to these ingestive behaviors, including peak forces, swallowing velocities, and timeseries load data, were collected. Preliminary comparisons of anonymized load recordings suggest distinctions can be observed between the sham and true lesions. Using these results, previously developed nominal [3] and robotic [7] models of *Aplysia* feeding neuromechanics can be adapted to incorporate the effects of I5. *Sun and Bennington contributed equally to this work.
References:[1] Cohen, et al. J. Neurophys. Vol 41, Iss 1, 1978[2] Kehl, et al. J. Exp. Bio. Vol 222, Iss 16, 2019.[3] Webster-Wood, et al. Bio. Cyber. Vol 114, Iss 6, 2020.[4] Gill, et al. eNeuro, Vol 7, Iss 3, 2020.[5] Orekhova, et al. J. Neurophys. Vol 86, 2001.[6] Hurwitz, et al. J. Neurophys. Vol 75, Iss 4, 1996.[7] Dai, et al. *Living Machines, Under Review.* 2022.

Disclosures: S. Sun: None. **M.J. Bennington:** None. **J.P. Gill:** None. **H.J. Chiel:** None. **V.A. Webster-Wood:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.17

Topic: E.06. Posture and Gait

Support: IRCC Seed Grant, IIT Bombay

Title: Time and frequency domain characterisation of postural control associated with a predictable perturbation

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Abstract: In the face of a predictable perturbation, human nervous system uses anticipatory postural adjustments (APAs) to prepare for the upcoming impact followed by compensatory postural adjustments (CPAs) to deal with the actual impact of the perturbation. Time domain analysis of postural control associated with predictable perturbation is well documented; however, a collective time and frequency domain characterisation that may yield critical insights into the underlying neural drive (recruitment and firing pattern of motor units (MUs)) is lacking. 12 healthy adults (26 to 34 years; 6 males; written informed consent obtained) were exposed to external predictable perturbations at shoulder level while standing (3 perturbation magnitudes: 1%, 3%, and 5% of subject's body weight; randomized in order). Surface electromyographic (EMG) signals from several leg and trunk muscles and body's centre of pressure displacements (COP) were recorded. Mean COP displacement (in m) and normalized EMG integrals (both backgrounds demeaned), and median frequency (MDF, in Hz) of EMG and COP were computed for background (BGD), APA, and CPA phases of postural control. Repeated measures ANOVA followed by post-hocs were performed. A significant decrease in EMG-MDF (Tibialis anterior (TA)- BGD: 61.65±14.93, APA: 34.27±18.08, CPA: 10.9±1.21, $p<0.01$; medial gastrocnemius (GASM)- APA: 41.08±13.44, CPA: 18.45±13.53, $p<0.01$) along with a significant increase in EMG integral (TA- BGD: ~0, APA: 0.48±0.3, CPA: 0.96±0.11, $p<0.01$; GASM- APA: -0.6±0.45, CPA: 0.32±0.66; $p<0.01$) was observed over the control phases. Although a significant increase in mean COP displacement (BGD: ~0, APA: 0.01±0.007, CPA: 0.03±0.006, $p<0.01$) was seen from BGD to APA to CPA, there was no corresponding change in COP-MDF ($p>0.05$). Patterns were consistent across muscles and perturbation magnitudes. A significant scaling effect of perturbation magnitude was seen in time domain parameters ($p<0.05$) but not in frequency parameters ($p>0.05$) for both EMG and COP. The decrease in EMG-MDF with an increase in integral could be an outcome of a predominant occurrence of synchronous firing of MUs along with recruitment of new MUs and increase in firing frequency of the active MUs. At biomechanical level, these neural activation patterns resulted in greater COP displacement with no change in frequency across the phases, thereby, indicating a precise control of stability that allows optimal body displacement without excessive oscillatory movement. These findings thus provide a foundation for future investigations of altered neural drive underlying control of perturbed stance in individuals with impaired postural control.

Disclosures: R. Choudhuri: None. **N. Kanekar:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.18

Topic: E.06. Posture and Gait

Support: EPSRC Doctoral Training grant EP/L505079/1
European Research Council Grant (640012) (MCG)

Title: Moving Anchors: Ground Reaction Force Dynamics at the Substrate Interface in Drosophila melanogaster larvae

Authors: J. H. BOOTH[1,3], A. MEEK[3], N. KRONENBERG[3], M. C. GATHER[3,1], ***S. R. PULVER**[2];
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Abstract: Soft-bodied animals must interact with their substrates in order to generate the forces required for locomotion. Traditionally, measuring such forces has been difficult due to the lack of techniques with sufficient spatial, temporal and force sensitivity resolutions. By contrast, the cellular mechanobiology community has developed a suite of techniques capable of mapping substrate interactions of individual cells and resolving subcellular force patterns. Here, we adapt and apply one such technique, elastic resonator interference stress microscopy (ERISM), to record maps of the ground reaction forces produced by freely behaving *Drosophila* larvae, achieving micrometre spatial and millisecond temporal resolution. We found that these animals, though legless, use 'protopodia' - foot-like protrusions - which exert 1-8 μN for each segment upon the substrate during peristaltic crawling. Force exertion follows an intricate temporal pattern somewhat resembling the stance and swing phases found in legged animals. Measurements of force dynamics in behaving animals revealed stability promoting processes akin to anchoring and the use of a set of anatomical structures for locomotion not previously documented in these animals. We also observed previously unobserved preparatory, whole-body anchoring behaviours performed by larvae when performing bilaterally asymmetric behaviours which are inaccessible to conventional microscopy. Anatomical analysis of ventral acute muscles (VA1-3) attached to tendon cells within protopodia and ventral oblique muscles (VO4-6) attached to tendon cells within the naked cuticle revealed distinct patterns of muscle attachment that enable protopod control. Imaging of protopod associated muscle activity in semi-intact preparations confirmed that these muscles undergo cycles of contraction and relaxation during protopod movements. This work represents the first detailed study of substrate interaction in *Drosophila melanogaster*, significantly advancing our understanding of the biomechanics underlying soft-bodied locomotion. Overall, we provide a framework for further exploration of previously understudied aspects of soft-bodied biomechanics using a genetically tractable model organism.

Disclosures: **J.H. Booth:** None. **A. Meek:** None. **N. Kronenberg:** None. **M.C. Gather:** None. **S.R. Pulver:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.19

Topic: E.06. Posture and Gait

Support: ERC Starting Grant 715022 EmbodiedTech
ERC Grant 813713

Title: Assessment of Augmented Hands Synergies

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Abstract: Extra robotic fingers are gaining interest as an augmentation technology. Successful functional integration of an extra robotic finger will critically depends on our ability to assess its interactions with the hand. In a previous study, changes in biological hand synergies during use of the robotic Third Thumb (TT, Dani Clode Design) were assessed with a data glove. But this approach doesn't account for the TT and can further encumber hand-use . An alternative for pose estimation are regression models based on deep convolutional neural network, which proved to be extremely effective in tracking body landmarks from video recordings. Here, we combine solutions from Google Mediapipe (GMP), DeepLabCut (DLC) and Anipose (AP) to track the 3D poses and joint angles of a TT-augmented hand (TT-aH). To track TT-aH kinematic, videos from 3 cameras were recorded and aligned. We trained the TT tracking network on 6 landmarks using DLC; a total of 1050 frames from 6 subjects performing ecological manipulation in two environments were used. Network errors were evaluated at 2.15/4.87px on the training/test sets (0.6 cutoff threshold). New videos were analyzed with this trained network directly within AP, which has built-in support for DLC and allows filtering of the 2D landmarks. To overcome the need to train the network for biological hand poses, the 21 hand landmarks were estimated using the GMP hands solution API. We formatted the GMP output to match the other syntax and file formats and imported the output to AP for filtering. Upon calibration of the cameras' parameters, the filtered TT and hand 2D landmarks were triangulated to estimate 3D coordinates with AP. We are now applying this pipeline to assess TT-aH kinematics in 2 groups of participants (n=50 in total) before and after a week of training to either use the TT or play the piano. Both paradigms are expected to produce altered hand synergies. We hypothesised that differences in TT-aH synergies will be reflected in the sensorimotor representation of the TT-aH. For this, we

use fMRI to assess the similarity across activation patterns for the biological fingers and the TT in active tapping and passive touch. We predict training with the TT will result in higher fingers-TT representational similarity, where a stronger finger-TT synergy will lead to closer finger-TT sensorimotor representations. This work will help us understand how extra robotic body parts are incorporated into the motor synergies and representations of the biological body.

Disclosures: G. Dominijanni: None. **L. Dowdall:** None. **M. Molina:** None. **D. Clode:** None. **S. Shokur:** None. **S. Micera:** None. **T.R. Makin:** None.

Poster

722. Posture and Gait: Kinematics, Biomechanics, Exercise, and Fatigue II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 722.20

Topic: E.06. Posture and Gait

Title: Recurring patterns of postural control in Biathletes in balance control while shooting

Authors: *K. J. SLOMKA[1], J. MICHALSKA[2], R. ZAJąC[2], D. GERASIMUK[2], G. JURAS[3]; [1]AWF Katowice, [2]AWF Katowice, Katowice, Poland; [3]The Jerzy Kukuczka Acad. of Physical Educ., Katowice, Poland

Abstract: Balance can be a key success factor in many disciplines, and biathlon is a good example. A more stable posture can be a key factor in shooting outcomes. The center of foot pressure (COP) is commonly recorded when evaluating postural control. Because COP measurements are very inconsistent and non-stationary, non-linear deterministic methods, such as entropy, are more appropriate for COP displacement analysis. The objective of our study was to determine whether the longitudinal effects of biathlon training can induce specific changes in postural control. National level biathletes, 15 non-athletes who prior to the experiment took part in 3 months of shooting training, and 15 non-athletes with no prior rifle shooting experience took part in our study. The data were obtained with a force plate. Participants performed three balance tasks in quiet standing, the shooting position (internal focus participants concentrated on maintaining the correct body position and rifle), and aiming at the target (external focus participants concentrated on keeping the laser beam centered on the targets). Biathletes obtained significantly lower values of sample entropy compared to the other groups during the shooting and aiming at the target trials ($p<0.05$). External and internal focuses influenced the process of postural control among participants who had prior rifle shooting experience and the control group; they obtained significantly higher values of sample entropy while shooting and aiming at the target compared to the quiet standing trial ($p<0.05$). The biathletes obtained significantly lower values of sample entropy in the aiming at the target position compared to the quiet standing trial. Specific balance training is combined with the ability to manage a more difficult, non-specific task. The biathletes seemed to employ a different motor control strategy than the beginners and control group, creating repeating patterns (more regular signal for COP) to keep one's balance during the shooting and aiming at the target positions.

Disclosures: **K.J. Slomka:** None. **J. Michalska:** None. **R. Zając:** None. **D. Gerasimuk:** None. **G. Juras:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.01

Topic: F.01. Neuroethology

Support: JSPS KAKENHI grant number 16H06544
JSPS KAKENHI grant number 21H05295
JSPS KAKENHI grant number 21K06259

Title: Spatial resolution of active mechano-sensing by cricket antennal system

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Abstract: Insects use their antennal mechanosensory system to perceive surrounding space and to guide their locomotion. Nocturnal insects such as crickets actively and repetitively contact their antennae with objects in the near-head space to precisely localize them. The crickets exhibit escape behavior in response to air-puff stimulus detected as an approaching predator signal by the cerci, which is abdominal mechanosensory organ different from the antennae. Recently, we reported that the crickets modulate the wind-elicited escape behavior while they detect obstacles such as 'wall' by the antennal system (Ifere et al., 2022). This result revealed a general use of antennal mechanosensory information for behaviors elicited by various sensory inputs, suggesting 'spatial awareness' of crickets mediated by the active mechano-sensing. However, it remains unknown how accurately the crickets assess the object scale and location using their antenna. For successful escape in the field, perception of the size and location of the obstacles relative to their body would be important for animals to determine the travel path or escape to shelter. To explore the spatial resolution of the antennal system, we placed a wall with opening gap of different width in front of the cricket so that it could be detected by the antennae, and examined the modulation of their escape response to the air puff from rear. When the wall with no opening gap was placed, the stimulated crickets moved to either side to avoid collision of the wall, whereas the crickets escaped more straight-forward as the gap width increased. When the gap width was smaller than 12 mm, the walking direction variance significantly increased compared to the no-wall condition. Considering the width of cricket's body (6.95 ± 0.07 mm), the crickets possibly assessed whether the travel route was wide enough for their body size to pass through by using antennal system. In addition, the larger gap width, the shorter the reaction time and the longer the walking distance. This indicated that the cricket likely delayed the escape start and suppress the escape movement depending on the width of the expected escape route.

Next, we placed a rounded wall with an opening gap that was located in different orientations at the same distance to the crickets' head and examined the impacts of the wall on the wind-elicited escape behavior. Depending on the location of the gap, they altered the walking direction. Taken together, by using the antennal system, crickets were likely able to perceive the width and location of the escape route sufficient to accommodate the body size to avoid collision.

Disclosures: **N.O. Ifere:** None. **H. Shidara:** None. **N. Sato:** None. **H. Ogawa:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.02

Topic: F.01. Neuroethology

Support: JSPS KAKENHI grant number 16H06544
JSPS KAKENHI grant number 21H05295
JSPS KAKENHI grant number 21K06259

Title: Firing response and morphology of wind-sensitive interneurons in the cricket brain

Authors: *H. CHIDA[1], H. SHIDARA[2,3], H. OGAWA[2];
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Abstract: Animals compute the location of a stimulus source from sensory inputs and exhibit a goal-oriented behavior based on that spatial information. However, the neural circuits linking between the sensory and motor pathways that control the oriented movements is still unclear. To explore the whole picture of sensory-motor association in the goal-oriented behavior, we used the wind-elicited escape behavior of crickets. Crickets detect surrounding airflow via a pair of cercal organs, which is the abdominal mechanosensory system. The sensory information such as direction and speed of airflow are processed within the terminal abdominal ganglion and conveyed to the brain by several ascending projection neurons such as giant interneurons (GIs). Then, descending signals from the brain to the thoracic ganglia are necessary for the directional control in the escape behavior. These facts suggest that the neural circuits in the brain process the directional information of airflow and decide to orient the escape movement. To explore the brain neural circuit underlying the oriented escape behavior, we examined the firing responses of the brain interneurons to airflow stimuli by using an intracellular recording. Based on morphology of the recorded cells, the wind-sensitive interneurons were classified into three types, ascending neurons (AsNs, n=25), local interneurons (LINs, n=36), and descending neurons (DsNs, n=26). Most of AsNs showed excitatory responses with transient spike bursts, whereas LINs and DsNs had large variation in their responses including lasting of the evoked spikes and suppression of spontaneous firing. Bilateral LINs, which had a neurite across the midline of the brain, especially showed biphasic response with a short spike burst followed by

suppression. The LINs had longer latency of response to airflow than AsNs. The latency of excitatory response in unilateral LINs, of which neurites were contained within hemisphere of the brain, was shorter than that in bilateral LINs. These suggest that the airflow information would firstly be provided by GIs into the unilateral LINs in the brain. The AsNs showed directional preference for the side ipsilateral to their axon. The LINs was weak preference for the posterior of cricket. DsNs varied in both preferred direction and sharpness of the selectivity. These differences in the directional selectivity among cell types of wind-sensitive interneurons suggested that they are responsible for different processes of sensory-motor association. Further exploration of the wind-sensitive brain neurons in behaving animals could reveal the neural circuits for sensory-motor association to direct the escape behavior.

Disclosures: H. Chida: None. **H. Shidara:** None. **H. Ogawa:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.03

Topic: F.01. Neuroethology

Support: NIH Grant 1R01NS121220

Title: An instance of one behavior driving the next: A multi-component chain mechanism for behavioral sequencing in Tritonia.

Authors: *E. S. HILL[1], I. R. POPESCU[2], J. WANG[2], W. N. FROST[1];
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Abstract: The neural mechanisms by which ordered behavioral sequences are generated are poorly understood. Two widely considered schemes for this are chain sequencing and parallel-activation. While chain sequencing is appealing in its simplicity, to our knowledge just one study, in birdsong, has provided evidence supporting this type of scheme. Here we contribute a second example - that controlling the marine mollusk *Tritonia diomedea's* swim/crawl escape behavioral sequence. *Tritonia* responds to suitably aversive stimuli with a rhythmic escape swim followed by many minutes of elevated crawling. Here we describe a chain scheme for this sequence, mediated by a suite of interacting cellular mechanisms operating during the swim that also provide the drive for post-swim crawling. First, in semi-intact preparations, spike trains in either the C2 or DSI neurons of the swim CPG produce delayed-onset activation of the foot cilia that mediate crawling. Second, the DSIs modulate one another to produce the elevated post-swim DSI tonic firing that drives crawling. Third, we identify a long-postulated inhibitory cell that under resting conditions mediates polysynaptic reciprocal inhibition between the DSIs. During the swim, C2 inhibits this I-neuron, enabling the DSIs to fire in unhindered fashion to both generate the swim and induce the self-modulation that renders them tonically active after the

swim to drive crawling. Fourth, modulation of C2 by the DSIs induces strong positive feedback from the CPG to the swim command neuron that drives the DSIs, promoting their contribution to both swimming and crawling.
Conceptual contributions of the present study are: 1) the demonstration of only the second example of a chain sequencing scheme, and 2) the delineation of a complex suite of mutually-reinforcing mechanisms that promote self-modulation of neurons in the circuit for the first motor program so that they continue firing for several minutes afterward to drive the next motor program.

Disclosures: E.S. Hill: None. **I.R. Popescu:** None. **J. Wang:** None. **W.N. Frost:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.04

Topic: F.01. Neuroethology

Support: NSF IOS 1845673

Title: The α1,3-fucosyltransferase encoded by the FucTA gene regulates the larval pain response in Drosophila

Authors: *L. ZAVALA[1], L. HOLT[2], E. STANT[2], A. ARTHUR[3], S. L. BALLARD[2,3], T. R. SHIRANGI[1];
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Abstract: When a *Drosophila melanogaster* larva is probed with a noxious stimulus, it rolls its body in a corkscrew-like motion as a means to escape the stimulus. In a genetic screen, we uncovered a mutation in *Drosophila* called S89 that causes an abnormal pain response to larvae to exhibit an abnormal reaction when poked with a heated soldering iron. Chromosomal deficiency screening revealed that the *S89* mutation maps onto a gene on the third chromosome called *FucTA*, which encodes an *α1,3-fucosyltransferase* that adds fucosyl sugars onto target proteins. Neural silencing and RNAi-based experiments have mapped FucTA function in regulating pain to a small subset of neurons in the larval central nervous system. Our studies on *FucTA* provide new insights into the genetics and neurobiology underlying pain perception in *Drosophila* larvae, which may have broad implications for pain biology and management in humans.

Disclosures: L. Zavala: None. **L. Holt:** None. **E. Stant:** None. **A. Arthur:** None. **S.L. Ballard:** None. **T.R. Shirangi:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.05

Topic: F.01. Neuroethology

Support: NICHD Division of Intramural Research

Title: Gaba signaling coordinates escape circuit activity in zebrafish

Authors: R. DOCTOR[1], *H. A. BURGESS[2];
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Abstract: Zebrafish perform different modes of escape response to auditory cues prompted by differing perceived stimulus threat levels. Short latency c-start (SLC) responses to acute threats are mediated by Mauthner cells, whereas long latency c-start (LLC) responses to less threatening attacks are mediated by a cluster of prepontine neurons. How activity in these pre-motor neurons is coordinated to ensure a single behavioral response is not understood. Previous work indicated that ethanol exposure suppresses LLCs but does not affect SLCs. We hypothesized that this is because there are GABAergic interneurons in the escape circuit that inhibit LLC production. One possibility is that these GABAergic neurons operate to suppress LLCs once an SLC has been initiated. Consistent with this, gaboxadol (GABAA receptor agonist) reduced LLC responses, whereas bicuculline (GABAA receptor antagonist) application resulted in a selective increase in LLCs. Additionally, we inhibited GABAergic transmission to the prepontine neurons required for LLC production by expressing an intracellular loop (ICL) of the γ-2 subunit of GABAA receptors in y293-Gal4, UAS:ICL transgenic fish. In previous studies, ICL expression prevented anchoring of GABA subunits to the postsynaptic density. Similar to the effect of bicuculline, expression of the ICL in prepontine neurons resulted in an increase in LLC responses. We also examined the function of these neurons using high-speed video analysis of escape responses. Video analysis showed that bicuculline-exposed fish failed to acutely suppress LLCs after initiating an SLC, significantly more frequently than in controls. These results demonstrate that GABAergic signaling downstream of Mauthner cell firing promotes execution of an optimal escape by blocking LLCs from interfering with ongoing SLCs.

Disclosures: R. Doctor: None. **H.A. Burgess:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.06

Topic: F.01. Neuroethology

Support: NIH R01NS110866

Title: A pair of command-like neurons elicits thoracic grooming in Drosophila

Authors: *S. YOSHIKAWA[1], P. TANG[1], G. NOVACK[1], J. S. PHELPS[2], B. MARK[3], J. C. TUTHILL[3], W.-C. A. LEE[4], J. H. SIMPSON[1];
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Abstract: Mechanosensation is a critical way for animals to receive information about their environment and it can trigger behaviors from escape to grooming. When flies groom in response to mechanosensory cues, anterior body parts (eyes, antenna, proboscis) are cleaned by the forelimbs while posterior parts (abdomen, wings) are cleaned by the hindlimbs. The notum or thorax is an exception: it can be cleaned by either forelimbs or hindlimbs depending on which of the mechanosensory bristles are stimulated (Vandervorst & Ghysen, 1980).
We identified a pair of command-like neurons that we named Mago-no-te (MGT: meaning "back-scratcher" in Japanese), whose optogenetic activation elicits thoracic grooming by the hindlimbs in both undusted and dusted flies. MGT are cholinergic interneurons with two distinct branches. The ventral medial branch contains post-synaptic sites between the T1 and T2 neuromeres, (the region of the ventral nerve cord that receives sensory information from the thorax), while the dorsal lateral branch contains a majority of the pre-synaptic sites, mostly concentrated in the T3 neuromere, close to the dendrites of the motor neurons innervating the hindlimb. This sensory-to-motor circuit connectivity is supported by fluorescent microscopy (GRASP analysis) and electron microscopy connectome reconstruction. MGT receive direct synaptic inputs from some of the thirteen pairs of macrochaete bristle mechanosensory neurons on the notum, notably the posterior ones that trigger hindlimb scratch reflexes. While there were fewer direct mechanosensory connections than expected, connectomic analysis revealed many indirect ones, converging through a network of interneurons whose functions can now be investigated by genetic targeting reagents. In addition, MGT receives pre-synaptic connections from more than 15 additional neuron types, and make post-synaptic outputs that include direct and indirect pre-motor connections. The circuit around MGT may explain how sensory stimuli recruit specific limbs to perform thoracic grooming, or why it is normally last in the hierarchy of grooming movements.

Disclosures: S. Yoshikawa: None. **P. Tang:** None. **G. Novack:** None. **J.S. Phelps:** None. **B. Mark:** None. **J.C. Tuthill:** None. **W.A. Lee:** None. **J.H. Simpson:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.07

Topic: F.01. Neuroethology

Support: NSF 1926793

Title: Central Nervous System Control and Serotonergic Modulation of Hindgut Motility in Crayfish

Authors: *N. PEÑA-FLORES[1], S. PATHAK[2], W. LOSERT[2], J. HERBERHOLZ[1,3];
[1]Neurosci. and Cognitive Sci. Program, [2]Physics, [3]Psychology, Univ. of Maryland, College Park, MD

Abstract: The gut-brain axis (GBA) is a bidirectional neural pathway recently identified as a key modulator of physical and mental health. However, the neuroanatomical complexity and reduced accessibility of current mammalian models has limited the identification of the cellular-molecular mechanisms that regulate it. Invertebrate animal models provide a promising alternative since the basic anatomy, neurochemistry, and physiology of the GBA is highly conserved across evolution. Crayfish offer a reduced GBA consisting of a single nerve (N7) connecting the Central Nervous System (CNS) to the posterior part of their digestive system, the hindgut. Like mammalian models, this system carries bidirectional neural signals and exhibits wave-like propagation of gut muscle contractions modulated by serotonin. Recently, our lab developed a crayfish *ex vivo* preparation to study GBA components related to gut motility. Using neuropharmacology combined with optical flow analysis, a machine vision technique, we studied the effects of N7 denervation and exogenous 5-HT on hindgut motion in 30 *ex vivo* preparations (all male). Measuring changes in hindgut motion using 90 min video recordings, we compared saline bath perfusion (control), N7 denervation after 30 min of baseline, and application of 3 different 5-HT concentrations (1, 10 or 100μM) after N7 denervation. Our results show that overall gut motility was stable throughout 90 mins of control conditions whereas eliminating CNS innervation significantly reduced hindgut wave power and temporal regularity but did not significantly affect frequency or wave direction preference. This suggests partial CNS control over hindgut motility and a parallel, intrinsic mechanism that is independent of CNS innervation. Application of 5-HT significantly changed hindgut wave power and temporal regularity across all concentrations, but did not restore these parameters to normal baseline levels. This indicates that exogenously applied 5-HT is able to broadly modulate several features of hindgut motion while finely-tuned control requires CNS inputs. We also used electrophysiology to measure the effects of CNS activity on gut behavior and found that high frequency electrical stimulation of the anterior part of the abdominal nerve cord evoked discrete neuronal activity in N7 and corresponding changes in gut motility. This will allow us to further investigate CNS regulation, including serotonergic contributions, of hindgut motor patterns. By providing a multiscale analysis framework to study GBA dynamics, our work aims to lay the groundwork for the real-time study of the cellular-molecular mechanisms governing the GBA in a crayfish model.

Disclosures: N. Peña-Flores: None. **S. Pathak:** None. **W. Losert:** None. **J. Herberholz:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.08

Topic: F.01. Neuroethology

Support: NSF CRCNS 2113028
NSF 2015317

Title: What makes walking behavior 'naturalistic'? Feedback signaling the rate of change of force (dF/dt) in serially homologous legs of insects

Authors: *S. N. ZILL[1], C. J. DALLMANN[2], S. S. CHAUDHRY[1], N. S. SZCZECINSKI[3];
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Abstract: Animal behaviors can be remarkably fluid and graceful. We have studied how signals from sense organs that monitor forces contribute to feedback control of walking in insects. Sensory activities of receptors that encode forces via strains in the exoskeleton (tibial campaniform sensilla, CS Groups 6A and 6B) were recorded extracellularly. Forces were applied to the front legs of stick insects using conventional and 'naturalistic' waveforms (joint torques calculated from experiments in freely walking animals, including steps with variance from the mean). These studies have shown that discharges of front leg 6B sensilla 1) most closely follow increases in the rate of change of force (dF/dt) rather than the force magnitude and 2) show substantial hysteresis to transient force decrements. Firing of 6A sensilla, which can signal large force decreases in middle and hind legs, was longer in duration during front leg stepping, in part due to the smaller forces generated by front legs. Discharges of receptors in front legs, therefore, form a continuum monitoring force variations in walking, and potentially in other behaviors such as tactile exploration. We are currently also characterizing the sensitivities of front leg CS by using waveforms that increase gradually (exponentially) to a level and include transient perturbations: studies to date have confirmed the sensitivities of tibial sensilla to transient force increments and decrements in dF/dt. We have also used these data in tests of a mathematical model of the receptors and replicated the findings for front leg receptors. The model results support the notion that the recorded discharge patterns result from the comparison between one fast- and one slowly-responding component in the system. Dynamic properties such as discharge adaptation in response to constant force and responses to decreasing forces emerge from this single mechanism. Overall, our biological data and modeling studies show that tibial campaniform sensilla in all legs monitor the rate of change of force (dF/dt) and support the idea that these signals can be used to adjust muscle contractions to aid in generating the smooth accelerations and decelerations characteristic of 'naturalistic' movements that occur in walking.

Disclosures: S.N. Zill: None. **C.J. Dallmann:** None. **S.S. Chaudhry:** None. **N.S. Szczecinski:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.09

Topic: F.01. Neuroethology

Support: Swiss National Science Foundation Eccellenza Grant (PCEFP3_187001)

Title: Linear and nonlinear computations in the Nucleus of the Optic Tract

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Abstract: Motion in the visual field can cause retinal slip, which must be compensated by the visual system. One fundamental response to retinal slip is the optokinetic reflex (OKR), an oculomotor behavior initiated during slow environmental motion or head rotation. The horizontal OKR is driven by the nucleus of the optic tract (NOT), which, in mice, receives direct input from direction selective (DS) retinal ganglion cells (RGCs) tuned to temporal motion. In the visual cortex, direction selectivity is a hierarchical computation involving both linear and nonlinear mechanisms. It is unknown whether similar rules apply to upstream stages. Here, we studied how NOT represents motion direction at the population level, by performing extracellular recordings (Neuropixels) in anesthetized mice as they were presented with white noise and moving grating visual stimulation. In 79% of our sample (n=400), Spike Triggered Average (STA) failed to identify a receptive field (RF), indicating strong nonlinear input integration. Consistently, 75% of cells were marked as nonlinear (‘phase invariant’) by a phase modulation index (MI). Of note, phase invariance and nonlinear RFs are also features of cortical complex cells. Conversely, clear RFs were found in 84 cells. RF size distribution ranged from ~2° to ~50°, suggesting that NOT cells can pool from up to 5 RGCs. RFs were mostly located at the screen midline, suggesting retinotopic representation of the horizontal meridian. Oddly, this subpopulation was also marked as nonlinear by the MI index. However, screening MI values for each grating direction revealed ‘phase locking’ (i.e. response linearity), but only for vertical directions, that is orthogonal to the preferred, horizontal direction. Interestingly, in 52% of cases, RF structure was clearly elongated and horizontally tilted. Phase locking and elongated RF structure are also features of cortical simple cells. In sum, we found that NOT cells integrate retinal inputs nonlinearly at the population level. However, a subpopulation shows an unusual combination of both linear (simple-like) and nonlinear (complex-like) profiles. Our analysis could hint at the way NOT integrates linear and nonlinear inputs to represent motion direction. For instance, inhibitory mechanisms are known to be crucial in motion processing. We aim to test, by computational modeling, if the 'simplex' cells described here provide the network with suppressive input about orthogonal motion, with the hypothesis that they integrate over both DS and non-DS (and/or inhibitory) input.

Disclosures: F.B. Rosselli: None. **M. Buettner:** None. **C. Mitelut:** None. **F. Franke:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.10

Topic: F.01. Neuroethology

Support: NIH grant R01MH118203

Title: Decoding Macaques' Natural Behavioral Repertoire from Neuronal Activity

Authors: *C. TESTARD[1], S. TREMBLAY[1], R. W. DITULLIO[2], F. PARODI[1], M. L. PLATT[1]; [2]Otorhinolaryngology, [1]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Navigating complex and diverse relationships is a fundamental challenge for human and nonhuman primates alike. Precisely how the primate brain dynamically negotiates species-typical social interactions, in all their richness and complexity, remains largely unknown. Here we report neural correlates of an unprecedently diverse array of species-typical behaviors in unrestrained, socially-interacting rhesus macaques. We recorded single neuron activity from mono-synaptically connected inferior temporal area TEO and prefrontal area 45 in two male macaques interacting with female partners, while varying the identity of neighboring monkeys. Monkeys exhibited a rich repertoire of species-typical behaviors (n=29), including grooming, foraging, aggression, and mating. Behaviors of recorded monkeys were reliably decoded from simultaneous activity of several hundred neurons, extending over many minutes where the sensorimotor environment changed considerably. Most neurons encoded both subject's behavior and social context, including whether grooming was reciprocated, initiated, or occurred after a threatening event, and the identity and behavior of neighboring monkeys. Neuronal activity was also modulated by the female partner's actions, yielding parallel representations of behavioral states for self and other. Surprisingly, decoding performance and single unit responses were similar in temporal and prefrontal cortices, with implications for models of social information processing. Our findings demonstrate that neuronal ensembles in prefrontal and inferior temporal cortex carry a wealth of information about species-typical social stimuli, behaviors, and contexts, which is required for life in the real world.

Disclosures: C. Testard: None. **S. Tremblay:** None. **R.W. DiTullio:** None. **F. Parodi:** None. **M.L. Platt:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.11

Topic: F.01. Neuroethology

Title: Pathways and genes involved with MEIS1 gene in restless legs syndrome model.

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Abstract: Restless leg syndrome (RLS) is a chronic sleep-related sensorimotor disorder characterized by a strong impulse to move the legs to relieve uncomfortable sensations. A GWAS in 2000 has identified an association between RLS and three genomic regions. One of the regions was the intronic variants in the homeobox gene MEIS1. MEIS1 is a gene that increases the risk of developing RLS by 50% and has an association with iron homeostasis and the dopaminergic system. Although studies described a correlation between iron deficiency and the dopaminergic system, the neurobiology of RLS remains unclear. Our study aims to use a simple and strong genetic model (*Caenorhabditis elegans*) to understand the neurobiology of RLS. This approach can give us new targets, that can be confirmed in more complex models and used for treatments in the future. In *C. elegans*, the ortholog for *MEIS1* is *unc-62* and exhibits a robust impaired movement phenotype. Because of the phenotype, we perform an unbiased drug screen analysis with almost 4,000 compounds using WMicrotrackerTM ONE. With 108 hits, we are now proceeding to confirm the results and test the best candidates on plates using Wormlab software. Wormlab software (MBF Bioscience) can detect several quantitative parameters (including growth, size, progeny production, appearance, feeding behavior, locomotion, and mortality). Since differences in the dopaminergic system were described in *C. elegans* MEIS1 model, we want to further investigate the dopaminergic neurons in *unc-62(e644)* animals and how the compounds (selected in the drug screen) modulate these differences. To complete these experiments, we are constructing a strain with an unc-62 background that expresses GFP dopaminergic neurons and observing differences between treated and non-treated animals. RNA-seq will be used to provide important information on gene function by analyzing which genes are turned on in a specific model. Our findings will be tested and confirmed in cell culture and will give us a better understanding of the neurobiology of RLS and hopefully new pathways and drugs that can be used to improve patients' quality of life.

Disclosures: R. De Barros Oliveira: None. **C. Maios:** None. **A. Parker:** None. **P. Dion:** None. **G. Rouleau:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.12

Topic: F.01. Neuroethology

Support: Life Sciences Research Foundation HHMI Fellowship
Putnam Grant from Harvard University Museum of Comparative Zoology

HHMI Investigator Program
JVS0027401 Janelia Visiting Scientist Project

Title: The neural basis of the evolution of skilled climbing behavior in deer mice (Peromyscus maniculatus)

Authors: *K. M. TYSSOWSKI[1], K. CORTINA[1], E. R. HAGER[1], C. K. HU[1], J. COHEN[2], V. MENON[3], A. W. HANTMAN[2], H. E. HOEKSTRA[1];
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Abstract: Animals have evolved a variety of skilled motor behaviors that are essential for interacting with, and surviving in, their local environments. However, how molecular and circuit changes lead to the acquisition of new motor abilities is not well understood. To address this question, we capitalize on large, innate differences in skilled motor behavior between deer mouse subspecies (*Peromyscus maniculatus*) that occupy distinct habitats. While prairie subspecies are poor climbers, following the last glacial retreat 10,000 years ago, several subspecies independently colonized newly available forest habitat, where they evolved skilled climbing behavior. We have identified two ways in which motor behavior, and related neural circuitry, differs between forest- and prairie-dwelling subspecies. First, when crossing a thin rod between two platforms, two independent subspecies of forest mice cross faster, spend more time upright, right themselves more quickly when they fall, and use different gaits as compared to their prairie counterparts. To identify potential circuit mechanisms underlying these differences, we performed single-nucleus RNA sequencing of the lumbar spinal cord of five subspecies. We found several neuronal populations putatively involved in limb coordination that show differential abundance in two independent forest populations compared to their nearby prairie counterparts. The second behavioral difference we found is that forest-dwelling mice show greater dexterity in a pellet-reaching assay. Given the essential role of motor cortex in dexterous behaviors, we performed anterograde tracing from motor cortex, which revealed larger corticospinal tracts in forest compared to prairie subspecies. We then performed retrograde viral tracing from both cervical and lumbar spinal cord and found that, consistent with our anterograde tracing, forest mice have a greater number of neurons projecting from frontal motor cortex to cervical spinal cord. This tracing also revealed that forest mice have a larger number of neurons projecting from the red nucleus to both cervical and lumbar spinal cord. In sum, forest-dwelling Peromyscus maniculatus subspecies may have expanded specific circuit elements to support new motor abilities that promote survival in forested habitats.

Disclosures: K.M. Tyssowski: None. **K. Cortina:** None. **E.R. Hager:** None. **C.K. Hu:** None. **J. Cohen:** None. **V. Menon:** None. **A.W. Hantman:** None. **H.E. Hoekstra:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.13

Topic: F.01. Neuroethology

Support: NSF (CRCNS 1822550; 2203119)
Vannevar Bush Faculty Award (ONR N000142012828)

Title: Neuronal mechanisms of somersaulting in Hydra vulgaris

Authors: *W. YAMAMOTO, R. YUSTE;
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Abstract: Cnidarians are extant representatives of the first animals to evolve a nervous system to produce distinct motor behaviors. *Hydra vulgaris*, a freshwater cnidarian, is a sedentary polyp that shows repeated cycles of elongation and contraction, with its foot attached to the substrate. In addition to this contraction cycle, *Hydra* can somersault: acrobatic locomotion performed by attaching the head to the substrate, releasing the foot, swinging the body to the other side of the head, reattaching the foot, and finally releasing the head to stand at the new position. How a distributed nervous system composed of a few hundred neurons can robustly exercise sensory-motor coordination to achieve this sophisticated behavior remains a mystery. We have previously developed methods to image the activity of all neurons and all muscles in *Hydra*. However, studying *Hydra* neuronal activity during somersaulting remains challenging, due to the difficulty of maintaining neurons in focus as they move in a large three-dimensional space. To address this, we used *Hydra* expressing the calcium indicator GCaMP6s to image neuronal activity during somersaulting performed in a confined space (mounted preparation: 150-200 µm thickness). By applying DeepLabCut-tracking methods based on a deep convolutional network, we found that the progression through most steps of somersaulting was not significantly different between free and mounted preparations ($p > 0.05$, two-way logistic regression). Using the mounted preparation, we found that the activity of the rhythmic potential 1 (RP1) neurons, a neuronal ensemble in which synchronous firing neurons distributed throughout the body, was significantly increased (0.05 ± 0.01 vs 0.50 ± 0.03 Hz, $p < 0.0001$) at start of somersaulting. There was no significant difference in time for increased RP1 activity (RP1 burst) and the time for the basal disc muscle activation (17.80 ± 2.15 vs 16.63 ± 4.98 sec prior to the foot detachment, $p > 0.05$). Activation of nematocytes on the tentacles also occurred at this time point (3.55-fold increase in fluoresce, $p < 0.0001$), which correlates with the tentacle attachment. To investigate the role of RP1 activity in somersaulting, we altered RP1 activity in somersaulting. Firstly, reducing the total number of neurons with 0.04% colchicine abolished somersaulting ($p < 0.01$). Secondly, increasing the osmolarity of the medium (with 50 mM sucrose) decreased RP1 activity (0.45 ± 0.03 vs 0.20 ± 0.02 Hz, $p < 0.0001$) and generated a 63.6 % decrease in the number of somersaults. Our results indicate that RP1 neurons control basal disc muscles and nematocytes in precise order and timing, leading to complex behaviors such as somersaulting.

Disclosures: W. Yamamoto: None. **R. Yuste:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.14

Topic: F.01. Neuroethology

Support: JSPS KAKENHI Grant 21H00222
JSPS KAKENHI Grant 19H04885
JST Moonshot R&D Grant JPMJMS2294
AMED Brain/MINDS JP15dm0207001

Title: Cortical dynamics of efference copy revealed by large-scale cortical ECoG during marmoset vocalization

Authors: *K. IIJIMA[1,2,3], M. KOMATSU[3,4,2], W. SUZUKI[2], Z. NARITA[1], T. YAMAMORI[3], N. ICHINOHE[2], M. MATSUMOTO[1,2,3];
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Abstract: The sensations associated with one's own movements are suppressed by efference copy derived from motor commands and predictions of outcomes. It has been suggested that auditory hallucinations in schizophrenia may be caused by abnormalities in efference copy of vocalizations. However, the neural dynamics of efference copy of vocalizations have not been fully elucidated. In this study, a 96-channel electrocorticography (ECoG) electrode array designed to cover the frontal, parietal, occipital, and temporal lobes, including the primary auditory cortex, was placed on the dura of marmosets (*Callithrix jacchus*). Taking advantage of the marmoset's characteristic reciprocal exchange of calls, ECoG was recorded during the vocalization of phee calls in response to phee calls of another individual (the "vocalization condition") and during listening to their own calls recorded in the vocalization condition (the "listening condition"). The brain activities recorded from each electrode were compared between the two conditions to examine how sensory responses to vocalizations are suppressed in the presence of motor commands and their efferent copy. In the vocalization condition, a large suppression of brain activity in the high gamma frequency band (80-200 Hz) was observed at multiple electrodes, mainly in the temporal lobe, but also in the parietal and frontal lobes. This suppression began approximately 500 ms before the onset of vocalization. In the listening condition, on the other hand, an increase in the high gamma frequency band was observed at multiple electrodes around the temporal lobe after the presentation of the vocal stimulus. When both conditions were compared, significant differences were obtained at multiple electrodes around the temporal lobe. These observations were stable across individuals. These results were consistent with the hypothesis that the premotor cortex sends inhibitory signals to the auditory cortex during spontaneous vocalizations to distinguish between its own vocalizations and those of others. It is known that schizophrenic patients with positive symptoms and severe auditory hallucinations show reduced inhibition of activity in the auditory cortex during vocalization. Thus, this study provides a prototype experimental system for abnormalities in efference copy in animal models of schizophrenia.

Disclosures: K. Iijima: None. **M. Komatsu:** None. **W. Suzuki:** None. **Z. Narita:** None. **T. Yamamori:** None. **N. Ichinohe:** None. **M. Matsumoto:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.15

Topic: F.01. Neuroethology

Support: UK Medical Research Council (MR/T046619/1)

Title: Micro computed X-ray tomography reconstruction of the anatomy of the buccal mass in the sea-slug Aplysia californica

Authors: *S. M. ROGERS[1], B. KUNDU[2], G. P. SUTTON[2];
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Abstract: The feeding apparatus, or buccal mass, of mollusks is a complex muscular structure composed of several distinct muscles but which completely lacks hard skeletal elements. Movement is therefore produced by the individual muscles interacting directly with each other without the benefit of rigid supports and levers. To understand how the buccal mass can accomplish a variety of feeding behaviors it is essential to understand and quantify the complex three-dimensional anatomy of its individual muscular components and how they attach to each other. We used Micro computed X-ray tomography (micro CT), a non-destructive imaging technique to reconstruct the anatomy of the buccal mass at ten micron resolution. Buccal masses were fixed in 70% ethanol before staining in Lugol's solution (0.5% I2/KI in a phosphate buffer) for one month to give the muscle tissue sufficient X-ray opacity and imaged on a SkyScan1272 micro ct scanner (60 kV, 166 micro A). These scans have revealed the three-dimensional muscular anatomy of the buccal mass in unprecedented detail. Jaw cartilages and the teeth of the central grasping structure (the odontophore) were clearly visible, allowing detailed analysis of the shape of these structures. We found complex geometric interactions between superficial muscles of the buccal mass and muscles internal to the odontophore. Moreover, differing muscle fibre orientations within larger buccal muscles suggest that these may be composites of a number of smaller muscles. This 3-D imaging will form an essential component in the ongoing development of models of neuro-muscular control in soft-tissue systems.

Disclosures: S.M. Rogers: None. **B. Kundu:** None. **G.P. Sutton:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.16

Topic: F.01. Neuroethology

Support: NIH grant U19MH114823-01
NIH Director's Pioneer Award 1DP1MH129954-01

Title: Cortical glutamatergic projection neuron types contribute to distinct functional subnetworks.

Authors: *H. MOHAN[1], X. AN[1], H. KONDO[2], X. XU[1], S. ZHAO[1], K. S. MATHO[2], S. MUSALL[3], P. P. MITRA[2], Z. HUANG[1];
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Abstract: The cellular basis of cerebral cortex functional architecture remains not well understood. A major challenge is to monitor and decipher neural network dynamics across broad cortical areas yet with projection neuron (PN)-type resolution in real time during behavior. Combining genetic targeting and wide-field imaging, we monitored activity dynamics of subcortical-projecting (PT^{Fezf2}) and intratelencephalic-projecting (IT^{PlxnD1}) types across dorsal cortex of mice during different brain states and behaviors. IT^{PlxnD1} and PT^{Fezf2} neurons showed distinct activation patterns during wakeful resting, spontaneous movements, and upon sensory stimulation. Distinct IT^{PlxnD1} and PT^{Fezf2} subnetworks were dynamically tuned to different sensorimotor components of a naturalistic feeding behavior, and optogenetic inhibition of subnetwork nodes disrupted specific components of this behavior. Lastly, IT^{PlxnD1} and PT^{Fezf2} projection patterns are consistent with their subnetwork activation patterns. Our results show that, in addition to the concept of columnar organization, dynamic areal and PN type specific subnetworks are a key feature of cortical functional architecture linking microcircuit components with global brain networks.

Disclosures: H. Mohan: None. **X. An:** None. **H. Kondo:** None. **X. Xu:** None. **S. Zhao:** None. **K.S. Matho:** None. **S. Musall:** None. **P.P. Mitra:** None. **Z. Huang:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.17

Topic: F.01. Neuroethology

Title: Roundup® And glyphosate's impact on GABA to elicit extended proconvulsant behavior in caenorhabditis elegans

Authors: *A. S. NARAINE[1,2], R. AKER[2], I. SWEENEY[2], M. KALVEY[2], A. SURTEL[2], V. SHANBHAG[3], K. DAWSON-SCULLY[4];
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Boca Raton, FL; [3]Chem. and Physics, [4]Psychology and Neurosci., Nova Southeastern Univ., Ft. Lauderdale, FL

Abstract: As 3 billion pounds of herbicides are sprayed over farmlands every year, it is essential to advance our understanding how pesticides may influence neurological health and physiology of both humans and other animals. Studies are often one-dimensional as the majority examine glyphosate by itself. Farmers and the public use commercial products, like Roundup®, containing a myriad of chemicals in addition to glyphosate. Currently, there are no neurological targets proposed for glyphosate and little comparison to Roundup®. To investigate this, we compared how glyphosate and Roundup® affect convulsant behavior in *C. elegans* and found that glyphosate and Roundup® increased seizure-like behavior ($p<0.01$). Key to our initial hypothesis, we found that treatment with an antiepileptic drug rescued the prolonged convulsions ($p<0.001$). We also discovered over a third of nematodes exposed to Roundup® did not recover from their convulsions, but drug treatment resulted in full recovery. Notably, these effects were found at concentrations that are 1,000-fold dilutions of previous findings of neurotoxicity, using over 300-fold less herbicide than the lowest concentration recommended for consumer use. Exploring mechanisms behind our observations, we found significant evidence that glyphosate targets GABA-A receptors. Pharmacological experiments which paired subeffective dosages of glyphosate and a GABA-A antagonist yielded a 24% increase in non-recovery compared to the antagonist alone. GABA mutant strain experiments showed no effect in a GABA-A depleted strain, but a significant, increased effect in a glutamic acid decarboxylase depleted strain. Our findings characterize glyphosate's exacerbation of convulsions and propose the GABA-A receptor as a neurological target for the observed physiological changes. It also highlights glyphosate's potential to dysregulate inhibitory neurological circuits.

Disclosures: A.S. Naraine: None. **R. Aker:** None. **I. Sweeney:** None. **M. Kalvey:** None. **A. Surtel:** None. **V. Shanbhag:** None. **K. Dawson-Scully:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.18

Topic: F.01. Neuroethology

Support: Helen Hay Whitney Foundation
Chen Institute Grant
NIH Brain Initiative Grant

Title: To flex or flee: investigating defense behavior and its neural control during symbiotic interactions in rove beetles

Authors: *J. K. KANWAL[1,2], J. OMOTO[1,2], D. MILLER[2], M. DICKINSON[2], J. PARKER[2]; [2]Biol. and Biol. Engin., [1]Caltech, Pasadena, CA

Abstract: How do organisms evolve to interact with one another? What changes to neural structure and function enable adaptive interspecies interactions? We are using rove beetles as a model system to investigate the behavioral motifs and neural architecture underlying the evolutionary origins of symbiotic behavior. Free-living beetle species have repeatedly evolved into symbiotic myrmecophiles that socially interact with specific host ant taxa. To assess the origins of such specialized behavior, we have quantified the behavioral motifs underlying beetle-ant interactions in the ancestral, free-living species, Dalotia coriaria. Dalotia possess a flexible abdomen with a benzoquinone-secreting chemical defense gland that functions as a potent ant deterrent. Using multi-view behavioral imaging and tracking, we find that Dalotia exhibit robust abdomen flexion defense response such that flexion angle increases as the distance between Dalotia and ant decreases. Such behavior is olfactory mediated, as anosmic beetles (orco mutants) have a significantly reduced flexion angle upon ant approach.
To build a foundation for probing the neural circuits that enable such behaviors, we are developing a detailed anatomical atlas of the rove beetle nervous system. In particular, we are examining changes in neural architecture that may mediate the transition to sociality. To this end, we have developed a comprehensive map of major brain regions and the ventral nerve cord (VNC) of both the free-living, Dalotia, and the symbiotic myrmecophile, Sceptobious lativentris, beetle species. Our preliminary data demonstrate species-specific differences in the pattern of neuromere (segmented modular ganglia) fusion in the VNC, potentially underlying differences in the innervation pattern of the VNC-gland module. Overall, our behavioral and anatomical work begins to lay the foundation for using rove beetles to examine the evolution of interspecies interactions.

Disclosures: J.K. Kanwal: None. **J. Omoto:** None. **D. Miller:** None. **M. Dickinson:** None. **J. Parker:** None.

Poster

723. Neuroethology: Sensory Motor Systems II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 723.19

Topic: I.03. Anatomical Methods

Support: NIH
NSF NeuroNex
Samsung Scholarship

Title: Robotic, automated assessments of fruit fly behavior

Authors: *S. WOO[1], C. HUANG[1], J. SAVALL[1,2,3], B. L. CONRAD[1], M. J. SCHNITZER[1,2,3]; [1]James H. Clark Center, Stanford Univ., Stanford, CA; [2]CNC Program, Stanford Univ., Stanford, CA; [3]Howard Hughes Med. Institute, Stanford Univ., Stanford, CA

Abstract: The fruit fly, *Drosophila melanogaster*, is a widely used species in neuroscience and other areas of biology. Increased automation of behavioral assays would greatly facilitate many aspects of research, but implementation of automated assays has been hindered by the difficulty of handling individual flies in a mechanized way. To overcome this limitation, we built a robot that can collect an un-anesthetized adult fly, inspect it with machine vision and then assess its behavior. The robot rapidly lifts and holds individual flies by the thorax using gentle suction. Once picked, the fly can be manipulated in 3 translational and 2 rotational degrees of freedom, allowing us to bring the fly to different inspection and experimental stations. Typically, a picked fly first undergoes machine vision analyses that use convolutional neural networks to determine the quality of the pick and the fly's sex. Subsequently, the robot can bring the fly to another station to assess visuo-motor behavior. To characterize the throughput with which our system can prepare picked flies, we automatically collected and inspected 1615 individual flies (Canton-S wild type) within 17 hours. Of these flies, the robot properly picked 1007 on the thorax with less than ±10 deg. of deviation in the roll dimension. 505 of these properly picked flies were male; 502 were female. Since the picked flies had pitch angles ranging from -15 to 45 deg., we used the robot's rotational control to correct for this variation by precisely aligning the flies in the pitch dimension.
To check if robotic handling of a fly might affect its health, we compared survival rates and climbing performances of flies that had been handled by the robot to those of control flies that had not. Our statistical evaluations compared female and male flies on both assays (8 groups; 94 to 100 Canton-S flies per group) and showed that survival rates and climbing performances were not significantly affected by robotic handling. To make automated assessments of visuo-motor behavior, the robot held individual flies atop a trackball that monitors fly locomotion as the fly watches a video display. This station also has a temperature control unit for thermogenetic manipulations. With this unit we manipulated T4 and T5 cells in the medulla that are responsible for ON and OFF motion detection, respectively (T4 line, R54A03-GAL4; T5 line, R42H07-GAL4; shibire line, UAS-shi^{ts1}; 8-10 flies per group), as we recorded visually evoked locomotor responses. Overall, our robotic system can pick and characterize large numbers of individual flies and thereby paves the way to behavioral and neural screens of unprecedented scale and precision.

Disclosures: S. Woo: None. **C. Huang:** None. **J. Savall:** None. **B.L. Conrad:** None. **M.J. Schnitzer:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.01

Topic: F.01. Neuroethology

Support: JSPS research fellow 20J20319

Title: Novel enhanced learning ability elicited by interspecific hybridization of songbirds

Authors: *Y. SHIBATA[1], N. TOJI[2], S. TATSUMOTO[3], H. ISHIKAWA[3], Y. GO[3], K. WADA[2]; [1]Grad. Sch. of Life Sci., [2]Fac. of Sci., Hokkaido Univ., Sapporo, Japan; [3]Natl. Inst. for Physiological Sci., Okazaki, Japan

Abstract: Learned behaviors are an essential adaptive trait for survival and reproduction, meanwhile species-specifically constrained. However, how the genetic constraints restrict learning attributes is not fully elucidated. Here, we established interspecific first-generation (F_1) hybrid songbirds between zebra and cherry finches as a source of divergent learned phenotypes in song acquisition. The parental species that produced distinct characteristic songs were restricted to learning only conspecific songs when tutored with both species' songs. Instead, the F_1 hybrids showed heterosis in song learning to acquire both species' songs as two independent song modalities. The enhanced learning of F_1 hybrids was not innately predisposed to generate multiple song types, but rather elicited by the input of the song model to learn. Consistent with this, when tutored with genetically-unrelated species songs, such as the owl finch and canary songs, F_1 hybrids still learned the songs with a certain similarity. To elucidate the neural basis underlying the transgressive song learning in the F_1 hybrids, we examined the anatomical and transcriptomic characteristics in the neural circuit specialized for song learning and production. Although the song nuclei size and neuron numbers in the vocal motor pathway were not different between parental species and F_1 hybrids, the single-cell transcriptome analysis revealed prominent differences in transcriptional signature in glutamatergic projection neurons in the vocal motor nuclei. Notably, compared with other cell types in song nuclei and neurons outside of song nuclei, the glutamatergic projection neurons transcribed more non-additive genes with biased expression towards either of their parental species or higher/lower expression compared to both parental species. In addition, the non-additive genes in the glutamatergic projection neurons were enriched with signaling-related genes, including receptors and cell adhesion molecules. These results suggest that a new transcriptional combination of non-additive genes could be a molecular basis for generating a phenotypic novelty in learned behavior.

Disclosures: Y. Shibata: None. **N. Toji:** None. **S. Tatsumoto:** None. **H. Ishikawa:** None. **Y. Go:** None. **K. Wada:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.02

Topic: F.01. Neuroethology

Support: KAKEN Grant 20K15891
Kawai Foundation For Sound Technology & Music

Title: Transcriptomic signatures in glutamatergic projecting neurons reveal species-specific vocal learnability in songbirds

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Abstract: Species-specific behaviors have evolved with physiological and anatomical speciation in the cellular molecule basis at the related-neural circuits. However, the speciation process of the neural circuits for learned behaviors has largely unknown. Songbirds learn and generate species-specific songs through singing practice in the juvenile stage. Songs are generated by a neural circuit called the song system, which is well conserved among songbird species. To elucidate the cellular molecule speciation in the neural circuits related to learned vocalization, we performed the single-cell transcriptome analysis at two vocal motor nuclei (HVC and RA) in closely-related four species (zebra finch, owl finch, cherry finch, and Bengalese finches). In the interspecies transcriptome comparison focusing on multiple neural and non-neural cell types, we found significant differences in species-specific gene expression accumulated in excitatory projection neurons in both HVC and RA compared to other cell types. The differentially expressed genes in the excitatory projection neurons between species were selectively enriched in ion channels and neurotransmitter/modulator receptors and significantly located on Z sexual chromosome. This result suggested that a certain way of genomic alteration changes the excitatory properties in the neural circuits underlying the species-specific learned behavior. In addition, although the species-specific transcriptional signatures were detected even at the initiation stage of vocal babbling, they became more salient through the song learning period, indicating the epigenetic regulation for the cell-type and species-specific gene expression. We are currently analyzing the potential relationship between the transcriptional signatures and their learned song phenotype.

Disclosures: N. Toji: None. **Y. Shibata:** None. **S. Tatsumoto:** None. **H. Ishikawa:** None. **Y. Go:** None. **K. Wada:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.03

Topic: F.01. Neuroethology

Support: NIH Grant SC1GM112582
HHMI EJ1

Title: Whole transcriptome profiling supports parallel “core” and “shell” vocal learning circuits in a parrot

Authors: *G. L. GEDMAN[1,2], C. DARNEY[3], E. D. JARVIS[4], T. F. WRIGHT[1];
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Abstract: Animals have evolved a diverse array of neural circuits for the control of complex behaviors. For instance, vocal learning species (humans, songbirds, parrots, etc.) have evolved specialized forebrain circuitry for the acquisition and production of learned sounds used in social communication. Humans and songbirds exhibit molecular convergence within these specialized circuits, suggesting strong evolutionary constraints for their development. Less is known about the molecular markers of the vocal control system in parrots, and whether they exhibit similar molecular convergence with other vocal learning taxa. Recent work in parrots suggests the existence of a secondary "shell" system surrounding the anatomically distinct "core" system. With only a small number of genes assessed thus far, whole transcriptome profiling is necessary to confirm the existence of these parallel brain circuits in parrots. Here, we isolated "core" and "shell" portions of the principal nuclei (MMSt, MO, NAO, NLC, and AAC) of the vocal control system from the budgerigar parakeet *(Melopsittacus undulatus*), as well as samples from the non-vocal motor regions surrounding each nuclei using laser capture microscopy. We profiled these regions using bulk RNA sequencing and conducted pair-wise differential gene expression analyses to assess their molecular diversity. We found robust molecular convergence between several of the budgerigar "core" nuclei (MMSt, NLC, NAO) and their songbird analogs (Area X, HVC, LMAN), further extending the instances of molecular convergence for this trait in vocal learning species. As in songbirds, we found that the downregulated genes in these budgerigar "core" nuclei were enriched for axon guidance and cell signaling functions, suggesting that restriction of gene expression is a powerful means of functional specialization. Additionally, we found robust molecular markers of a "shell" region, distinct from the "core" and non-vocal motor surround, in the posterior vocal production nuclei (NLC, AAC) but not in the anterior sensory acquisition nuclei (MMSt, MO, NAO), suggesting an important functional segregation for vocal motor production in this species. We hypothesize these "core" and "shell" systems provide parallel innervation to distinct sets of motor neurons in the XIIth nucleus that controls the syrinx and tongue, enabling the coordination of these separate muscles groups to produce the complex vocal repertoires of parrots. This work provides the first complete molecular profile of parrot core and shell vocal control system and offers important insights into the molecular constraints for the evolution of vocal learning in nature.

Disclosures: G.L. Gedman: None. **C. Darney:** None. **E.D. Jarvis:** None. **T.F. Wright:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.04

Topic: F.01. Neuroethology

Support: R56 NS110951

Title: Developmental shifts in chromatin accessibility spanning the onset of sensory song learning in juvenile zebra finches

Authors: *G. KUNZELMAN, S. E. LONDON;
Univ. of Chicago, Chicago, IL

Abstract: Neural properties that regulate developmental learning are particularly difficult to define because both maturation and experience influence cell number, subtype, functionality, and connectivity, all features that influence learning and memory. The complement of protein coding and noncoding RNAs transcribed from the genome largely determines these properties. Transcription is regulated by transcription factors (TF), proteins that bind genomic regions at transcription factor binding sites (TFBS). Epigenetic modifications, such as those on histone proteins, modulate TFBS accessibility. H3K27ac is a histone modification that denotes accessible TFBSs. To determine the neural properties that support learning of complex behavior, we performed chromatin immunoprecipitation for H3K27ac and high-throughput DNA sequencing (ChIP-seq) on post-hatch (P) day 23 and P30 male and female zebra finches. Sensory song learning begins at P30 in males and experimental data suggest it begins at a similar time in females. We assayed the auditory forebrain, a region required for sensory song learning. We bioinformatically identified differentially accessible regions (DAR) of the genome and TFBSs in juveniles differing in age, sex, and prior song experience, factors central to regulating developmental song learning. Our data suggest sex differences in sensory song learning mechanisms. Males at the two experimental timepoints had a 10-fold greater number of DARs than age-matched females. Compared to the male DAR data, female DARs were located at different genomic locations and were enriched for different TFBSs. While distinct, both male and female TFBS profiles have been implicated in the various stages of neural development and organization critical for supporting learning and memory formation. Comparisons of age-matched male and female birds suggest that sex has greater influence over chromatin accessibility than development within this period. Notably, the vast majority of DARs between age-matched males and females were located on sex chromosomes. Examination of TFBS enriched in both age-matched comparisons suggest that binding sites for many of the same TFs are enriched in DARs attributed to both sexes, but that there are TFBSs uniquely enriched in each sex and age. For example, binding sites for EGR1, a well-studied song responsive immediate early gene TF, were only accessible in DARs demonstrating greater enrichment in males. Together, our evaluation of epigenetically defined accessible regulatory regions allows for novel insight into the emergence of neural learning circuits in a brain area required for developmental learning of a complex behavior.

Disclosures: G. Kunzelman: None. **S.E. London:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.05

Topic: F.01. Neuroethology

Support: NIH R01 NS075044
imons Collaboration on the Global Brain

Title: Heterogeneous network contributions of identified GABAergic subtypes in a zebra finch premotor circuit

Authors: *E. HOZHABRI[1], A. CORREDERA ASENSIO[1], M. ELMALEH[1], P. FRAZEL[1], J. DIMIDSCHSTEIN[2], G. J. FISHELL[3], M. A. LONG[1];
[1]Neurosci. & Physiol., New York Univ., New York, NY; [2]Broad Inst., Broad Inst., Cambridge, MA; [3]Harvard Med. Sch., Cambridge, MA

Abstract: GABAergic interneurons enrich the computational power of neural circuits, with different subpopulations often proposed to play distinct roles within a network. In the mammalian brain, separate categories can be defined based on their morphological, physiological, molecular, and connectivity profiles. Although these classes have been well-characterized in sensory cortices, the roles of distinct inhibitory cell types in the production of complex motor behaviors are still poorly understood. To address this issue, we investigated the role of GABAergic interneurons within the zebra finch song production pathway, which has the distinct advantage of a complex, but highly tractable, behavior mediated by a set of well-characterized brain regions. In a key premotor locus, called HVC, inhibition mediated by local circuit interneurons plays several distinct roles in song learning and production. Furthermore, we and others have characterized heterogeneity within the HVC interneuron population. However, the degree to which these diverse profiles mediate distinct roles within the HVC circuit remains unclear.
We begin to address this issue by characterizing molecularly defined interneurons across a range of behaviors. We first explored the genetic diversity of HVC interneurons using single-nuclei transcriptomics and found distinct clusters of HVC interneurons consistent with recently published findings. We then categorized electrophysiological responses of HVC interneurons in different behavioral contexts using chronically implanted silicon probes. To link these observations, we used *in vivo* 2-photon targeted recordings of HVC interneurons virally labeled with GFP followed by post hoc immunolabeling with antibody markers for major transcriptomically defined interneuron subclasses. Using this approach, we have begun to relate specific physiological roles of interneurons with their molecular designations.

Disclosures: E. Hozhabri: None. **A. Corredera Asensio:** None. **M. Elmaleh:** None. **P. Frazel:** None. **J. Dimidschstein:** None. **G.J. Fishell:** None. **M.A. Long:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.06

Topic: F.01. Neuroethology

Support: National Institutes of Health grant R01 NS075044 (MAL)
Simons Collaboration on the Global Brain 527742 (MAL)
National Institutes of Health grant F31 NS116933-01 (ME)

Title: Thalamus drives vocal onsets in the zebra finch song sequence

Authors: *F. W. MOLL, D. KRANZ, A. CORREDERA ASENSIO, M. ELMALEH, L. A. ACKERT-SMITH, M. A. LONG;
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Abstract: While motor cortical circuits contain information related to specific movement parameters, long-range inputs also play a critical role in action execution. Thalamic projections can shape premotor activity and have been suggested to mediate the selection of short, stereotyped actions comprising more complex behaviors. However, the mechanisms by which the thalamus interacts with motor cortical circuits to execute such movement sequences remain unknown. Here we find that thalamic drive engages a specific subpopulation of premotor neurons within the zebra finch song nucleus HVC (proper name) and that these inputs are critical for the progression between vocal motor elements (i.e., 'syllables'). In vivo 2-photon imaging of thalamic axons in HVC revealed consistent song-related activity, and online perturbations of thalamic function caused song to be truncated at syllable boundaries. We used thalamic stimulation to identify a sparse set of thalamically-driven neurons within HVC, representing ~15% of the premotor neurons within that network. Surprisingly, this population of putative thalamorecipient neurons is robustly active immediately preceding syllable onset. Through selective targeting of these 'starter cells', thalamic input may be initiating individual song components. These findings highlight the motor thalamus as a director of cortical dynamics in the context of an ethologically-relevant behavioral sequence.

Disclosures: F.W. Moll: None. **D. Kranz:** None. **A. Corredera Asensio:** None. **M. Elmaleh:** None. **L.A. Ackert-Smith:** None. **M.A. Long:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.07

Topic: F.01. Neuroethology

Support: Farouk Jabr Foundation
University Research Board

Title: Neural network mechanisms underlying the combination sensitivity property in the HVC of songbirds

Authors: *Z. MERAABE[1], Y. GHAMLOUCHE[1], D. MARGOLIASH[2], A. DAOU[1,2];
[1]Biomed. Engin. Program, American Univ. of Beirut, Beirut, Lebanon; [2]Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: Temporal order of information processing in the brain is an important code in many acoustic signals including speech, music, and animal vocalizations. Despite its significance, surprisingly little is known about its underlying cellular mechanisms and network manifestations. In the songbird telencephalic nucleus HVC, a subset of neurons show temporal combination sensitivity (TCS). These neurons respond in a facilitatory or inhibitory manner to patterns of distinct spectral elements in a signal, when they occur in a specific temporal order. HVC neuron types include basal-ganglia-projecting HVC_X, forebrain-projecting HVC_{RA}, and interneurons (HVC_{INT}), each exhibiting distinct cellular, electrophysiological and functional properties. In this work, we develop conductance-based neural network models connecting the different classes of HVC neurons via different network architecture patterns with the aim of unveiling the intrinsic and synaptic mechanisms that orchestrate the combination sensitivity properties exhibited presumptively by HVC_X, as well as replicating *in vivo* firing patterns observed when TCS neurons are presented with various auditory stimuli. The model neurons in each class are designed to express pharmacologically identified ionic currents and the neurons are connected via pharmacologically identified synaptic currents, rendering our networks biologically plausible. We present for the first time several realistic scenarios in which the different types of HVC neurons can interact to produce this behavior. The different networks highlight intrinsic and synaptic mechanisms that could help to explain combination sensitivity, including 1) interplay between inhibitory interneurons' activity and the postinhibitory firing of the HVC_X neurons enabled by T-type Ca^{2+} and H currents, 2) temporal summation of synaptic inputs at the TCS site of opposing signals that are time-and frequency- dependent, and 3) reciprocal inhibitory and excitatory loops as a potent mechanism to encode information over many milliseconds. The result is a plausible network model characterizing auditory processing in HVC. Our next step is to test the predictions of the model.

Disclosures: Z. Meraabe: None. **Y. Ghamlouche:** None. **D. Margoliash:** None. **A. Daou:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.08

Topic: F.01. Neuroethology

Support: Farouk Jabr Foundation
University Research Board

Title: Neural networks underling the generation of neural sequences in the HVC

Authors: *Z. BOU DIAB[1], M. CHAMMAS[1,2], D. MARGOLIASH[3], A. DAOU[1,3];
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Abstract: The neural mechanisms of sequential behaviors are intensively studied, with songbirds a focus for learned vocal production. We are studying the premotor nucleus HVC at a nexus of multiple pathways contributing to song learning and production. The HVC consists of multiple classes of neuronal populations, each that has its own cellular, electrophysiological and functional properties. During singing, a large subset of motor cortex analog-projecting HVC_{RA} neurons emit a single 6-10 ms burst of spikes at the same time during each rendition of song, a large subset of basal ganglia-projecting HVC_{X} neurons fire 1 to 4 bursts that are similarly time locked to vocalizations, while HVC_{INT} neurons fire tonically at average high frequency throughout song with prominent modulations whose timing in relation to song remains unresolved. This opens the opportunity to define models relating explicit HVC circuitry to how these neurons work cooperatively to control learning and singing. We developed conductance-based Hodgkin Huxley models for the three classes of HVC neurons (based on the ion channels previously identified from *in vitro* recordings) and connected them in several physiologically realistic networks (based on the known synaptic connectivity and specific glutaminergic and gabaergic pharmacology) via different architecture patterning scenarios with the aim to replicate the *in vivo* firing patterning behaviors. We are able through these networks to reproduce the *in vivo* behavior of each class of HVC neurons as shown by the experimental recordings. The different network architectures developed highlight different mechanisms that might be contributing to the propagation of sequential propagation of activity (continuous or punctate) in the HVC and to the distinctive firing patterns that each class exhibits during singing. Examples of such possible mechanisms include: 1) post-inhibitory rebound in HVC_{X} and their population patterns during singing, 2) different subclasses of HVC_{INT} interacting via inhibitory-inhibitory loops, 3) mono-synaptic HVC_{X} to HVC_{RA} excitatory connectivity, and 4) structured many-to-one inhibitory synapses from interneurons to projection neurons, and others. Replication is only a preliminary step that must be followed by model prediction and testing.

Disclosures: Z. Bou Diab: None. **M. Chammas:** None. **D. Margoliash:** None. **A. Daou:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.09

Topic: F.01. Neuroethology

Support: NIH F31 NS116933 (ME)
Simons Collaboration on the Global Brain (ML)
NIH R01 NS NS075044 (ML)

Title: Behavioral modulation of interhemispheric coordination in the zebra finch

Authors: *M. ELMALEH[1,2], M. A. LONG[2], L. ACKERT-SMITH[2];
[1]NYU Langone Med. Ctr., NYU Neurosci. Inst., New York, NY; [2]NYU Sch. of Med., New York, NY

Abstract: Complex behaviors often require the coordination of brain regions across hemispheres. During the courtship song of the zebra finch, coordinated bilateral activity is required to control the syringeal muscles on the left and right sides of the vocal organ even though direct interhemispheric connections across forebrain song control nuclei are lacking. To examine the nature of bilateral coordination in the zebra finch brain, we used high-density silicon probes to record dozens of neurons within the robust nucleus of the arcopallium (RA) on both hemispheres. During song, we find that RA neurons are coordinated across hemisphere at a sub-millisecond level. To determine whether this precision is unique to behavior, we examined hemispheric coordination outside of song. We find that the tonic baseline firing rate is tightly coordinated across hemispheres and can be used as a sensitive measure of global arousal state. Dips in this arousal metric correspond to epochs of intense network bursting, which is when 'sleep replay' occurs. A closer examination of these bursting events, however, reveals that replay is not synchronized across hemispheres as it is during song. Sleep replay can occur independently, with one hemisphere replaying while the other remains in the tonic firing state and even when both hemispheres are replaying the song, they are often replaying different portions of the song. Together, these findings demonstrate that precise coordination of forebrain song circuits is modulated by behavioral state and points to a dedicated synchronizing mechanism during song. Our results further highlight the power of examining offline activity for studying behaviorally relevant circuit organization.

Disclosures: **M. Elmaleh:** None. **M.A. Long:** None. **L. Ackert-Smith:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.10

Topic: F.01. Neuroethology

Support: NSF award EF-1822476 (DZJ)

Title: A computational model investigating the plausibility of generating precisely timed and highly reliable bursts in songbird nucleus HVC

Authors: *D. SEDERMAN[1], Y. TUPIKOV[3], N. NIKBAKHT[4], M. S. FEE[5], D. Z. JIN[2];
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Abstract: Zebra finch song is driven by precisely timed and highly reliable bursts of projection neurons in the sensory-motor nucleus HVC (proper name) that form ultra-sparse burst sequences. The neural mechanism for the bursts is currently debated. One view is that bursts are generated in HVC through a synaptic chain mechanism (Long et al., 2010 and Egger et al., 2020). An alternative is that the thalamic nucleus Uvaeformis (UVA) drives HVC bursts as part of a distributed network through the brainstem, UVA, HVC, and RA (Hamaguchi et al., 2016). Here we computationally assess the plausibility of the distributed model. Single neuron recordings in UVA during singing show that UVA neurons that project to HVC contain timing information during the song, but compared to HVC projection neurons, fire densely in time and are much less reliable. To examine if convergence of UVA projection neurons to HVC can produce the precision and reliability of the HVC bursts, we use a resampling technique to scale up the number of UVA neurons. This allows the number of sampled UVA neurons to match the number of UVA projection neurons while preserving the timing and reliability of recorded UVA neurons. Using the sampled UVA neurons, we create a procedure to train model HVC projection neurons. Each model HVC neuron is trained to burst at a putative time in response to direct excitatory UVA input and indirect inhibitory input through HVC interneurons. Training is performed with learning rules similar to those previously used to characterize learning capacities of neuronal circuits (Memmesheimer et al., 2014). HVC projection neurons are simulated with an integrate-and-fire model and a more biologically informed two-compartment model that includes a dendritic calcium spike. In both models, trained HVC projection neurons produce precise, sparse bursts only when the convergence from UVA to HVC is high enough to overcome the inconsistency of UVA firing patterns. However, this level of convergence is not supported by experiments that have traced the axons from UVA to HVC. When realistic convergence is used, trained HVC projection neurons are unable to reproduce the precision and reliability experimentally observed in HVC. Noise in HVC interneurons further exacerbates this issue. Our work casts doubt on the mechanism of UVA driving HVC bursts.

Disclosures: D. Sederman: None. **Y. Tupikov:** None. **N. Nikbakht:** None. **M.S. Fee:** None. **D.Z. Jin:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.11

Topic: F.01. Neuroethology

Support: NSF Grant EF-1822476

Title: Effects of deafening on Bengalese finch song syntax analyzed through partially observed Markov model

Authors: J. LU[1], S. SURENDRALAL[2], K. E. BOUCHARD[3], **D. Z. JIN**[1];
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Abstract: Songs of the Bengalese finch consist of variable sequences of syllables. The sequences follow probabilistic rules, and can be statistically described by partially observable Markov models (POMMs). Each state is associated with a syllable type in the song, and a single syllable type can be associated with multiple states. This many-to-one mapping from the states to the syllable types distinguishes a POMM from a simple Markov model, for which one syllable type is associated with one state. The multiplicity of the states encode context dependence of syllable sequences. Here we present a method for deriving a POMM with minimal number of states for a set of finite number of observed sequences. We apply the method to construct POMM syntax for six adult male Bengalese finches before and after deafening. The models range from a simple Markov model for one bird to a POMM requiring four states for single syllables for another. Deafening reduces the many-to-one mapping for the five birds with non-Markovian syntax. For two birds the models become Markovian, while for the other three birds the many-to-one mapping persists. These observations indicate that auditory system contributes to but is not the only source of the context dependence in the Bengalese finch song.

Disclosures: J. Lu: None. **S. Surendralal:** None. **K.E. Bouchard:** None. **D.Z. Jin:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.12

Topic: F.01. Neuroethology

Support: Swiss National Science Foundation 31003A_127024
Swiss National Science Foundation 31003A_182638

Title: Birdsong plasticity requires sensory feedback exclusively for cumulative changes

Authors: *A. T. ZAI[1], A. E. STEPIEN[1], N. GIRET[2], R. H. R. HAHNLOSER[1];
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Abstract: One striking parallel between songbirds' vocal behaviors and human speech is the seeming requirement of vocal exploration for skillful mastery of vocal output. Similar to infants, songbirds learn their song through extensive vocal exploration in attempts to imitate a tutor song heard during a critical period early in life. Young birds undoubtedly need practice to imitate a vocal target, but can adult birds, similar to humans, make targeted changes to their song in a practice-free manner without intermittently singing? Growing evidence shows that vocal exploration is highly nonlinear and might not be necessary for all forms of learning. For

example, young birds are already surprisingly capable of adult-like singing (Kojima & Doupe, 2011) when appropriately stimulated; and a large portion of the daily vocal space covered by a juvenile is close to orthogonal to the overall song-learning direction (Kollmorgen et al. 2020). Furthermore, the requirement for singing was rooted in the belief that vocal plasticity requires auditory feedback. However, the importance of auditory feedback for song plasticity has recently been challenged, when we demonstrated selective song reinforcement in deaf adults using light as a reinforcing stimulus in substitution of sound (Zai et al. 2020). Thus, as much as auditory feedback is not essential for targeted adaptation of song, song maintenance may be possible without feedback too, casting doubt on the requirement of song practice for song plasticity. To explore these ideas, we tested whether adult zebra finches subjected to pitch reinforcement can instantaneously retrieve a previous song variant. First, we drive one syllable of their song away from baseline, then we withdraw reinforcement and subsequently mute or deafen the birds to deprive them of song experience. In this deprived state, birds barely change their songs and do not show the typical rapid recovery of baseline song, revealing a requirement of song practice and auditory feedback for full song recovery. We confirmed birds' failed song recovery in the group of birds from our previous study that were deafened before reinforcement and contingently reinforced using a light stimulus, which rules out that failure to fully recover baseline song is caused by the (muting or deafening) surgery. Nevertheless, when birds experienced target mismatch prior to deafening, they make small but non-random song changes in the direction of their baseline song when deaf, which provides support for short-range neural flexibility of vocal output. Thus, our work reveals vocal plasticity in songbirds independent of sensory experience but suggests a limit to internally guided vocal flexibility.

Disclosures: **A.T. Zai:** None. **A.E. Stepien:** None. **N. Giret:** None. **R.H.R. Hahnloser:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.13

Topic: F.01. Neuroethology

Support: Swiss National Science Foundation Projects 31003A_127024 and 31003A_182638
Swiss national Science Foundation NCCR Evolving Language, Agreement #51NF40_180888

Title: Behavioral signatures and remote detection of copulations in freely behaving zebra finches

Authors: *T. TOMKA[1,2], L. RÜTTIMANN[1,2], H. YAMAHACHI[1], H. HÖRSTER[1], R. H. R. HAHNLOSER[1,2], M. D. ROCHA[1];
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Abstract: Copulation is the sexual reproduction strategy of many animal species including mammals and birds. In the past, it has been challenging to systematically study copulations in birds because of their brevity and the need for work-intensive human visual inspection of video records. To alleviate the latter problem, we developed an automated copulation detection method using wearable frequency-modulated (FM) radio transmitters. We attached such battery-powered transmitters to the backs of zebra finches. We observed that during copulation, the carrier frequency of the female's transmitter is modulated by the physical mounting of the flying male. We detect hypothetical copulation attempts (HCAs) by the simultaneous occurrence of this frequency modulation on the female together with wing flaps by the male, as signaled by the vibration sensor on his back. We identify the (true) copulation attempts (CAs) by inspection of video recordings around HCAs, spending a total video-watching time that is reduced by several orders of magnitude compared to naive examination of the full data set. In addition, we evaluate the method's recall by watching a significant subset of the video recordings and find no false negative detections. By analyzing vocal and non-vocal behaviors around CAs, we identify behavioral signatures of copulations, such as female nest/whine calls. The identification of reliable copulation-predictive factors could help us gain a better understanding of courtship displays on one side and of behavioral signatures of solicitation on the other side, which may lead to the improvement of animal caretaking practices through timely interventions.

Disclosures: T. Tomka: None. **L. Rüttimann:** None. **H. Yamahachi:** None. **H. Hörster:** None. **R.H.R. Hahnloser:** None. **M.D. Rocha:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.14

Topic: F.01. Neuroethology

Support: NIH Grant R01-NS094667-06

Title: Joint neural control of social gestures and vocalizations in parrots

Authors: *H. TEOH[1], A. C. ROESER[1], R. CHEN[3], C. JONES[1], T. NWOKELEME[2], E. KIM[2], I. COHEN[2], J. H. GOLDBERG[1];
[1]Cornell Univ., [2]Cornell Univ., Ithaca, NY; [3]MIT, Cambridge, MA

Abstract: When Confucious said, "Tell me who are your friends, and I'll tell you who you are," he was noticing that how we behave and communicate is shaped by who we choose to hang out with every day. We constantly mimic the mannerisms and behaviors of friends and loved ones, yet the neural basis of how we imitate, and more importantly who we choose to imitate and why, is largely unknown. Parrots provide a powerful yet untapped model system for social learning. Like humans and some non-human primates, parrots live in a specific type of 'fission-fusion' social network in which selectively making and maintaining friendships is a key to fitness. Like

humans, parrots signal these affiliations to one another and to the larger group by imitating the vocal signatures of their carefully selected companions. Parrots also have a discrete neural circuit - possibly analogous to the songbird 'song system' - that is experimentally tractable for neural recording and manipulation. But because parrot and songbird song systems diverged over 50 million years ago and may have independently evolved, it remains unclear if some anatomical similarities are of functional significance. As a first step towards strengthening parrots as a model in systems neuroscience, we recorded neural activity in the vocal motor cortical output of the parrot 'song system' (nucleus AAC) simultaneously in pairs of bonded male budgerigars engaged in natural social interactions over months. We used directional microphones, cameras, and head-mounted accelerometers to analyze neural activity alongside vocalizations as well as gestures. In these first-ever neural recordings from behaving parrots, we find that the activity of AAC neurons is highly correlated with the production, but not the perception of both simple calls and more complex warble vocalizations. Surprisingly, the activity of AAC neurons could also be time-locked to the production of expressive gestures such as kissing, head-bobbing, and allogrooming, even during periods of silence. This joint vocal and gestural neural control, observed in human Broca's area but not in songbirds, means that parrots have a neural substrate for coordinated vocal-gestural communication. More generally, it suggests that what was thought to be a songbird-like 'song system' dedicated to vocalization may actually be a more general human-like system for social expression.

Disclosures: **H. Teoh:** None. **A.C. Roeser:** None. **R. Chen:** None. **C. Jones:** None. **T. Nwokeleme:** None. **E. Kim:** None. **I. Cohen:** None. **J.H. Goldberg:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.15

Topic: F.01. Neuroethology

Support: Simons Collaboration on the Global Brain

Title: Visual and tactile access are required for coordinated vocal interactions in the budgerigar

Authors: *Z. YANG, M. ELMALEH, M. A. LONG;
NYU Neurosci. Inst. and Dept. of Otolaryngology, New York Univ. Langone Med. Ctr., New York, NY

Abstract: Investigating how the brain enables interactive behaviors is central for understanding social communication. A particularly intriguing species in this regard is the budgerigar (or budgie), a small parrot that lives in large groups and is highly interactive. In addition to their rich social behavioral repertoire (e.g., coordinated head bobbing, grooming, beak-touching, etc.), budgies produce a range of vocalizations, many of which are learned through imitation. Behavioral studies in budgies have largely been restricted to single birds, and a detailed

characterization of their behavior in a social context remains elusive. Here we introduce a new arena consisting of two conjoined circular cages equipped with cameras and microphones that enable the quantitative tracking of a wide range of communicative behaviors. We use this platform to document the social and vocal interactions of budgies across a 24-hour period, and we analyze the behavioral states and vocalizations of each budgie with the aid of machine learning based video tracking and head-mounted piezoelectric microphones. We find that visual access is necessary for vocal coordination as opaque barriers separating the pair caused significantly greater interference of vocal behaviors compared to a clear separator. When the barrier between cages was removed and the budgies could freely physically engage, this vocal interference was abolished. Our paradigm thus enables the study of naturally interacting budgies and paves the way for dissecting neural mechanisms underlying interactions in this highly social species.

Disclosures: Z. Yang: None. **M. Elmaleh:** None. **M.A. Long:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.16

Topic: F.01. Neuroethology

Support: NIH Grant 7N026-00 02

Title: Relative weighting of syllable features during vocal learning in zebra finches

Authors: Y.-C. CHOU, *D. LIPKIND;
York College, CUNY, Jamaica, NY

Abstract: Birdsong learning hinges on an internal evaluation of the similarity between self-generated sounds and memorized target sounds. However, sounds are characterized by multiple distinct dimensions, such as amplitude envelope, pitch, entropy (noisiness), frequency modulation etc. What happens if a self-generated sound is similar to a target sound in one feature, but dissimilar in another? How would the bird learner “decide” which features are more important than others for similarity evaluation purposes? Humans face the same problem when learning the phonological system of a language - they weigh different features of target speech sounds in a manner that depends of the statistics of the language, i.e., the weighting is learned. Here we test how juvenile zebra finches weigh two different features of song syllables, mean pitch and duration, when learning to modify their song to match a new target song presented by an artificial tutor. We find that birds use idiosyncratic weighting strategies, with some learners giving higher weight to syllable duration - and consequently modifying syllable pitch to match a target syllable with the same duration and a different pitch, while other learners give a higher weight to syllable pitch - and consequently modify duration to match a target with the same pitch but a different duration. This flexibility in the weighting of different song dimensions raises the

question of whether the weighting itself is adapted to prioritize the most distinctive features of the bird's target song, as is thought to be the case in human speech learning.

Disclosures: Y. Chou: None. **D. Lipkind:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.17

Topic: F.01. Neuroethology

Support: NSF Grant EF-1822476
NSF Grant DGE1255832
NSF CRCNS EF1822478
Simons Collaboration on the Global Brain

Title: Classification of budgerigar vocalizations

Authors: *A. R. ZENDER[1], L. E. TAVARES[1], L. ACKERT-SMITH[2], Z. YANG[2], M. A. LONG[2], D. Z. JIN[1];
[1]Physics, Pennsylvania State Univ., University Park, PA; [2]Neurosci. institute, NYU Sch. of Med., New York, NY

Abstract: Parrots are capable of an astounding degree of vocal learning and rich social interactions, making them an important model system for understanding the neural basis of communication. However, the interactive vocal repertoire of the parrot remains poorly understood. Here we devise a method for automatic classification of the vocalizations of the budgerigar, a small Australian parrot. Pairs of adult male birds were recorded continuously, producing 4,000-20,000 vocal elements per day, including warble, contact call and alarm call, which motivates the need for automated labeling of these different vocalization types. The most complex of these vocalization types is warble, which consists of continuous vocal gestures lasting variable lengths of time. Additionally, acoustic features in warbles can resemble vocalizations in other categories, as well as cage noises due to birds' movement. These properties pose challenges to many schemes designed for birdsong syllable classification. Inspired by the fact that neurons in higher auditory areas respond to complex acoustic features, we devised a new approach that utilizes feature detectors to categorize the vocal elements into the three vocalization types and cage noises. To create a detector, we train a support vector machine (SVM) to distinguish a 30 ms snippet randomly selected from one type against vocal elements from other types and cage noises. Feature detectors for cage noises are similarly trained against all vocal elements. For each type, we typically train about 200 feature detectors. We find that this feature detector method performs remarkably well on budgerigar vocalizations, producing over 96% accuracy in identifying alarm call, contact call, and cage noise elements, and 90% accuracy in identifying warble elements compared to human annotated categorization.

Our approach therefore shows great potential for identifying budgerigar vocalization types automatically from continuous recordings over a long period of time.

Disclosures: **A.R. Zender:** None. **L.E. Tavares:** None. **L. Ackert-Smith:** None. **Z. Yang:** None. **M.A. Long:** None. **D.Z. Jin:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.18

Topic: F.01. Neuroethology

Support: UCLA Scheibel Undergraduate Scholarship

Title: Language meets technology: application of a machine learning algorithm to zebra finch birdsong suggests distinct sensorimotor learning strategies

Authors: *A. M. FERNANDEZ, S. DE FLORENCIO, L. FAMBLE, E. COOKE, S. A. WHITE;
UCLA, Los Angeles, CA

Abstract: The ability to produce and comprehend speech is a key aspect of human social and cognitive development. Yet, the neural learning strategies that infants use to develop and modify speech production are still being understood. To study sensorimotor vocal learning, we use the well-established model of zebra finches (*Taeniopygia guttata*). Male zebra finches acquire their courtship song via a sensorimotor learning phase that includes vocal imitation of a tutor bird, akin to human infants learning how to speak by listening to adults. Prior behavioral studies in our field have primarily used the program Song Analysis Pro (SAP) to assess song similarity and learning scores between finches. However, this program is limited by small sample sizes (10 - 20 birdsong motifs) and ability to compare only two data sets at a time. Therefore, in this project, we assessed whether a machine learning algorithm, initially developed by Keen et al. (2021) for birdcall differentiation, could offer a more robust method for assessing and visualizing song learning in the zebra finch model. The algorithm extracts roughly 200 acoustic features from birdsong motifs, sorts them using random decision tree forests, and uses non-linear dimensionality reduction approaches to cluster motifs based on similarity, which are then visualized via t-SNE. First, we analyzed whether the algorithm could handle large sample sizes of motifs. 576 tutor song motifs and 582 motifs from a pupil aged at day 65 were manually clipped and inputted into the algorithm (n = 1,158 total motifs). We found that the algorithm was effectively able to separate the tutor and pupil motifs into distinct clusters. Next, we assessed whether the algorithm could be utilized to compare motifs from different timepoints/datasets. We inputted 86 motifs from a pupil aged at 50 days, 100 motifs from the same pupil at 65 days old, and 100 motifs from the tutor. As expected, we found that the 65 day-old pupil song motifs clustered closer to tutor motifs compared to motifs at 50 days old. Surprisingly, we found that the

pupil day 65 motifs appeared to show two distinct cluster trajectories, an upper and lower arm, which both approach the tutor motif cluster. This suggests that the zebra finch may be utilizing distinct learning strategies to crystallize their birdsong. Future studies will aim to better characterize these learning pathways and their underlying neural bases. Ultimately, these findings indicate that this machine learning algorithm will benefit future neuroethological studies in the zebra finch by allowing for analysis of larger sample sizes of birdsong motifs and for visualization of learning trajectories throughout development.

Disclosures: A.M. Fernandez: None. **S. de Florencio:** None. **L. Famble:** None. **E. Cooke:** None. **S.A. White:** None.

Poster

724. Vocal/Social Communication - Avian II

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 724.19

Topic: E.04. Voluntary Movements

Support: U.S. NIH National Institute on Deafness and Other Communication (R01DC008358, R01DC018446)

Title: Single trial reconstruction of vocal sequences in freely moving songbirds

Authors: *L. STANWICKS[1], E. M. ARNEODO[2], B. H. THEILMAN[5], P. TOSTADO[3], V. GILJA[4], T. GENTNER[6];
[1]UCSD NGP, San Diego, CA; [2]Biocircuits Inst., UCSD, La Jolla, CA, CA; [3]Bioengineering, [4]Electrical and Computer Engin., UCSD, La Jolla, CA; [5]UC San Diego, La Jolla, CA; [6]Psycholgy, Univ. Of California San Diego Neurosciences Grad. Program, La Jolla, CA

Abstract: Skilled motor behavior likely involves coordinated activity across large populations of neurons, carrying representations of motor commands and planned behavioral goals tied to current motor states. Advances to in-vivo electrophysiological methods have brought about the ability to observe the dynamics of large, simultaneously active neuronal populations in awake behaving animals. The birdsong system provides an excellent opportunity to explore complex motor control networks in the context of a learned natural vocal communication signal with parallels to human speech. Here, we examine representation strategies for vocal motor output within the dynamics of large single-neuron populations in the pre-motor robust nucleus of the arcopallium (RA), which innervates brainstem motor neurons and is essential for the execution of song. We recorded simultaneous spiking activity from hundreds of single units in the RA of freely moving, singing male zebra finches, Taenopygia guttata, and European starlings, Sturnus vulgaris. We computed the explicit relationship between spiking activity in each neuron to the mean and covariance of acoustic features of the vocal output (song) using a maximum noise entropy (MNE) model. We then define a combinatorial code, as the maximized log likelihood of the spiking probabilities of the single neuron MNE models across the population activity. This

code can then be used to accurately reconstruct vocal output from the patterns of active and inactive neurons, codewords, at each moment in time. These results suggest kinematic information about ongoing complex vocal signals is carried in both single RA neurons and the collective pattern of activity across neurons.

Disclosures: L. Stanwicks: None. **E.M. Arneodo:** None. **B.H. Theilman:** None. **P. Tostado:** None. **V. Gilja:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuralink, Paradromics. F. Consulting Fees (e.g., advisory boards); Paradromics. **T. Gentner:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.01

Topic: F.03. Stress and the Brain

Support: The Cole Fund

Title: The effects of acute restraint stress in adolescent and adult rats on the brain and behavior

Authors: *M. K. CLEMENT, A. PHILIPPE, J. A. MCGAUGHY;
Univ. of New Hampshire, Durham, NH

Abstract: Stress exposure during adolescence exacerbates attentional impairments in many neuropsychiatric disorders, but the neurochemical bases of these impairments remain unresolved. Previous work from our lab has shown that healthy adolescent rats are more susceptible to distraction and more cognitively rigid than adult rats. These deficits have been linked to immaturity of monoaminergic systems in the cingulate cortex (ACC) and prelimbic cortex (PL), respectively. These same prefrontal sub-regions are critical to adapting to acute stress. We hypothesize that acute stress in combination with high levels of attentional demands overloads these systems to significantly impair cognition. To assess this, we exposed rats to one hour of restraint stress (stressed) or an equal amount of time in a clean cage with the restraint tube present (unstressed) prior to testing in a previously validated attentional set shifting task (ASST). The ASST measures distractibility, and the ability of subjects to form and shift an attentional set. Differences in cellular activity were measured in the ACC, PL, infralimbic cortex, orbitofrontal cortex, and locus coeruleus (LC) using c-Fos double-labeled for norepinephrine transporters. Stressed adolescent subjects showed an increase in cFos positive cells in the ACC, PL, and LC compared to stressed adults and age matched controls, which correlates with impairments in filtering salient distractions and cognitive rigidity. All stressed subjects showed an increased susceptibility to distraction compared to unstressed subjects which was exacerbated in adolescent subjects. Stress uniquely exacerbated this cognitive rigidity in adolescents. The current data suggests that acute stress results in specific impairments in executive function, and that adolescent subjects are more susceptible to this stress than adult subjects. We hypothesize that

acute stress and the cognitive demands of the ASST require overlapping neural circuits that become overloaded. This overlap produces a demand for cortical norepinephrine beyond what can be produced by adolescents, thus exacerbating cognitive impairments in adolescent subjects.

Disclosures: M.K. Clement: None. **A. Philippe:** None. **J.A. McGaughy:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.02

Topic: F.03. Stress and the Brain

Support: AA017447
AA007456
AA027700
AA021491
AA006420
AA013498
The Pearson Center for Alcoholism and Addiction Research

Title: Intermittent social isolation during adolescence increases ethanol preference in juvenile males and females and alters irritability-like behaviors and synaptic transmission in the CeA in adult males.

Authors: *V. VOZELLA[1], B. CRUZ[1], P. C. BIANCHI[1,2], M. BAJO[1], R. VLKOLINSKY[1], R. CICCOCIOPPO[3], E. P. ZORRILLA[1], M. ROBERTO[1];
[1]The Scripps Res. Inst., La Jolla, CA; [2]Univ. Federal de São Paulo, São Paulo, Brazil; [3]Univ. of Camerino, Camerino, Italy

Abstract: Chronic stress during adolescence increases the susceptibility to many neuropsychiatric diseases in adulthood, including anxiety-like and alcohol drinking behaviors. Social isolation is a particularly profound stressor with increasing human relevance, especially during the COVID-19 pandemic, when millions of adolescents have faced prolonged periods of isolation. However, preclinical rodent models of adolescent social stress have produced mixed results that are often sex, species and strain-dependent. Here we examined the effect of intermittent social isolation on alcohol intake and preference during adolescence (PND28-56) and the long-term effects of social isolation and alcohol drinking on anxiety, irritability, and synaptic transmission in both male and female Wistar rats. Additionally, we studied genetically selected Marchigian Sardinian alcohol-preferring (msP) rats to compare the effects of social isolation in a rat strain of increased alcohol preference vulnerability and high sensitivity to anxiety. We developed and utilized a new model of social isolation and alcohol exposure whereby adolescent (PND28) male and female rats were intermittently socially isolated for 24h prior to 2-bottle choice (2BC) access to ethanol (20% *v/v*, 2h/session, Tues/Thur/Sat) vs. water,

for 4 weeks. Two weeks later (young adults), all rats were tested for anxiety in the novelty induced hypophagia test and irritability-like behavior in the bottle brush test, and a subset was used to record spontaneous inhibitory GABAergic postsynaptic currents (sIPSCs) in the central nucleus of the amygdala (CeA). Social isolation increased alcohol preference in both male and female Wistars when compared to the group-housed controls, starting from week 1 and throughout adolescence. All msP rats displayed escalation of drinking during week 1 and 2 and the effect of the isolation was observed starting from week 3 in males only. No isolation effects were observed in female msPs throughout the 4 weeks. Social isolation and alcohol drinking during adolescence increased aggressive-like behavior in male adult Wistar rats, but not females, and did not alter anxiety measures. Baseline frequency of sIPSCs were decreased in socially isolated male Wistar and msP adult rats vs. group-housed, while rise times, amplitudes, and decay times remained unchanged, indicating reduced basal presynaptic GABA release in the CeA. Together, these findings suggest that an intermittent social isolation produces increased alcohol preference in Wistar rats of both sexes and in male msPs, as well as synaptic changes in the CeA.

Disclosures: **V. Vozella:** None. **B. Cruz:** None. **P.C. Bianchi:** None. **M. Bajo:** None. **R. Vlkolinsky:** None. **R. Ciccocioppo:** None. **E.P. Zorrilla:** None. **M. Roberto:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.03

Topic: F.03. Stress and the Brain

Support: Adelante Summer Research Program
Graduate Equity Fellowship Program
Graduate Student Research Funding

Title: Social Isolation impacts depression, anxiety, and drug vulnerability in adolescent mice

Authors: *G. ALDANA[1], P. REZAIE BOROON[2], J. ECHEVERRIA[3], A. VASQUEZ[1], S. BATES[2];
[2]Psychology, [1]California State University, Chico, Chico, CA; [3]California State Univeristy, Chico, Chico, CA

Abstract: Social isolation due to the COVID-19 pandemic has precipitated many stress-related mental illnesses, particularly in adolescents. Social isolation can lead to increased levels of depression and anxiety, as well as increase the risk of substance abuse. It is important to explore how this particularly relevant stressor can affect adolescent brain development. Moreover, due to rising rates of prescribed antidepressants, it is important to analyze how these medications impact adolescents. The purpose of this study is to examine whether mice that undergo a prolonged period of isolation during adolescence demonstrate differences in depression- and

anxiety-like behaviors and cocaine sensitization. To examine the effects of isolation and whether antidepressants influence the previously stated behaviors, mice are weaned and divided into four groups: isolated with a concentrated mixture of fluoxetine and water, isolated with water, socially housed with a concentrated mixture of fluoxetine and water, and socially housed with water. After 28 days of isolation, depression-like behaviors are assessed in the forced swim test, anxiety-like behaviors were examined in the elevated plus maze and open field test, and social preference was examined in a social interaction test. Preliminary data demonstrate socially housed mice showed decreased depression- and anxiety-like behaviors when compared to isolated mice suggesting that social support has a stress-reducing effect. The results of this study will allow us to further understand the effect of adolescent social isolation and potential methods to ameliorate these effects, including the use of antidepressants like fluoxetine. This will be crucial for the development of new treatment strategies for adolescent stress.

Disclosures: G. Aldana: None. **P. Rezaie Boroon:** None. **J. Echeverria:** None. **A. Vasquez:** None. **S. Bates:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.04

Topic: F.03. Stress and the Brain

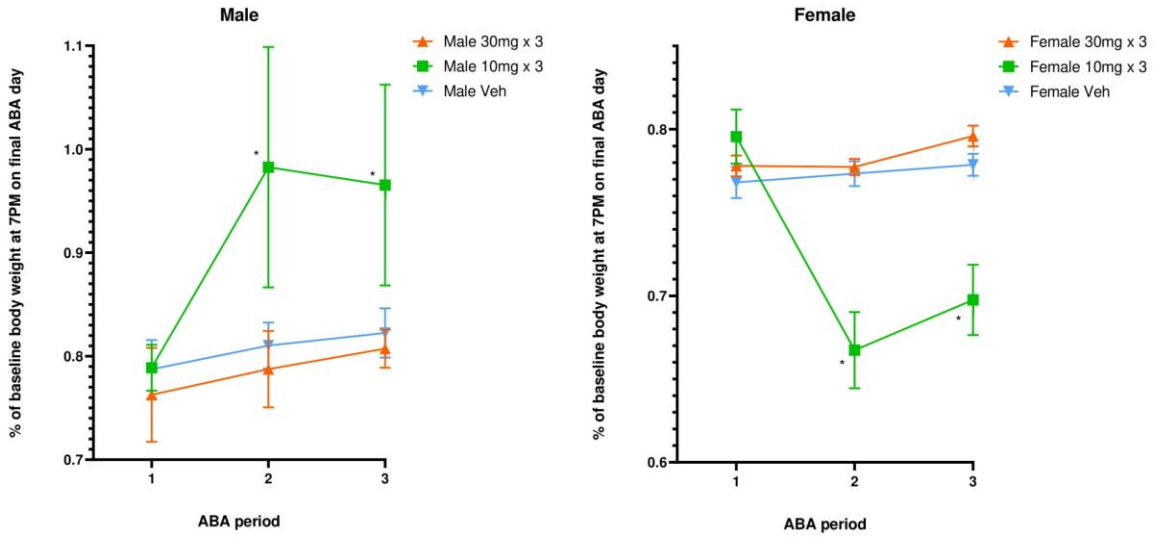
Support: Vulnerable Brain Project Grant
NIH Grant 2R25NS080686
NSF Grant DBI-1950649
NIH Grant P30 EY13079
Dean's Undergraduate Research Fund Grant

Title: Multiple ketamine injections during a second induction of activity-based anorexia in late adolescence exacerbate female weight loss and reduce male weight loss both acutely and two weeks later

Authors: *S. GOODWIN-GROEN[1], Y. DONG[2], C. J. AOKI[1];
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]Biobehavior Sci., Columbia Univ., New York, NY

Abstract: Anorexia Nervosa (AN) is the psychiatric condition with the highest mortality and relapse rates outside of opioid use disorder, yet there are no accepted drug therapies. AN also emerges most often during adolescence, alongside developmental changes in neurochemistry and brain pathways. Previous work showed that ketamine delivered in mid-adolescence ameliorates weight loss and hyperactivity in activity-based anorexia (ABA), a mouse model of AN, immediately and through its 2nd ABA exposure 14 days later (https://doi.org/10.1002/eat.22937). However, when ketamine was delivered for the first time

two weeks later, during the 2nd ABA induction in late adolescence, it exacerbated weight loss (https://doi.org/10.1007/978-1-0716-0924-8_15). Human ketamine treatment in adulthood for depression and AN relapse involves repeat dosing to amplify plasticity, so we delivered three doses of ketamine to ABA mice in late adolescence, during the 2nd ABA induction, at either 30mg/kg or 10mg/kg. Mice (n=61, 25 M, 36 F) underwent three periods of ABA induction/food restriction beginning in mid-adolescence, spaced to allow body weight recovery, with ketamine administered during the 2nd ABA (late adolescence). Body weights were recorded before each of the three ABA induction periods and just before (7 pm) and just after each ABA day's 2-hours of food access. All groups behaved similarly during the 1st ABA, but in the 2nd ABA, 10mg/kgx3 females lost more body weight (p=0.00004, n=20, compared to the female vehicle group), while 10mg/kgx3 males lost so much less (p=0.001, n=16) that multiple animals achieved a net weight gain despite food restriction. This effect was stable for two weeks as shown by similar results during the 3rd ABA (female p=0.0003, male p=0.001). Ketamine's effects are thus dose-, sex-, and age-dependent. We will investigate the relationship of this dependency to synaptic plasticity through electron microscopic immunocytochemistry. Running activity and EPM data were also recorded and these data will be compared in another poster (Yiru Dong et. al.).



Disclosures: **S. Goodwin-Groen:** None. **Y. Dong:** None. **C.J. Aoki:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.05

Topic: F.03. Stress and the Brain

Support: MOST 110-2320-B-002-030-MY3

Title: Sleep deprivation induces maladaptation in the dopamine system of adolescent mice through escalating corticotrophin-releasing factor signaling

Authors: L.-H. TUAN[1], ***J.-W. YEH**[2], J.-H. LEE[3], L.-J. LEE[4];
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Abstract: Sleep disruption is highly associated with the pathogenesis and progression of a wild range of psychiatric disorders. Furthermore, appreciable evidence shows that experimental sleep deprivation (SD) on humans and rodents evokes anomalies in the dopaminergic (DA) signaling, which are also implicated in the development of psychiatric illnesses such as schizophrenia or substance abuse. Since adolescence is a vital period for the maturation of the DA system as well as the occurrence of mental disorders, the present studies aimed to investigate the impacts of SD on the adolescent DA system. We found that 72 h SD elicited a hyperdopaminergic status, with increased sensitivity to the novel environment and Amphetamine (Amph) challenge. Also, altered neuronal activity and expression of striatal DA receptors were noticed in the SD mice. The abnormal neuronal activity was putatively provoked by an enhanced corticotrophin-releasing factor (CRF) signaling and sensitivity during the SD period. Together, our findings demonstrated that the consequences of SD in adolescents bear prominent similarities with many psychiatric disorders, with aberrant neuroendocrine and DA functions. Therefore, the current study highlighted sleep loss as a risk factor for the aberration and neuropathology of psychiatric disorders related to DA signaling.

Disclosures: L. Tuan: None. **J. Yeh:** None. **J. Lee:** None. **L. Lee:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.06

Topic: F.03. Stress and the Brain

Support: College of Arts and Sciences, Quinnipiac University
Psychology Department, Quinnipiac University
NARSAD
QUIP-RS, Quinnipiac University

Title: Maternal separation and the protective effects of minocycline on anxiety-like behavior, inflammation, microglia activation and receptor expression in stress sensitive regions of male and female rodents.

Authors: J. MIRRA, A. PACRIN, T. ZARIN, G. BURMAN, G. FORLENZA, L. O'CONNOR, S. KURPIEWSKI, K. CASTELL, H. JACK, J. HAIGHT, M. MIRRIONE, ***A. BETZ**;
Quinnipiac Univ., Hamden, CT

Abstract: Early life experiences and chronic stress have pronounced effects on brain function and behavior. Maternal separation in rodents is a widely accepted animal model used to induce early-life stress. This model has reliably demonstrated an increased risk of depressive-like behavior later in life. Clinically, adversity in early life increases the risk for the development of psychiatric disorders, such as Major Depressive Disorder (MDD), in adulthood. Given that patients with MDD display alterations in hippocampal and other stress-sensitive circuits, we hypothesized that early life adversity would be characterized by increased protein expression of inflammatory markers, orexin receptor density, morphological changes in microglia, and cellular matrix activity in regions such as prefrontal cortex, hippocampus, and paraventricular nucleus of the thalamus. Further, we proposed these effects to be rescued by the antibiotic, minocycline. Sprague Dawley male and female pups were separated from PND 2 to PND 14 for three hours a day and a control condition of non-separated pups was maintained. First, we examined behavioral tasks during adolescence and found that separated offspring spent more time in closed arms of an elevated plus-maze. Second, maternal separation and second stress reliably upregulated pro-inflammatory markers such as heightened nuclear factor kappa B (NF-κB). These effects were reversed with minocycline exposure during adolescence prior to second stress. Overall, our results may provide insight into the molecular mechanisms responsible for inflammation and cellular reorganization in cortico-limbic and cortico-thalamic circuits related to MDD from early life adversity and stress exposure

Disclosures: **J. Mirra:** None. **A. Pacrin:** None. **T. Zarin:** None. **G. Burman:** None. **G. Forlenza:** None. **L. O'Connor:** None. **S. Kurpiewski:** None. **K. Castell:** None. **H. Jack:** None. **J. Haight:** None. **M. Mirrione:** None. **A. Betz:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.07

Topic: F.03. Stress and the Brain

Support: 1T32GM144896-01

Title: The Effects of Adolescent Traumatic Events on Adulthood Cocaine Use Disorder

Authors: *J. PEREZ-TORRES, R. MORALES-SILVA, Y. PÉREZ-PÉREZ, J. ALVARADO-TORRES, G. RODRIGUEZ-TORRES, H. CARDONA-RODRIGUEZ, M. SEPULVEDA-ORENGO;
Ponce Hlth. Univ., Ponce, Puerto Rico

Abstract: Adolescent traumatic stress, such as being subjected to violence, and physical or sexual assault, has emerged as a substantial risk factor for substance use disorder (SUD) development. Neurobiological alterations that mediate this comorbidity, on the other hand, are poorly known. Preclinical studies suggest that stressful experiences as an adolescent have long-

term consequences on stress, anxiety, and the efficacy of synaptic transmission in adulthood. To identify groups at risk of developing SUD, researchers need first to elucidate the neurobiological mechanisms behind this comorbidity. We hypothesize that adolescent traumatic events will lead to higher cocaine-seeking behavior. To test this, the team will use the fear-conditioning paradigm as a traumatic event in adolescents (P30) Sprague Dawley rats. After 30 days, when the rats reached adulthood (P60), they were exposed to 12 days of short-access (2hr) cocaine self-administration, 15 days of extinction, and reinstatement sessions. Contrary to our hypothesis, the adolescent stressed group results showed no difference in cocaine consumption; however, the cocaine-primed reinstatement significantly decreased compared to the non-stress group. Therefore, we tested whether our previous results are due to cocaine sensitivity, using a dose-response paradigm (0.025, 0.05, 0.10, 0.20, 0.40 and 0.60mg/kg). However, our dose-response paradigm results showed no difference between the stress and non-stress group. These results suggest that a decrease in cocaine-induced seeking behavior is due to neurophysiological changes that occurred during the 15 days of the cocaine withdrawal and not in the acquisition phase. Hence, we will evaluate different withdrawal timepoint. Our results are similar to other studies in our lab. Next, we will be performing these experiments with female rats to determine whether female rats show similar results as male rats.

Disclosures: **J. Perez-Torres:** None. **R. Morales-Silva:** None. **Y. Pérez-Pérez:** None. **J. Alvarado-Torres:** None. **G. Rodriguez-Torres:** None. **H. Cardona-Rodriguez:** None. **M. Sepulveda-Orengo:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.08

Topic: F.03. Stress and the Brain

Support: Council of Scientific and Industrial Research, India (27(0369)/20/EMR-II)

Title: Early Life Stress and Nicotine Addiction during Adolescence

Authors: *S. SHARMA, Y. DORESWAMY, L. T RAO;
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Abstract: Previous studies from our lab have shown that repeated exposure to adverse experience in early life can increase the curiosity and the risk-taking behaviour during the adolescence and it is also shown to increase the risk for anxiety disorders later in life. Adolescent children, having elevated curiosity, may have a tendency to exhibit increased exploration, novelty-seeking, high risk-taking behaviour and substance abuse. Due to vigorous search for sensation and elevated curiosity adolescents might take the risk of indulging in activities that might have long-lasting impact in later stages of life like the use of tobacco, alcohol or drugs.

Nicotine addiction is a complex process that begins with self-administration. Hence nicotine self-administration studies have been extensively studied in rats and mice. However, research is very sparse on the effect of maternal separation on nicotine addiction and its rewarding effects.In the present study, ELS was induced by subjecting rat pups to maternal separation and isolation stress (MS) during stress hyporesponsive period (SHRP) from postnatal days (PND) 4 - PND 13 in the Sprague Dawley rats during light phase at 10 AM - 4.00 PM. The anxiety was assessed using the Light-Dark test and curiosity was assessed using object retrieval task, an indigenously designed paradigm. Further Nicotine preference test was applied by voluntary oral self-administration during adolescence age from PND 35 - PND 55. ELS-induced changes in the stress were confirmed by estimating the corticosterone level using the ELISA kit method.
Results showed that MS stress has increased anxiety. In the object retrieval task, MS rats exhibited heightened curiosity. In the Nicotine preference task, MS rats consumed more volume of nicotine over water. They preferred higher concentration of nicotine over the low concentration of nicotine, showing tendency for nicotine addiction. Finally, we found an association between heightened anxiety and curiosity. There was a positive correlation between anxiety and nicotine addiction in the MS rats. Higher plasma corticosterone was found in the MS rats, which can be correlated with anxiety and nicotine addiction. These findings, together, depict anxiety-induced nicotine addiction and corticosterone at adolescence age may be affiliated to an MS stress at stress hyporesponsive period.

Disclosures: S. Sharma: None. **Y. Doreswamy:** None. **L. T Rao:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.09

Topic: F.03. Stress and the Brain

Support: 16/12/2018(ii) EU-V

Title: Early life stress and risk taking behaviour in adolescence

Authors: *A. CHOWDHURY, S. RAO, L. T. RAO;
NIMHANS, Natl. institute of mental health and neuroscience (NIMHANS), Bangalore, India

Abstract: The objective of this work is to study the effect of early-life stress on adolescent behaviour in rats. Early life stress is the exposure of stress during critical window of development. Studies on rodent model have shown it can impair affective functions and cognitive functions. Evidences show that adolescent period is a time when an individual’s body and behaviour undergo a dramatic change. There is an increased novelty and sensation seeking behaviour, emotional instability, and impulsivity which eventually leads to an increased willingness to take risk. However, it is not known whether early life stress has any impact on such risk-taking behaviour during adolescent stage. Accordingly, the aim of the present study is

to assess whether stress during early stage of life has any impact on risk-taking behaviour at adolescence. Maternal separation and isolation stress has been done to induce stress in the rats during early life. In this procedure pups were separated from the mother and kept individually in separate cages daily during stress hyporesponsive period. There were two groups namely- normal control (NC) and maternal separation and isolation (MS) group. Both males and females were used in the study. Anxiety-like behaviour was assessed using the Light-Dark Test during late adolescence. A novel paradigm has been designed in our laboratory to evaluate the risk-taking behaviour. Behavioural paradigm was performed from PND 46-52. Risk-taking behaviour was significantly more in the MS group compared to NC and this effect was prominent in both males and females. Number of risk-takers were also more in MS group than NC group. Risk-assessment was reduced significantly in MS males compared to NC males; Risk assessment was less in MS females also compared to NC females but not significantly. Risk-index was significantly lower in MS males than NC males; risk-index was less in MS females compared to NC females but was not significant. Learning behaviour in adolescence was not affected by MS stress. Anxiety-like behaviour was exhibited by MS rats but not significantly.
Due to vigorous pursuit for sensation and elevated curiosity, adolescents might take the risk of indulging in activities that might have long-lasting impact in later stages of life like the use of tobacco, alcohol or drugs which in turn will lead to physical and mental health deterioration. In order to maintain an optimal risk-taking behaviour, the factors modifying this behaviour in adolescent age must be identified and our study enlists early-life stress as one of the factors.

Disclosures: A. Chowdhury: None. **S. Rao:** None. **L.T. Rao:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.10

Topic: F.03. Stress and the Brain

Support: NIH Grant K01MH116325
NIH Grant R01MH107479
NIH Grant R01MH107479-S1

Title: Childhood Threat Exposure Disrupts Associations between Cortisol Output in Response to Stress and Adaptive Neural Processes during Cognitive Reappraisal in Adolescent Girls

Authors: *S. MARTIN[1], M. GRUHN[2], A. PELLETIER-BALDELLI[2], M. SHERIDAN[2], K. PATEL[3], M. GILETTA[4], P. HASTINGS[5], M. K. NOCK[6], K. D. RUDOLPH[7], G. M. SLAVICH[8], M. J. PRINSTEIN[2], A. B. MILLER[2,9];
[1]UNC Chapel Hill Psychology and Neurosci. Dept, Univ. of North Carolina at Chapel Hill, CHAPEL HILL, NC; [2]Psychology and Neurosci., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Old Dominion Univ., Norfolk, VA; [4]Ghent Univ., Ghent, Belgium; [5]Univ. of California at Davis, Davis, CA; [6]Harvard Univ., Cambridge, MA; [7]Univ. of Illinois Urbana-

Champaign, Champaign, IL; [8]Univ. of California Los Angeles, Los Angeles, CA; [9]Res. Triangle Inst., Raleigh, NC

Abstract: Cortisol release in response to stress is associated with adaptive changes in brain activation during emotion regulation (ER) tasks (Langer et al., 2021), as reflected in greater activation in inhibitory regions (i.e., dlPFC) and decreased activation in regions implicated in emotion reactivity (i.e., amygdala) (Jenstal et al., 2019). There is evidence that childhood threat exposure alters ER processes in adolescents (Weissman et al., 2020); yet few studies have examined the extent to which threat also affects associations between cortisol output and neural processes underlying ER during adolescence, a period of substantial neurobiological change. We hypothesize that cortisol output will predict neural processes underlying ER in female adolescents, but this association will be moderated by childhood threat exposure. Specifically, high cortisol output will be more strongly associated with increased activation in inhibitory regions (i.e., dlPFC, vlPFC, vmPFC, ACC) and decreased activation in emotion-related regions (i.e., amygdala, insula) during an ER fMRI task in adolescents with low threat exposure. Participants were 120 females ages 9-17 (*M*=12.29) recruited into a larger longitudinal study. Salivary cortisol was assayed at baseline, pre- and 20-, 30-, and 40-min post-administrating the Trier Social Stress Test (Kirschbaum & Hellhammer, 1993). At follow-up, participants completed an fMRI emotion reactivity and regulation task and instructed to cognitively reappraise or passively view negative and neutral stimuli (Ochsner_et_al, 2004). Region of interest (ROI) analyses focused on activation during cognitive reappraisal relative to passive viewing of negative images. *A priori* ROIs were extracted using FSL-based atlases; we selected regions demonstrating associations with cortisol response to stress and ER in the literature (dlPFC, vlPFC, vmPFC, ACC, amygdala, and insula). Cortisol area under the curve with respect to ground (AUCg) was calculated, with higher values representing greater total cortisol output across all cortisol measures. Regression analyses revealed that the interaction between cortisol (AUCg) and threat predicted ACC activation, such that those with higher cortisol predicted greater ACC activation only among adolescents with low, but not high, threat exposure during ER (*p*=.03). Results suggest that although high cortisol (AUCg) in response to stress may be associated with adaptive emotion-related learning, threat exposure during childhood may disrupt this relationship. This extends existing literature on how threat disrupts biological processes relative to real-world functioning.

Disclosures: S. Martin: None. **M. Gruhn:** None. **A. Pelletier-Baldelli:** None. **M. Sheridan:** None. **K. Patel:** None. **M. Giletta:** None. **P. Hastings:** None. **M.K. Nock:** None. **K.D. Rudolph:** None. **G.M. Slavich:** None. **M.J. Prinstein:** None. **A.B. Miller:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.11

Topic: F.03. Stress and the Brain

Support: ES005605
ES013661
ES014901
ES031098

Title: Polychlorinated biphenyl (PCB) 52 but not its metabolites were detected in adolescent rat brains after acute nose-only exposure

Authors: *A. BULLERT[1,2], X. LI[2], H. WANG[2], A. ADAMCAKOVA-DODD[2], P. S. THORNE[1,2,3], H.-J. LEHMLER[1,2,3];
[1]Interdisciplinary Grad. Program in Neurosci., [2]Occup. and Envrn. Hlth., [3]Interdisciplinary Grad. Program in Human Toxicology, Univ. of Iowa, Iowa City, IA

Abstract: The ubiquitous presence of polychlorinated biphenyls (PCBs) in the environment can lead to adverse health effects in humans, including neurodevelopmental deficits. Inhalation of PCB-contaminated indoor air in older school buildings is increasingly recognized as a route of PCB exposure. However, the levels of PCBs and their metabolites in adolescent brain tissue following inhalation exposure have not been characterized. This study determined the levels of PCB 52, a PCB congener frequently detected in the indoor air of schools, and its metabolites in the adolescent rat brain following acute inhalation exposure to PCB 52. Sprague-Dawley rats (50-58 days of age, 210 ± 27 g; Charles River, Wilmington, MA) were randomly assigned to two exposure groups and exposed via 4 h inhalation to PCB 52 using a nose-only exposure system. Sham animals were exposed in parallel to filtered lab air only. At the end of the exposures, animals were perfused with saline before tissue collection. To characterize PCB 52 exposures, PCB 52 vapor in the exposure air was collected with XAD sorbent, extracted, and quantified by gas chromatography-tandem mass spectrometry (GC-MS/MS) with Multiple Reaction Monitoring (MRM) mode. Rats were exposed to 0.001 ± 0.001, 11 ± 2, and 18 ± 2 ug/kg/bw sham, low, and high exposures, respectively. The levels of PCB 52 and its hydroxylated metabolites were determined in the brain, visceral adipose, liver, serum, lung, feces, and cecum using GC-MS/MS. PCB 52 was detected at different levels in a general trend: lung > liver > adipose > brain > feces~cecum~serum. The primary hydroxylated metabolite, 4-OH-PCB 52, was detected in tissues with a rank order of feces > cecum > serum > lung > liver. An additional unidentified metabolite, which was tentatively assigned as monohydroxylated PCB 52 based on the MRM transition, was detected in feces > cecum > lung > liver. Neither metabolites of PCB 52 were detected in the brain of adolescent animals after acute nose-only exposure. The characterization of the levels of PCB 52 and its metabolites in target tissues lays the groundwork for future studies of the adverse effects of inhaled PCB 52 on the developing adolescent brain.

Disclosures: A. Bullert: None. **X. Li:** None. **H. Wang:** None. **A. Adamcakova-Dodd:** None. **P.S. Thorne:** None. **H. Lehmler:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.12

Topic: F.03. Stress and the Brain

Support: Adelante Research Summer Program
Graduate Equity Fellowship Program

Title: Binge-eating alters anxiety-like behaviors in adolescent female mice

Authors: *P. REZAIE BOROON, G. C. ALDANA, F. ROMAN, S. BATES;
Psychology, California State University, Chico, Chico, CA

Abstract: Despite the increase in adolescents suffering from binge eating disorder, this phenomenon is still widely unexplored in scientific research. Furthermore, females are more likely to develop binge-eating disorder than males. As adolescent brains are not fully developed, commonly observed behaviors such as problematic eating may play a harmful role in the way their brain properly processes reward. This is especially important considering such alterations can render the adolescent brain more vulnerable to anxiety and depression-like behaviors. This study uses a novel model of binge-like eating behavior in adolescent mice to identify the ramifications of binge-eating disorder. Female adolescent C57BL/6J mice were exposed to standard chow or high-fat diet (HFD) for 2-h a day, three days a week (PND 21-51), for four weeks. Twenty-four hours later, cocaine sensitivity and reward were assessed. We also examined anxiety-like behavior using elevated plus maze (EPM), and depression-like behavior using the forced swim test (FST) and splash test. Animals exposed to HFD demonstrated greater food consumption, indicative of binge eating, during the four-week intermittent cycle compared to the standard chow group. The HFD group spent more time in the open arms compared to mice given standard chow during EPM. While HFD mice were slightly less immobile in FST compared to standard chow mice, HFD mice also groomed themselves noticeably less than standard chow mice during the splash test, suggesting an increase in depression-like behavior. Lastly, both groups developed preference for the compartment paired with cocaine. Our research findings suggest that binge eating in adolescence may contribute to increased anxiety- and depression-like behaviors in this age group. Future studies should explore the neural mechanisms underlying these behaviors.

Disclosures: P. Rezaie Boroon: None. **G.C. Aldana:** None. **F. Roman:** None. **S. Bates:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.13

Topic: F.03. Stress and the Brain

Support: Vulnerable Brian Project Grant
NIH Grant 2R25NS080686

NSF Grant DBI-1950649
NIH Grant P30 EY13079

Title: Influence of adolescent experience of food restriction alone, or exercise alone, or the combination of the two on adult voluntary exercising.

Authors: *I. PAT-OSAGIE[1], C. J. AOKI[2];
[2]Ctr. for Neural Sci., [1]New York Univ., New York, NY

Abstract: Anorexia Nervosa (AN) is a psychiatric condition that is characterized by four components; a distorted self-image, voluntary food restriction, compulsive exercising, and severe weight loss. The animal model of AN, known as activity based anorexia (ABA) is used to study the neurobiological basis of this illness. The cornerstone of ABA is voluntary food restriction and the excessive exercising aspect of the illness. The driving question is: how is it that these animals (human or rodents), even though they are consuming insufficient caloric intake, are able to exercise excessively, some even to the point of death? This is what makes AN the most deadly of the psychiatric illnesses, even beating out depression. We hypothesized that there are two key components to ABA vulnerability: age and exposure to stress during adolescence. We examined three types of adolescent rearing: one was to experience food restricted (FR), with no wheel access (N=11), then exposed to a wheel for the first time as adults (FR ◊ EX). The second type had unlimited access to the wheel and were also FR as adolescents, this being the condition that induces ABA. These ABA animals are now being re-exposed to a wheel as adults, 2-3 months later, at ages P138 and P102, without food restriction (ABA ◊ EX) to determine whether FR+EX during adolescence has greater impact on wheel running as adults, compared to individuals with FR alone or EX alone as adolescents. The behavioral data gathered so far demonstrates two important ABA factors: age and individual differences. ABA Cohort 1 experienced ABA induction twice, with the first exposure being P44-47 and the second at P58/59-P62/63. Cohort 2 experienced ABA only once at an age range equal to that of Cohort 1's first: P44-P47. Cohort 1 demonstrated varying levels of daily wheel running, ranging from 6k to nearly 46k wheel rotations during the first ABA. Cohort 2's range of wheel running during the first ABA was 9k to 58k per day, comparable to that of Cohort 1's first ABA. Cohort 1's wheel activity during the second ABA was modestly greater (ranging from 12k to nearly 51k wheel rotations. Cohort 2 had the highest while Cohort 1 had the lowest wheel counts. Thus, while some individuals built a more resilient nature to cope with external (FR) or internal (hunger or distorted self-image) stressors by suppressing wheel running, others became even more vulnerable and ran more. We compared wheel running in adulthood across the first four days between our FR ◊EX and our ABA◊ EX and found no significant difference in their wheel running (mean+/-SEM =15757.18 +/- 2424.58 for FR◊ EX; 17116.46 +/- 2631.90 for ABA Ch1&2). However we are still gathering data for subsequent days.

Disclosures: I. Pat-Osagie: None. **C.J. Aoki:** None.

Poster

725. Stress and the Brain: Adolescence

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 725.14

Topic: F.04. Neuroimmunology

Support: Herman Dana Foundation

Title: Prospective cohort study of neuroendocrine reactivity and prognostic outcome among adolescents with restrictive Anorexia Nervosa

Authors: *T. GOLTSER[1,2], R. GIESSER[2], A. SHALEV[2], R. MASARWA[2], A. MELTZER[2], D. PEVZNER[1], L. CANETTI[1], E. GALILI-WEISSTUB[2], R. SEGMAN[1];
[1]Mol. Psychiatry Lab. - Dept. of Ps, Mol. Psychiatry Lab. - Dept. of Ps, Jerusalem, Israel; [2]1The Herman-Danna Div. of Pediatric Psychiatry, Dept. of Psychiatry, Hadassah - Hebrew Univ. Med. Center; Jerusalem Israel, Jerusalem, Israel

Abstract: Background: The aim of the current study is to prospectively characterize neuroendocrinereactivity among adolescent AN patients and correlate them with long term prognosticoutcomes.**Methods:** AN patients referred to the ambulatory clinic, day care facility and in patient unit ofthe Herman Dana Child Psychiatry Center were assessed using a structured clinicalinterview with repeated psychological and physical assessments. Hormonal assays weresampled at baseline and following treatment, correlated with treatment response measures,and compared with healthy age matched adolescents.**Results:** AN patients demonstrate a significant prospective increase in BMI compared withbaseline, and improvement in pathological eating attitudes at follow up. Findings replicatepreviously described hypercortisolism, partly adaptive to chronic malnourishment and that beinformative regarding long term weight restoration. Additional hormonal reactivity includingDHEA-S, and testosterone has been similarly analyzed and will be described.**Significance:** Reprograming of neuroendocrine function may be in part be adaptive and maybe informative regarding long term weight restoration.

Disclosures: T. Goltser: None. **R. Giesser:** None. **A. Shalev:** None. **R. Masarwa:** None. **A. Meltzer:** None. **D. Pevzner:** None. **L. Canetti:** None. **E. Galili-Weisstub:** None. **R. Segman:** None.

Poster

726. Stress, Cognition, and Behavioral Regulation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 726.01

Topic: F.03. Stress and the Brain

Support: U01DA041022
U01DA041028

U01DA041048
U01DA041089
U01DA041106
U01DA041117
U01DA041120

Title: Do protective environmental factors moderate the impact of stressful negative life events on cognition?

Authors: *E. WOLFGRAM[1], A. SANDERS[1], D. BARCH[1,2];
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Abstract: Exposure to negative life events (NLEs) in childhood and adolescence is associated with a wide range of cognitive dysfunctions, including deficits in executive abilities. Protective factors associated with resilience, however, are believed to positively impact the ways in which people succeed despite significant risk factors. Resilience is defined as a system's ability to overcome threats to the system function, survival, and development. Evidence suggests that there are common protective factors which can promote resilience to adversity. For youth, these factors include their caregiver's behavior, their school environment, and their friendships. Using data from the Adolescent Brain Cognitive Development Study (ABCD), we examined how protective social factors and protective parenting behaviors impact the relations of NLEs to cognition (n=10,087; 47.7% female; 21 sites). We hypothesized that NLEs endorsed at Time 1 (i.e., ages 10-11 years) would be negatively associated with performance on a range of cognitive tasks at Time 2 (i.e., 1-year follow-up at ages 11-12 years). Furthermore, we hypothesized that 1) protective social factors (i.e., peer and school relationships) and 2) protective parenting behaviors (i.e., acceptance and monitoring) would moderate this relationship. Specifically, NLE-exposed adolescents who reported greater levels of protective social and parental environments would score significantly higher on cognitive tasks than NLE-exposed adolescents from less supportive environments. Latent variables protective social factors and protective parenting behaviors were created using confirmatory factor analysis (CFA). NIH Toolbox summary scores were used for measures of cognition. Results suggested that there was a significant negative association between number of NLEs and performance on all cognitive tasks. Protective parenting behaviors moderated the relationship between NLEs and picture sequence memory task (PSM) performance ($t=-2.26$, $p=0.02$), with specific differences between children whose caregivers scored high (+1SD) vs. low (-1SD) on protective parenting behaviors ($B=-1.84$, $p<0.000$). Examining intercepts between groups, there were significant differences in PSM scores for youth who experienced 0-3 NLEs ($p<0.000$). However, there were no differences between the high vs low protective parenting groups on PSM scores when NLEs were >/= 4. There was no moderating effect of protective social factors on any cognitive measure. These findings suggest that protective parenting behaviors only serve as a buffer against the harmful cognitive effects of NLEs for youth who experienced a small number of negative events.

Disclosures: E. Wolfgram: None. **A. Sanders:** None. **D. Barch:** None.

Poster

726. Stress, Cognition, and Behavioral Regulation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 726.02

Topic: F.03. Stress and the Brain

Title: Stress resistance and reaction to moving object in qualified athletes

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Abstract: Taking into account the psycho-emotional state, the level of stress of athletes during the training and competitive process is extremely important, because these functions affect the level of athletic' achievements. The aim of the study was to assess the impact of psycho-emotional stress and the effectiveness of mental self-regulation on the functional state of the central nervous system in terms of response to moving objects (RMO) of qualified athletes specializing in cyclic sports (such as rowing) and untrained individuals (students). Methods. The study involved 30 qualified athletes (masters of sports, masters of sports of international class and honored masters of sports) of both sexes, aged 18-31 years, sport - kayaking and canoeing, sports experience - 3,5-19 years. The control group consisted of 11 students of both sexes, aged 18-22. Athletes were tested during the training period, students - during distance learning sessions. To monitor and predict the functional state of the central nervous system of athletes used RMO, which was measured using the diagnostic complex "Diagnost-1" (MV Makarenko, VS Lyzogub). To determine the level of stress, emotional stability, the level of effectiveness of mental self-regulation and adaptability in athletes and students used the M. Luscher test. Athletes compared to untrained individuals showed lower levels of stress and more optimal neuropsychological state, higher efficiency of mental self-regulation and adaptability. Athletes showed higher accuracy of RMO, less time and the number of delayed reactions compared to untrained individuals. In the group of athletes, RMO values for both hands did not differ significantly, while in the control group RMO accuracy of the dominant hand was higher, which indicates a decrease in functional asymmetry in experienced rowers as a result of effective adaptation to training. The coefficient for estimating the intensity of stress levels in athletes was related to the accuracy of RMO, the number and total time of delay in RMO. Correlation analysis of the obtained data revealed the relationship between the effectiveness of mental self-regulation and adaptability in athletes with RMO indicators also. Conclusions. According to the results, the level of stress in athletes is positively correlated with the accuracy of RMO, less number and time of delayed reactions, which may be associated with the activation of the nervous system as an adaptation to daily exercise. RMO indicators of athletes can be prognostic to assess the level of stress, the level of effectiveness of mental self-regulation and adaptability, as well as reflect the level of training.

Disclosures: S. Fedorchuk: None. **T. Kutsenko:** None. **O. Yaroshenko:** None. **O. Lysenko:** None. **O. Shynkaruk:** None.

Poster

726. Stress, Cognition, and Behavioral Regulation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 726.03

Topic: F.03. Stress and the Brain

Support: NIH HD060986

Title: Intergenerational effects of early malnutrition on attention and executive control: DNA Methylation Signatures

Authors: *A. RABINOWITZ[1], L. K. FISCHER[2], K. WILLIAMS[3], C. P. BRYCE[4], S. ANDERSON[5], C. J. PETER[6], P. GARG[7], A. J. SHARP[8], S. AKBARIAN[8], J. R. GALLER[9]; [1]McGill Univ., Montreal, QC, Canada; [2]Children's Natl. Med. Ctr., Washington, DC; [3]MassGeneral Hosp. for Children, Boston, MA; [4]Psychiatry, Queen Elizabeth Hosp., Bridgetown, Barbados; [5]Population Hlth. Sci., Univ. of the West Indies, Cave Hill St. Michael, Barbados; [6]Psychiatry, [8]Dept. of Psychiatry, [7]Icahn Sch. of Med. at Mount Sinai, New York, NY; [9]Psychiatry, Harvard Med. Sch., Brookline, MA

Abstract: **Objective:** The impact of malnutrition on attention and school performance is well documented, but studies examining intergenerational effects are limited. We assessed attention and executive function in a prospective study of adolescents and young adults who were offspring of Barbadian adults with histories of moderate to severe protein-energy malnutrition limited to the first year of life with good nutrition thereafter (MAL) and healthy controls (CON) as part of a 50+ year longitudinal study. Epigenetic changes associated with these outcomes were assessed using genome-wide DNA methylation analysis. **Methods:** Attention was assessed using the Connors Adult Attention Rating Scale and executive problems by the Behavior Rating Inventory of Executive Functioning in this cohort (mean age: 19.7(3.3) years; range: 16-31 years), whose parents had a history of infant malnutrition (N= 70) or healthy controls (N= 45). In order to identify genomic loci where epigenetic state was associated with these behaviors, we performed an epigenome-wide association study (EWAS) using DNA methylation profiles generated for a subset of 74 samples (N=44 MAL and N=30 CON), previously described in Peter et al. (2016). Malnutrition effects on behavior outcomes were estimated by adjusted mixed model multiple regression analyses. Next, we performed linear regressions of CAARS Subscale C (ADHD symptom score) and BRIEF metacognitive index scores with methylation beta values, blood cell counts, age, gender and parental socioeconomic factors as independent variables. **Results**: Healthy offspring of previously malnourished parents had increased behavior problems, including greater hyperactivity, inattention and ADHD symptoms (all $p<0.05$) and more executive function problems ($p<0.01$) when compared with offspring of control parents. We identified 183 differentially methylated regions where methylation levels were significantly associated with CAARS C and BRIEF scores, of which three (promoter regions of HOXB6, HLA-DPA1 and DPPA5) were previously found to be modified in their parents as a result of early malnutrition (Peter et al, 2016). **Conclusions:** Moderate to severe protein-energy malnutrition confined to the first year of life is associated with lasting epigenetic signatures correlated with elevated levels of attention and executive function problems in the well-nourished offspring of exposed individuals. These findings of potential intergenerational effects emphasize the persistent socioeconomic burden of childhood malnutrition and underscores the necessity to develop public health interventions that appropriately address long-term and behavioral outcomes.

Disclosures: A. Rabinowitz: None. **L.K. Fischer:** None. **K. Williams:** None. **C.P. Bryce:** None. **S. Anderson:** None. **C.J. Peter:** None. **P. Garg:** None. **A.J. Sharp:** None. **S. Akbarian:** None. **J.R. Galler:** None.

Poster

726. Stress, Cognition, and Behavioral Regulation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 726.04

Topic: F.03. Stress and the Brain

Support: The Charles E. Kubly Mental Health Research Center at Marquette University

Title: Effects of Chronic Stress and Prefrontal Cortical REDD1 Overexpression on Attentional Set Shifting Behavior in Mice

Authors: B. KURTOGLU[1], C. KRUEGER[2], A. EDWARDS[2], M. C. HEARING[2], *J. MANTSCH[1];
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Abstract: Behavioral (cognitive) flexibility, the ability to adapt behaviors in response to changes in the environment is an essential element for everyday life, with deficits commonly observed in neuropsychiatric disease states and reducing resilience to negative life events (e.g., stress). The rodent prelimbic cortex (PrLC) plays a critical role in processing information necessary for optimal cognitive flexibility and is known to undergo structural and functional changes following prolonged stress exposure -- thus PrLC dysfunction represents a likely substrate for stress-induced deficits in cognitive control. We have recently shown that chronic unpredictable stress (CUS) produces an enduring dysfunction in PrLC physiology and impaired cognitive flexibility using an operant-based attentional set shifting in male but not female mice, however what adaptations drive these deficits remains unclear. To gain more insight into this, our studies chose to focus on the protein REDD1 (regulated in development and DNA damage responses-1) (aka DDIT4, RTP801, Dig2) as it is increased in post-mortem PFC tissue from individuals diagnosed with depression. In line with these findings, we find that there is an increase in REDD1 expression and a decrease in Raptor phosphorylation, one of the key elements of the mTORC1 complex, in the PrLC after CUS, suggesting disrupted mTORC1 function. To determine if REDD1 overexpression is sufficient to produce deficits in attentional set shifting, we used a viral vector to overexpress REDD1 in the PrLC of male mice. Relative to GFP control mice, REDD1 mice required more trials to pass the extradimensional shift testing criterion that was equivalent to that produced by CUS. Notably, REDD1 overexpression did not impact acquisition of lever training, performance during a visual cue-based discriminative learning task, or measures of motivation for non-drug reward. The observation that CUS and REDD1 overexpression produce deficits in attentional set shifting in male mice likely has relevance for understanding a number of stress related disorders. Future research will assess the cell-type localization of REDD1 increases following stress in males, determine whether female mice are similarly affected by REDD1 overexpression and/or is upregulated in females following CUS, and examine the necessity of disrupted mTORC1 for stress effects.

Disclosures: B. Kurtoglu: None. **C. Krueger:** None. **A. Edwards:** None. **M.C. Hearing:** None. **J. Mantsch:** None.

Poster

726. Stress, Cognition, and Behavioral Regulation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 726.05

Topic: F.03. Stress and the Brain

Title: Tunnel vision, false memories, and intrusive memories following exposure to the Trier Social Stress Test

Authors: *C. N. CORDES[1], C. L. PFISTER[1], K. M. BOAZ[1], T. D. NIESE[1], S. L. PARKER[1], K. E. LONG[1], M. L. STANEK[1], M. S. RISNER[1], J. G. BLASCO[1], K. N. SUZELIS[1], K. M. SIEREVELD[1], S. B. CARNES[1], B. R. RORABAUGH[2], P. R. ZOLADZ[1];
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Abstract: Most research examining the impact of stress on learning and memory has exposed participants to a stressor and measured how it affects learning and memory for unrelated material (e.g., list of words). Such work has been helpful, but it has not been the most translational to the human condition. When considering phenomena such as intrusive memories in post-traumatic stress disorder (PTSD) or an eyewitness's memory for a crime, it is most useful to know what an individual remembers about the stress experience itself, not unrelated information. In prior work, investigators used a modified version of the Trier Social Stress Test (TSST) to quantify participant memory for the stressor. We aimed to replicate this work by examining participant memory for the TSST and extend on it by quantifying false and intrusive memories that result from TSST exposure. Forty-six undergraduate students from Ohio Northern University were exposed to the TSST or the friendly-TSST (f-TSST). The TSST required participants to deliver a ten-minute speech in front of two lab panel members as part of a mock job interview; the f-TSST required participants to casually converse with the panel members about their interests and hobbies. In both conditions, the panel members interacted with (central) or did not interact with (peripheral) several objects sitting on a desk in front of them. Participants' anxiety levels were assessed before and after the TSST or f-TSST, and saliva samples were collected to assay for cortisol. The next day, participants' memory for the objects that were present on Day 1 was assessed with recall and recognition tests. We also quantified participants' intrusive memories for each task by having them complete an intrusive memory questionnaire on Days 2, 4, 6, and 8. Participants exposed to the TSST exhibited greater recall of central objects than participants exposed to the f-TSST. There were no differences observed for the recall of peripheral objects or for recognition memory. Interestingly, TSST exposure increased false recall in males, but reduced it in females. Females exposed to the TSST also showed greater evidence of intrusive memories than males exposed to the TSST. Consistent with prior work, these findings show that stress enhances memory for the central details of a stressful experience. They also extend on prior work by showing that stressful experiences sex-dependently impact the manifestation of false and intrusive memories. This is the first study of which we are aware to quantify intrusive

memory formation with the TSST; the modified TSST paradigm may be useful in understanding differential susceptibility to intrusive memory formation and the development of PTSD.

Disclosures: C.N. Cordes: None. **C.L. Pfister:** None. **K.M. Boaz:** None. **T.D. Niese:** None. **S.L. Parker:** None. **K.E. Long:** None. **M.L. Stanek:** None. **M.S. Risner:** None. **J.G. Blasco:** None. **K.N. Suzelis:** None. **K.M. Siereveld:** None. **S.B. Carnes:** None. **B.R. Rorabaugh:** None. **P.R. Zoladz:** None.

Poster

726. Stress, Cognition, and Behavioral Regulation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 726.06

Topic: F.03. Stress and the Brain

Support: NIH R01 MH073136
P50 MH096889
T32 MH119049-02
UCI UROP

Title: High estrogen levels are required for acute multimodal stress to disrupt memory in male and female mice

Authors: *R. E. HOKENSON[1], Y. H. ALAM[2], A. K. SHORT[3], Y. CHEN[3], J. C. LAUTERBORN[1], S. A. SAMRARI[1], J. N. NIEVES[1], C. JANG[2], C. M. GALL[1], T. Z. BARAM[3]; [1]Anat. & Neurobio., [2]Biol. Chem., [3]Pediatrics, Univ. of California, Irvine, Irvine, CA

Abstract: Background: Chronic stress commonly provokes memory problems, which vary by sex, whereas acute stressors are generally benign. However, acute events such as mass shootings, assault, or natural disasters - events composed of simultaneous physical, social, and emotional components - are being recognized as significant sources of cognitive and emotional disturbances. We have established in male mice that multiple acute concurrent stresses (MAS) (or multimodal acute stress) enduringly impair hippocampus dependent memory and destroy dorsal CA1 synapses. In females, MAS impair memory in an estrous cycle-dependent manner: spatial memory is impacted in early-proestrous mice (high estrogen) but not in mice stressed during estrus (low estrogen). Notably, hippocampal estrogen levels are higher in males and proestrous females, both vulnerable to MAS, than in resilient estrous females. These findings suggest that high levels of hippocampal estrogen may enable MAS-induced memory disruptions. **Methods:** To understand how differences in levels of hippocampal estrogen may promote susceptibility or resilience of memory to MAS, we examined the impacts of MAS when estrogen production was blocked with aromatase inhibitors. To examine estrogen receptor (ER) contribution, we developed mice with ERα or ERβ conditionally deleted from the hippocampus. Additionally, wild-type mice were treated with selective blockers of estrogen receptors through indwelling hippocampal cannulae. Hippocampus-dependent memory was assessed using four

different tests. We quantified estrogen levels by enzyme-linked immunosorbent assay (ELISA) and mass spectrometry. To identify the mechanism by which estrogen promotes MAS susceptibility, we investigated how levels of membrane ERα or ERβ (relative to total) in the dorsal hippocampus change according to cycle or with infusion of estradiol.
Results: MAS enduringly disrupts memory in male mice and female mice stressed during proestrus. Blocking estrogen production by administering aromatase inhibitors prevented memory deficits after MAS compared to vehicle-treated males or proestrous females. In a separate experiment, blocking estrogen receptor (ER) activation by administering ERα (MPP) or ERβ (PHTPP) antagonists 90 minutes prior to stress protected mice from memory impairments in a dose- and sex-dependent manner. These findings implicate a role of estrogen in promoting memory disruptions following MAS.

Disclosures: R.E. Hokenson: None. **Y.H. Alam:** None. **A.K. Short:** None. **Y. Chen:** None. **J.C. Lauterborn:** None. **S.A. Samrari:** None. **J.N. Nieves:** None. **C. Jang:** None. **C.M. Gall:** None. **T.Z. Baram:** None.

Poster

726. Stress, Cognition, and Behavioral Regulation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 726.07

Topic: F.03. Stress and the Brain

Support: CIHR-Project Grant (FRN#PJT-156001)

Title: Short- and long-term stress differentially impact cognitive-affective phenotypes, and SK3 expression and glucose activation in the prefrontal cortex and dorsal raphe

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Abstract: Chronic stress is one of the most powerful risk factors for depression. The precise neuro-molecular pathway through which stress results in depressive episodes appears to be multifarious. We hypothesize that one of these pathways involve the small-conductance calcium-activated potassium channels (SKC). Overexpression of the SK3 subtype was found to cause cognitive deficits and hippocampal reduction in mice (Martin et al. Mol Neurobiol 2017), which are phenotypes related to preclinical depression. Using a behavioral test battery, RNAscope imaging of SK3, electrophysiology and biosensor recordings, our study aims to determine the role of SK3 in the short-term (ST = 2 weeks) and long-term stages (LT = 6 weeks) of unpredictable chronic mild stress (UCMS)-induced depressive-like phenotypes in male and female BALB/c mice. Our data show that ST UCMS mice show no significant differences in behavioral test performance, while LT UCMS mice performed poorly in the spontaneous alternation test, M_{diff} = .102, SD = .091, p = .020, r_{rb} = .625, and in the novelty suppressed

feeding test M_{diff} = -124, SD = 97.450, p = .025, r_{rb} = .594. They also had a significantly lower consumption in the sucrose preference test, F = 3.77, p = .004, η^2 = .132. These deficits are associated with increased SK3 channel mRNA in parvalbumin-positive cells in the hippocampus of LT stressed animals as compared to non-stressed LT. Simultaneous real-time regional glucose biosensor quantification revealed differential alterations in the medial prefrontal cortex (mPFC) and the serotonergic dorsal raphe nucleus (DRN) in response to the glucocorticoid agonist dexamethasone (DEX). ST and LT UCMS, when compared to controls, were associated with an increase and decrease, respectively, of mPFC glucose activity. These were accompanied by differential dysregulation of DRN activity. Further examination of the effects of SK3 antagonists, and other SKC subtypes, on behavioral and neurophysiological phenotypes of ST and LT UCMS are underway. Fiber photometry analysis is also being processed. Altogether, these data indicate that UCMS-induced upregulation of SK3 may underlie some of the behavioral and corticolimbic neurophysiological deficits relevant to depression, and can therefore represent a potential molecular target for preventive or therapeutic interventions.

Disclosures: D.L. Wan-Yan-Chan: None. **M. Corrigan:** None. **0.C. Dinesh:** None. **B.F. Hannam:** None. **F.R. Bambico:** None.

Poster

726. Stress, Cognition, and Behavioral Regulation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 726.08

Topic: G.05. Mood Disorders

Support: VA merit award BX000559
VA merit award BX003512
NIMH R01 MH053851

Title: Acute, but not chronic stress alters cognitive biases of rats in the ambiguous cue interpretation test

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Abstract: Major depressive disorder (MDD) is a highly prevalent and debilitating disorder, the pathogenesis of which is not fully understood. Whereas the two core symptoms of MDD are depressed mood and anhedonia, it is also associated with significant cognitive symptoms, including negative cognitive biases. Due to these cognitive biases, patients perceive, remember, or interpret information as being more negative than it actually is, which may account for their anhedonia and other symptoms. In order to study the neural mechanisms underlying cognitive biases, we used the ambiguous cue interpretation test in rats. In this task, rats are trained to make

distinct responses to two reference tones in order to either receive a sucrose reward or avoid an aversive air puff. During the test, rats are presented with ambiguous tones that are in between the frequencies of the two reference tones. The animal's response to the ambiguous tone is recorded and interpreted as their expectation of either a positive or negative outcome. Rats were trained and tested prior to stress to determine their baseline performance. Then, the animals underwent two days of inescapable foot shock stress (IS), in which one session consists of sixty 15 second foot shocks (0.8 mA). IS induced a negative cognitive bias in male rats, such that they increased their negative responses and decreased their positive responses when the ambiguous tone was played. However, IS did not alter female rats' cognitive biases in this task compared to their baseline performance. The effects of chronic unpredictable stress (CUS) were also tested. CUS consists of randomized daily stressors, including restraint, shake, wet bedding, 24hr lights on, tail pinch, and footshock, over the course of 2 weeks for males and 3 weeks for females. CUS did not induce a significant negative bias in neither male nor female rats. Future experiments will test the role of the medial prefrontal cortex in this behavioral task.

Disclosures: **A. Stephens:** None. **S. Way:** None. **F.R. Carreno:** None. **A. Frazer:** None. **D.A. Morilak:** None.

Poster

726. Stress, Cognition, and Behavioral Regulation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 726.09

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA R01 DA047265

Title: Post-weaning social isolation alters sociability in a sex-specific manner

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Abstract: Adolescence is a critical period for brain development in humans. Stressors during this time period can have lasting effects on behavior and brain development later in life. Social isolation and loneliness are particularly salient stressors that may lead to detrimental mental health outcomes in females, although most of the work on social isolation has been done in males. Stress primes microglia, prompting them to have a heightened pro-inflammatory response to a second immune challenge. The anti-inflammatory drug, minocycline, inhibits microglia, and administration of minocycline promotes active stress coping and reverses stress-induced depressive behavior. Our lab has previously shown that adolescent social isolation effects sensitivity to social reward, especially in males. The current study examined the effects of

minocycline on post-weaning social isolation and social interaction during adolescence and adulthood. Mice were isolated or group-housed at postnatal day 21 (PND21) and received daily injections of saline or minocycline until adolescence at postnatal day 45 (PND45). When tested on a three-chamber social interaction task at PND45, we found that minocycline did not alter sociability in either group of female mice, but decreased sociability in both group housed and isolated male mice. When tested again during adulthood (PND60), minocycline did not alter sociability in male mice, but increased sociability in isolated female mice. Taken together, adolescent social isolation leads to sex-specific effects on social interaction in adulthood. Inhibition of microglia with minocycline alters the effects of social isolation in females, but not in males. Ongoing work is examining the effects of post-weaning social isolation on microglial number and activity.

Disclosures: **E.A. Birmingham:** None. **T.M. Myers:** None. **B.T. Rhoads:** None. **A.G. McGrath:** None. **N.A. Miles:** None. **C.B. Schuldt:** None. **L.A. Briand:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.10

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH GM127251
NSF ASPIRE Fellowship to JSP
RISE Fellowship to VIN
Eloise E. and Patrick Wieland Fellowship to KN

Title: Atlas-based analysis of the neural projections from the lateral hypothalamic area middle group lateral tier dorsal region (LHAd) to the lower brainstem in the adult male rat

Authors: *J. V. SALCIDO PADILLA, V. I. NAVARRO, K. NEGISHI, S. DABBIRU, A. M. KHAN;
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Abstract: The lateral hypothalamic area (LHA) plays an important role in the control of complex functions such as sleep/wake cycles, energy balance, and motivated behavior. Although the LHA has been termed a feeding center, other regions within the brain such as the hindbrain, are known for the regulation of similar functions including glucosensing and feeding control. While many studies have reported projections from the LHA to the hindbrain, few have further investigated the hindbrain projection patterns from cytoarchitectonically-defined LHA subdivisions. To further our understanding of these subdivisions, we analyzed an LHA subdivision for which the inputs and outputs have not been previously reported: the lateral hypothalamic area middle group lateral tier dorsal region (LHAd). We injected a cocktail consisting of the retrograde tracer, cholera toxin B subunit (CTb), and the anterograde tracer,

Phaseolus vulgaris leucoagglutinin (PHA-L), in the male rat to visualize LHAd connections to the hindbrain. We used a standardized atlas, *Brain Maps 4.0* (*BM4.0*), from which hindbrain-encompassing *BM4.0* atlas levels 52-73 were mapped. Preliminary observations of the dataset indicate that LHAd-originating inputs to reticular hindbrain regions such as the gigantocellular reticular nucleus and parvicellular reticular nucleus. Moving caudally, scattered PHAL-immunoreactive (ir) neurites were observed in the nucleus of the solitary tract, lateral part (NTSl). Additionally, CTb-ir labeled perikarya were found to be distributed along the midline of the more rostral hindbrain sections. In caudal hindbrain sections, perikarya appeared to be present in overlapping PHA-L-labeled regions, such as the NTS and other reticular nuclei. These data provide evidence that supports the existence of an LHAd-hindbrain neural projection pathway. Mapping these projections to a standardized atlas provides a guiding framework that can be used to further our understanding of the regulation of gastrointestinal function and the control of feeding behavior, which, in turn, will be critical for the development of effective therapies.

Disclosures: J.V. Salcido Padilla: None. **V.I. Navarro:** None. **K. Negishi:** None. **S. Dabbiru:** None. **A.M. Khan:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.11

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH GM127251
Eloise E. and Patrick Wieland Fellowship to KN
RISE Fellowships to VIN, DS, AT
HHMI UTEP PERSIST Grant to AMK

Title: A topographically-defined cortico-striato-pallidal module with convergent projections to the lateral hypothalamic area

Authors: *K. NEGISHI, V. I. NAVARRO, J. M. GUERRA-RUIZ, D. SOTELO, A. TOCCOLI, A. M. KHAN;
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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 affect downstream structures such as pallidum and hypothalamus. Here, we elucidate a cortico-striatal-pallidal trio that includes the medial prefrontal cortex (mPFC), the dorsomedial tip of the nucleus accumbens (ACB), and a dorsomedial part of the substantia innominata (SI). We show, using high-spatial

resolution mapping and pathway tracing, that this trio forms unidirectional top-down projections in a topographically restricted manner. They also produce axon terminals that converge on the lateral hypothalamic area (LHA). To show this, we co-injected Phaseolus vulgaris leucoagglutinin and cholera toxin B subunit into the mPFC, ACB, and the LHA. 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. The present work makes clear that individual nodes of this trio are not embodied by the regions themselves. Instead, the nodes are remarkably restricted spaces within gray matter regions. We can appreciate the significance of this by relating our findings with behavioral observations made with intracranial stimulation experiments. Work done primarily by the Berridge lab has shown that stimulation of the mPFC and ACB segments of our trio revealed “hedonic hotspots”, whereas the relevant segment of SI suppressed hedonic impact of reward. We can speculate that activation of the ILA excites the ACB which in turn inhibits the SI, a region that otherwise dampens hedonic reactions. Further studies can determine whether these nodes are monosynaptically joined and could also explore the functional dynamics of the mPFC-ACB-SI circuit. Our mapping strategy provides a tractable starting point for such work and a methodological template that can effectively identify other such cortico-striato-pallidal motifs.

Disclosures: K. Negishi: None. **V.I. Navarro:** None. **J.M. Guerra-Ruiz:** None. **D. Sotelo:** None. **A. Toccoli:** None. **A.M. Khan:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.12

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH GM127251
NSF ASPIRE Fellowship to GPT

Title: Hindbrain catecholaminergic and non-catecholaminergic neuronal populations rapidly recruited during glycemic challenge: A fluorescent cell-detecting deep learning model for high-throughput tabulation and atlas-based mapping

Authors: *G. P. TAPIA[1], A. ARNAL[1], S. D. CHENAUSKY[1], J. V. SALCIDO[1], V. I. NAVARRO[1], K. NEGISHI[1], S. BALIVADA[1], O. FUENTES[2], A. M. KHAN[1];
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Abstract: Subgroups of hindbrain neuronal populations are well documented to respond robustly to glycemic challenge. These populations, however, lay scattered within a vast expanse of neural tissue that requires time, labor, and expertise to analyze quantitatively. To reduce this labor but maintain quality control from the expertise, we developed an algorithm that employs the deep

learning model, YOLOv5, to quickly and accurately annotate cells in epifluorescence photomicrographs. These cells include those that displayed rapid activation in association with an intravenous 2-deoxy-glucose challenge (250 mg/kg) relative to a saline-treated control group. The cells were identified using dual and/or triple-label immunohistochemistry for dopamine beta hydroxylase, choline acetyltransferase, and the cellular activation marker, phosphorylated-ERK1/2. The model was trained in-house on a subset of manual cell markings from both treatment groups in the locus ceruleus, nucleus of the solitary tract, and dorsal motor nucleus of the vagus to detect cellular positions. We reviewed the preliminary cell markings and manually adjusted the model predictions to remove false-positives and register cells that may have gone undetected by the program. The precision and recall of the model were evaluated so that it could reliably serve as a first-pass cell-locator for the reviewer of the data. This method will allow us to streamline our future data collection and analysis to map hindbrain chemoarchitecture and activated neuronal populations to an open-access rat brain atlas.

Disclosures: G.P. Tapia: None. **A. Arnal:** None. **S.D. Chenausky:** None. **J.V. Salcido:** None. **V.I. Navarro:** None. **K. Negishi:** None. **S. Balivada:** None. **O. Fuentes:** None. **A.M. Khan:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.13

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH GM127251

Title: Using high-spatial resolution atlas-based mapping to examine the organization of dopamine β-hydroxylase- and phenylethanolamine N-methyltransferase-immunoreactive fibers in the rat paraventricular thalamic nucleus

Authors: E. L. MUÑOZ, M. A. PEVETO, *A. M. KHAN;
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Abstract: The paraventricular thalamic nucleus (PVT) is a neurochemically-diverse brain region with a complex organization of neuroanatomical input pathways. As an integrator of diverse signals that help shape motivated behaviors, the PVT is involved in several homeostatic and hedonic functions, including those involving ingestive behaviors. Dopamine β-hydroxylase (DβH) and phenylethanolamine *N*-methyltransferase (PNMT) serve as biomarkers of neurotransmitters involved in feeding control. While previous work has established the presence of DβH- and PNMT-immunoreactive (ir) fibers within the PVT, their precise spatial distributions throughout its rostrocaudal extent have not been anatomically characterized using a standardized rat brain reference atlas. To do this, we have evaluated the distributions of DβH-ir and PNMT-ir fibers within the rat PVT as part of an ongoing effort to identify the topographic organization and

spatial relationships of feeding-related neuropeptide and neurotransmitter populations within this complex brain region. Coronal rat brain tissue sections were collected in series at 30 µm-thickness and immunohistochemically stained for DβH and PNMT. Nissl staining was performed on an adjacent series of tissue to aid with cytoarchitectural analysis. The plane of section was carefully determined for each tissue section utilizing formal atlas mapping techniques and the locations of DβH-ir and PNMT-ir neurites were mapped onto respective templates of a standardized rat brain atlas (L.W. Swanson, 2018; *J Comp Neurol* 526:935-943). We found populations of DβH-ir and PNMT-ir fibers which were consistent throughout the rostrocaudal extent of the PVT but denser in its posterior aspects. Both fiber types appear to have similar diameters, were confined to dorsolateral portions of the structure, and did not occupy the entirety of the structure's boundaries, especially in the posterior PVT. These two fiber systems appeared to co-cluster rostrocaudally, but are also secluded from one another in more ventral aspects of the posterior PVT. These results indicate a possible functional linkage between specific areas along the PVT and other brain structures involved in feeding-related systems which could be further explored by testing this circuitry. These maps serve as initial guidelines for future research to explore these precise connections.

Disclosures: E.L. Muñoz: None. **M.A. Peveto:** None. **A.M. Khan:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.14

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH GM127251

Title: Using high-spatial resolution atlas-based mapping to examine the distributions of neuropeptide Y-immunoreactive fibers in relation to calretinin-immunoreactive perikarya in the rat paraventricular thalamic nucleus

Authors: *M. PEVETO, A. M. KHAN;
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Abstract: The paraventricular thalamic nucleus (PVT) is a uniquely complex area which is structurally well-situated to integrate and respond to homeostatic and/or hedonic signals underlying feeding behavior. The PVT harbors diverse neurotransmitter and neuropeptide systems which can influence ingestive behaviors. Neuropeptide Y (NPY) has been shown to have powerful orexigenic effects and NPY-immunoreactive (-ir) fibers innervate the PVT. Recent evidence has also identified the calretinin (CR) neuronal population within the PVT as a potential system involved in directing arousal towards appetitive behaviors. Previous anatomical evidence has established the existence of NPY-ir fiber and CR-ir cell populations within the PVT. However, few studies have reported on the direct spatial relationships between these two

neurochemical systems. More generally, most data on the chemical neuroanatomy of the PVT have not been charted carefully within a standardized rat brain atlas. In this study, we evaluated the topographic distributions of NPY-ir fibers and CR-ir cells within the rat PVT. Rat brain tissue sections (30 µm-thick) underwent immunoperoxidase reactions to identify CR-ir cells and NPY-ir fibers, which were visualized using 3,3'-diaminobenzidine, with and without nickel-intensification, respectively. Nissl staining of an adjacent tissue series aided in cytoarchitectural analysis. The plane of section was determined carefully for each tissue section and the locations of CR- and NPY-immunoreactive perikarya and neurites were transferred onto levels 22-33 of the *Brain Maps 4.0* rat brain atlas (Swanson, 2018; *J Comp Neurol* 526:935). Throughout the rostrocaudal extent of the PVT, we found a consistently dense population of CR-ir perikarya and an abundance of NPY-ir fibers, both of which were confined to more dorsolateral aspects of the structure. The distributions of CR-ir perikarya and NPY-ir neurites partially overlapped within the anterior PVT and more so in the medial and posterior PVT. CR-ir perikarya displayed a bipolar morphology, with graded intensities of immunoreactivity. NPY-ir fibers bearing boutons were denser in bilateral patches, especially in the posterior PVT. These results provide an initial framework to further examine the neuroanatomical organization of feeding-related control systems within the PVT, including interactions of other neuropeptide/neurotransmitter systems with CR neurons. By mapping their observed distributions to a standardized rat brain atlas, these results also provide a set of maps to allow for the registration of other experimental datasets in relation to these systems.

Disclosures: M. Peveto: None. **A.M. Khan:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.15

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH GM127251
Richard Westbrook Jr. Student Excellence Endowment to LPM
Eloise E. and Patrick Wieland Fellowship to KN

Title: Topographic analysis of the dorsal agranular insular area outputs to the striatum in the male rat using an atlas framework

Authors: *L. P. MONTES, K. NEGISHI, A. M. KHAN;
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Abstract: The insular region (INS) is known to be an integration hub involved in behaviors ranging from interoception to decision making. Anatomically is connected to a wide variety of brain regions as well as to different subregions of the striatum, which are involved in the basal ganglia circuits and reward systems such as the caudoputamen (CP) and accumbens nucleus

(ACB), respectively. Functional and anatomical connections between the ACB and INS have been more studied than connections from the INS to CP in rodents. Nonetheless, the topographic patterns of these connections have not been mapped into a standardized reference atlas. To examine this, a cocktail combination of antero- and retrograde tracers (Phaseolus vulgaris leucoagglutinin (PHA-L) and cholera toxin B (CTb)) was injected into the dorsal agranular insular area (AId) to map its outputs and inputs. PHAL and CTb tracers were visualized in coronal rat brain sections by 3,3′-diaminobenzidine (DAB) and nickel-enhanced DAB reactions, respectively. Adjacent tissue sections were Nissl-stained, and regional boundaries were assigned based on cytoarchitecture, using as reference the Brain Maps 4.0 ((BM4.0) L.W. Swanson, 2018; J Comp Neurol.). Output distributions from the AId injections were mapped into a high-spatial resolution atlas, the BM4.0. Preliminary data from the AId injections showed different projection patterns in the striatum, mainly along the rostrocaudal axis. Projections in the rostral CP were restricted to the ventral portion of the region. In contrast, these projections travel from ventral to mediodorsal portions of the CP caudally. Additionally, differences along the mediolateral axis were present, projections in rostral levels of the CP showed preferences in the lateral portion, where caudal levels were mainly in the medial portion surrounding the lateral globus pallidus (GPl). On the other hand, PHAL transport in the ACB was present at rostral levels around the olfactory limb of the anterior commissure (aco). Caudally, these projections were more in the lateral portions of the ACB rather than medially. Furthermore, as expected from previous studies, any of these regions had retrograde transport since they only received outputs from the INS. Overall, these patterns are consistent in our two AId injections, and analyzing their connectivity patterns under a high-spatial resolution framework provides insight to target these connections and study their role under specific behaviors.

Disclosures: L.P. Montes: None. **K. Negishi:** None. **A.M. Khan:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.16

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH GM127251
RISE Fellowship to VIN

Title: Standardized mapping of chemical neuroanatomy in the rat: Structural organization of five immunoreactive neuronal populations and their axonal fiber system within the hypothalamus and/or zona incerta

Authors: *V. I. NAVARRO[1], E. PERU[1], A. ARNAL[1], A. PINEDA SANCHEZ[1], D. SOTELO[1], A. R. TOCCOLI[1], K. NEGISHI[1], S. BALIVADA[1], J. GUERRA RUIZ[1], C. E. D'ARCY[1], L. M. BARRAZA ESCUDERO[1], E. M. WALKER[1], L. SOTO ARZATE[1], A. GUEVARA[1], R.

GUZMAN[1], M. QUINTANA[1], M. ORTEGA-NEDER[1], O. FUENTES[2], A. M. KHAN[1];
[1]Biol. Sci., [2]Computer Sci., The Univ. of Texas at El Paso, El Paso, TX

Abstract: Conventional approaches to mapping chemo- and cytoarchitectural elements using standardized brain atlases typically use one animal as a representation of the distributions across various brains. This can be very informative yet limited when considering that each individual brain contains variations that might reveal fields of differing probability for the presence of these neuropeptides. In the present study, we have provided two sets of high spatial-resolution maps for neuronal populations containing the immunoreactive presence of various key feeding-related peptides: alpha-melanocyte-stimulating hormone, melanin-concentrating hormone, hypocretin 1/orexin A, neuronal nitric oxide synthase, and copeptin. Immunoreactivities for these molecules were mapped across the mediolateral and dorsoventral extents of the hypothalamus with reference to the open-access rat brain atlas, *Brain Maps 4.0* ((*BM 4.0*) Swanson, 2018; *J Comp Neurol*) from levels 23-30. A combined 3,3′-diaminobenzidine/nickel-intensification reaction was used to distinguish the neuronal populations in reactions involving antibodies against these neuropeptides. An adjacent tissue series was Nissl-stained to delineate cytoarchitectonic boundaries and assign levels according to *BM4.0*. Chemoarchitectural distributions for each of the immunostained neuronal populations were mapped using two novel approaches. First, they were generated across multiple animals in order to serve as the basis for probability maps (*i.e.*, isopleth maps). Second, they include fiber systems that are mapped to a standardized rat brain atlas. These isopleth maps allowed us to identify regions of consistent and variable presence for each of these neuropeptides with a greater spatial resolution that is independent of cytoarchitectural boundaries. Thus, the quantitative analysis of neuropeptide distributions is not limited by binning immunoreactive neurons into brain regions but instead allows for visualization of patterns within and across regions. We also provide the isopleth maps generated from this study as a resource that can facilitate further exploration of these neuron populations with techniques that require targeted delivery of molecules, such as optogenetics, chemogenetics, and tract-tracing studies. These datasets will also benefit researchers who use techniques where it is difficult to survey large areas to find targeted interactions, such as patch-clamp electrophysiology or electron microscopy. Overall, these data provide us with a better understanding of neuropeptide distributions in the adult rat brain and how hypothalamic circuitry is organized.

Disclosures: V.I. Navarro: None. **E. Peru:** None. **A. Arnal:** None. **A. Pineda Sanchez:** None. **D. Sotelo:** None. **A.R. Toccoli:** None. **K. Negishi:** None. **S. Balivada:** None. **J. Guerra Ruiz:** None. **C.E. D'Arcy:** None. **L.M. Barraza Escudero:** None. **E.M. Walker:** None. **L. Soto Arzate:** None. **A. Guevara:** None. **R. Guzman:** None. **M. Quintana:** None. **M. Ortega-Neder:** None. **O. Fuentes:** None. **A.M. Khan:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.17

Topic: F.08. Food and Water Intake and Energy Balance

Support: NSERC Canadian Graduate Scholarship
Queen Elizabeth II Scholarship
NSERC Discovery Grant RGPIN-2017-06272
ACT to Employ
Eloise and Patrick Wieland Graduate Fellowship
I-CUREUS
NIH GM127251

Title: Brain-wide projections of dopaminergic cells in the medial zona incerta

Authors: *Y. DUMIATY[1], B. S. BONO[1], K. NEGISHI[2], M. S. PONCE RUIZ[2], T. C. AKINBODE[1], E. MEJIA[2], D. P. SPENCER[1], K. S. SCHUMACKER[1], M. GUIRGUIS[1], A. HEBERT[1], A. M. KHAN[2], M. J. CHEE[1];
[1]Carleton Univ., Ottawa, ON, Canada; [2]Univ. of Texas at El Paso, El Paso, TX

Abstract: The zona incerta (ZI) is a predominantly GABAergic region involved in feeding, hunting, fear, and motor control. We recently showed that ZI GABA neurons co-express tyrosine hydroxylase (TH) and produce dopamine, but the role of dopamine from the ZI is poorly understood. We mapped the distribution of dopaminergic projections from *Th-cre* cells to elucidate possible roles of ZI dopamine release. We validated *Th-cre* expression in the ZI by generating *Th-cre;L10-Egfp* mice and colocalizing *Gfp* and *Th* mRNA with TH-immunoreactivity (TH-ir). Most ZI *Egfp* cells (96%) co-expressed *Th* mRNA, but *Egfp* colocalization with TH-ir was more prevalent in the medial ZI and present in only a few (3%) *Egfp* cells in the lateral ZI. Furthermore, the lateral ZI contained more ectopic *Egfp* cells that did not express *Th* mRNA or TH-ir. Therefore, in order to identify dopaminergic projection targets, we labeled *Th-cre* cells in the medial ZI using a cre-dependent adeno-associated virus encoding mCherry or tdTomato in a *Th-cre* (75 nl) or *Th-cre;L10-Egfp* (25 nl) mouse, respectively. We visualized the projections of cells transduced by dsRed-ir, then traced and mapped dsRed-labeled fiber projections onto *Allen Reference Atlas* templates to delineate the distribution pattern of medial *Th-cre* ZI cells. To assess common projection targets between the two injection cases, we overlaid the fiber maps from each case in Adobe Illustrator and applied the *Intersect* tool in the Pathfinder panel to define the brain areas containing fibers from both cases. The motor-related regions of the midbrain, primarily the periaqueductal gray area and superior colliculus, contained the highest density of dsRed+ projections. Considerable fiber coverage was also observed in the polymodal association and sensory-motor regions of the thalamus, which included the paraventricular thalamus and the subparafascicular nucleus, respectively. Importantly, fiber density was not associated with the size of the region area, as some brain regions, such as the striatum and isocortex, comprise a large area but had virtually no visible dsRed+ projections. The *Intersect* tool permitted an unbiased approach to derive common projection targets across injection cases and revealed that the motor-related regions of the midbrain and thalamus were the most robust targets of *Th-cre* cells. These regions are consistent with the known roles of ZI GABA neurons in motor control and suggests that dopamine and GABA signals may converge to provide similar functions. Future work will determine if *Th-cre* neurons in the ZI innervate motor-related regions by GABA and/or dopamine release.

Disclosures: **Y. Dumiaty:** None. **B.S. Bono:** None. **K. Negishi:** None. **M.S. Ponce Ruiz:** None. **T.C. Akinbode:** None. **E. Mejia:** None. **D.P. Spencer:** None. **K.S. Schumacker:** None. **M. Guirguis:** None. **A. Hebert:** None. **A.M. Khan:** None. **M.J. Chee:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.18

Topic: F.08. Food and Water Intake and Energy Balance

Support: Natural Sciences and Engineering Research Council Discovery RGPIN-2017-06272
Natural Sciences and Engineering Research Council Canada Graduate Scholarships – Master's
Queen Elizabeth II Graduate Scholarship in Science and Technology
Internship-Carleton University Research Experience for Undergraduate Students

Title: Distribution and activation of melanin-concentrating hormone receptor at dopaminergic, GABAergic, and glutamatergic neurons in the ventral tegmental area

Authors: *D. P. SPENCER, J. WILLIAMS-IKHENOBA, R. G. NIKOLOVA, M. J. CHEE; Carleton Univ., Ottawa, ON, Canada

Abstract: Melanin-concentrating hormone (MCH) is a key regulator of energy homeostasis. MCH or MCH receptor (MCHR1) deletion consistently leads to a hyperdopaminergic state that increases energy expenditure and hyperactivity. MCH can suppress dopamine (DA) release from the mesocorticolimbic DA pathway originating in the ventral tegmental area (VTA), but it is not known if MCH-regulated DA release is ascribed to the activity of VTA neurons. Our preliminary findings show that *Mchr1* gene expression in the VTA was comparable to that in the hypothalamus and hippocampus, and we also detected MCHR1 immunoreactivity on VTA cells. To characterize MCHR1 expression in the VTA, we analyzed the distribution of *Mchr1* hybridization in DA, GABA, and glutamate VTA cells by determining its colocalization with tyrosine hydroxylase (TH) immunoreactivity, *Vgat* mRNA, and/or *Vglut* mRNA, respectively. We quantified and mapped the distribution of *Mchr1* hybridization rostrocaudally using the *Allen Reference Atlas*. A high number of *Vglut2* neurons were present in the anterior VTA, and *Mchr1* was consistently expressed in about half (54 ± 5%, n = 3) of *Vglut2* cells. TH neurons were more prominent in the middle sections of the VTA, where the majority (79 ± 10%, n = 3) of TH VTA neurons expressed *Mchr1*. The caudal VTA comprised predominantly *Vgat* cells, and 38% (± 3%, n = 3) of which expressed *Mchr1*.
To determine if MCH directly regulates the activity of DA, GABA, or glutamate VTA cells, we performed whole-cell patch-clamp recordings from *Th-cre:L10-Egfp, Vgat-cre:L10Egfp*, or *Vglut2-cre:L10-Egfp* mice, respectively. Bath application of 3 µM MCH hyperpolarized 38% of *Th* cells (−4.2 ± 0.9 mV, n = 6) and 36% of *Vgat* cells (−4.8 ± 2.4 mV, n = 5) in an activity-

independent manner. MCH did not alter the membrane potential of *Vglut2* cells. As both GABAergic and glutamatergic afferents to *Th* cells can regulate DA release, we assessed synaptic input to *Th* cells. MCH increased the frequency of excitatory (sEPSC) but not inhibitory postsynaptic current (sIPSC) events at *Th* cells. We then assessed if a GABA-mediated input underlies the increase in sEPSC frequency at *Th* neurons and found that MCH decreased sIPSC frequency at *Vglut2* cells.
These findings suggest that MCH can directly inhibit DA and GABA VTA cells. Furthermore, inhibiting GABA VTA cells may disinhibit glutamatergic input within the VTA and provide bidirectional regulation of DA VTA cells. MCH may thus be able to acutely suppress dopamine release while also initiating local glutamatergic signaling to restore dopamine levels. These findings support the VTA as a putative target of MCH action in the maintenance of energy homeostasis.

Disclosures: D.P. Spencer: None. **J. Williams-Ikhenoba:** None. **R.G. Nikolova:** None. **M.J. Chee:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.19

Topic: F.08. Food and Water Intake and Energy Balance

Support: NSERC Discovery Grant RGPIN-2017-06272
NSERC CGS M (ASS)
I-CUREUS (PAM, JWI)

Title: Spatial and electrophysiological comparison of melanin-concentrating hormone cells coexpressing cocaine- and-amphetamine-regulated transcript in male and female mice

Authors: *P. A. MILLER, J. WILLIAMS-IKHENOBA, A. S. SANKHE, M. J. CHEE; Carleton Univ., Ottawa, ON, Canada

Abstract: Melanin-concentrating hormone (MCH) cells in the hypothalamus contribute to key physiological behaviors like feeding and stress in a sex-dependent manner. They are also neurochemically diverse, and one prominent subpopulation of MCH cells coexpresses cocaine- and amphetamine-regulated transcript (CART). Currently, the functional difference between MCH/CART+ versus MCH-only cells is unknown. Thus, we sought to assess the distribution and electrical properties of these two cell types to elucidate their anatomical heterogeneity and distinct contributions to network excitability. We quantified MCH-only and MCH/CART+ cells, by examining the colocalization of CART-immunoreactivity with native EGFP fluorescence in the hypothalamus of male (n = 2) and female (n = 2) *Mch-cre;L10-Egfp* mice. To compare their distribution, we created maps of MCH/CART+ and MCH-only cells in both sexes by parcellating an adjacent Nissl-stained brain slice using *Allen Reference Atlas* templates. About

half (44 ± 1%) of MCH cells counted coexpressed CART, and there were no differences in the number or spread of MCH/CART+ or MCH-only cells between the sexes. Notably, in both males and females, MCH/CART+ cells were more abundant medial to the fornix, while MCH-only cells were found lateral to the fornix. As the topographical division of MCH subpopulations suggests that these cells may be implicated in different cellular networks, we also analyzed their electrical properties. We obtained whole-cell patch-clamp recordings from *Mch-cre;L10-Egfp* cells, which were biocytin-filled and processed *post hoc* for CART immunoreactivity to define their neurochemical phenotype. There were no differences in the resting membrane potential or rheobase between MCH/CART+ and MCH-only cells of either sex. However, female MCH/CART+ cells had lower input resistance and elicited greater current flow at negative voltage steps. In males, MCH/CART+ cells displayed a significant decrease in the frequency of firing following a sustained current injection. In sum, MCH/CART+ cells may underlie sex-dependent differences in MCH functionality, as these cells display unique electrical properties between sexes. Overall, while these results demonstrate an anatomical division between MCH/CART+ and MCH-only cells consistent between male and female mice, MCH/CART+ cells show sex-dependent electrophysiological differences that may contribute to the functional diversity of MCH cells. To further investigate the role of MCH/CART+ cells in the scope of MCH-mediated behaviors, we plan to analyze sex differences in synaptic connectivity at the targets of MCH/CART+ cells.

Disclosures: P.A. Miller: None. **J. Williams-Ikhenoba:** None. **A.S. Sankhe:** None. **M.J. Chee:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.20

Topic: F.08. Food and Water Intake and Energy Balance

Support: NSERC Discovery Grant RGPIN-2017-06272 (MC)
NSERC-PGSD (MP)
Ontario Graduate Scholarship (MP)
Queen Elizabeth II Graduate Scholarship in Science and Technology (MP)
NSERC CGS-M (DS)
Queen Elizabeth II Graduate Scholarship in Science and Technology (DS)
Act to Employ

Title: Melanin-concentrating hormone regulation of lateral septum neurons

Authors: *M. A. PAYANT, D. P. SPENCER, H. B. EL KHALILI, M. GUIRGUIS, M. J. CHEE;
Dept. of Neurosci., Carleton Univ., Ottawa, ON, Canada

Abstract: Melanin-concentrating hormone (MCH) neurons also produce glutamate, thus they may release MCH and/or glutamate to mediate their diverse functions like energy balance, sleep, and stress. The lateral septum (LS) receives dense input from MCH neurons, and we previously showed that the LS is directly innervated by glutamate release from MCH neurons. However, it is not known if both glutamate and MCH are released in the LS or how MCH regulates LS neurons. Our preliminary findings showed that synaptophysin-labelled nerve terminals from MCH neurons were more prominent dorsally in the rostral LS subregion (LSr), while MCH-immunoreactive fibers were denser ventrally in the LSr. We thus focused on the ventral regions of the LSr as a target site of MCH action and employed neuroanatomical and electrophysiological approaches to define and characterize MCH receptor (MCHR1) activation in the LS.
We found that the distribution of *Mchr1* mRNA and protein in the LS overlapped with MCH-immunoreactive fibers especially along the lateral border of the LSr. We thus performed whole-cell patch-clamp recordings from LS neurons within this MCHR1-rich area to assess if MCH can functionally regulate LS neurons. Bath application of 3 μM MCH reversibly hyperpolarized the resting membrane potential (RMP) of LS neurons (Δ RMP = −6.1 ± 1.1 mV, n = 12). This MCH-mediated hyperpolarization persisted in tetrodotoxin (−7.7 ± 1.5 mV, n = 7) but was blocked by the MCHR1 antagonist, TC-MCH 7c (1.7 ± 0.3 mV, n = 5). MCH elicited a membrane current that reversed (V_{rev} = −63.7 ± 8.1 mV, n = 8) near the equilibrium potential for chloride ions (E_{Cl} = −63.1 mV). Furthermore, the MCH-mediated inhibition and current change were also abolished by pretreatment with bicuculline, a $GABA_A$ receptor antagonist. MCHR1 signalling may activate protein kinase C (PKC) to regulate $GABA_A$ receptor trafficking and increase chloride conductance, and pretreating LS cells with the PKC inhibitor calphostin C abolished the MCH-mediated hyperpolarization (2.3 ± 1.1 mV, n = 5). These findings suggested that MCH acts postsynaptically on LS cells, but it did not alter presynaptic GABAergic or glutamatergic input to the LS.
Taken together, our findings indicate that the LS is an important site underlying the functions of MCH. However, in contrast to the synaptic release of glutamate, MCH may reach its target site within the LS by volume transmission. MCH directly inhibited LS cells by increasing a $GABA_A$ chloride conductance, such as via PKC activation. This implicated a novel chloride-mediated mechanism for MCH to regulate neuronal excitability.

Disclosures: **M.A. Payant:** None. **D.P. Spencer:** None. **H.B. El Khalili:** None. **M. Guirguis:** None. **M.J. Chee:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.21

Topic: F.08. Food and Water Intake and Energy Balance

Title: Mapping accumbal TRHergic efferents activated by α-MSH: potential implications in feeding regulation

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Abstract: Feeding is a complex behavior involving aspects such as locomotion, emotional valence, learning and memory processes, and it fulfills both homeostatic and hedonic needs through the interaction of several molecules acting in different brain regions. The nucleus accumbens (NAc) is part of the reward neural circuit and is implicated in controlling the motivational and hedonic aspects of feeding. In the NAc resides a neuronal population that expresses thyrotropin-releasing hormone (TRH), a neuromodulatory peptide that has anorectic effects. Additionally, the NAc receives inputs from regions that regulate homeostatic feeding such as the hypothalamic arcuate nucleus (ARC), in particular from ARC neurons that contain proopiomelanocortin (POMC) and its cleavage product, the α-melanocyte stimulating hormone (α-MSH). Moreover, the α-MSH receptor, MC4R, is highly expressed in the NAc and when α-MSH is administered in this region, TRH mRNA increases and the intake of regular chow and palatable food decreases in rats, suggesting that TRH is downstream the α-MSH feeding regulatory actions in the NAc. Although functional studies associate accumbal TRH expression with the modulation of appetite, the pathway by which TRH neurons convey their input across the brain to ultimately inhibit food intake remains unclear. Hence, we aimed to map the efferents of accumbal TRH neurons that are activated by α-MSH. Male Wistar rats were injected into NAc shell with the anterograde neuronal tracer PHAL (2.5%) by iontophoresis using a constant current source (6μA positive current, pulsed on-off at 7-second intervals); rats were allowed to survive for 11-13 days; on the last day, they were injected with α-MSH (0.5 μg/μl) in the same region to enhance TRH expression and euthanized after 2 h. We analyzed the co-localization of PHAL and TRH immunoreactivities in the forebrain by fluorescent immunohistochemistry (PHAL-A594, TRH-A488). The distribution of PHAL/TRH fibers were found in areas such as the lateral hypothalamus, the hypothalamic paraventricular nucleus (PVN), the bed nucleus of the stria terminal (BNST) and the hippocampus. All those regions express TRH receptors and are involved in the regulation of different aspects of feeding; for example, in the spatial location of food source (hippocampus), in the control of hyperphagia-induced thermogenesis (PVN), in the higher motivation to work for a food reward (lateral hypothalamus), and in the inhibition of food intake (BNST). Overall, our findings suggest that accumbal TRH could regulate energy balance by modulating homeostatic and hedonic feeding as being part of neural circuits that affect different aspects of food intake.

Disclosures: C. Garcia-Luna: None. **E. Alvarez-Salas:** None. **B. Contreras-Cisneros:** None. **P. de Gortari:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.22

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH Grant 1P20-GM135002 (EQC)

Title: Cytoarchitectural Map of Galanin-expressing Lateral Hypothalamic Neural Circuits in Mice

Authors: *A. T. ATTAH[1], A.-J. LI[1], R. TOWNSEND[2], A. JUNEAU[2], H. MÜNZBERG[2], E. QUALLS-CREEKMORE[1];
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Abstract: Metabolic diseases such as diabetes and obesity are two common disease burdens around the world. Over the years, studies have shown that stress and emotion play key roles in the modulation of feeding behaviors. There is research to suggest that exposure to prolonged stress triggers craving for palatable foods (a kind of coping mechanism), which could lead to metabolic disorders over time. The lateral hypothalamus (LH) is well known for its role in feeding and has more recently been implicated in stress and emotion. We have previously shown that galanin-expressing neurons in the LH are stress-responsive and that chemogenetic activation of these neurons attenuates anxiety-like behaviors and promotes motivated feeding behaviors in mice. However, the extended circuits involved are not well understood. This study explored the neuroanatomical circuitry of LH galanin neurons from the anterograde and retrograde perspectives. We used a viral neuronal tracing technique to determine projections and termination targets of LH galanin neurons, and secondly mapped the inputs to LH galanin neurons. To do this, we stereotaxically injected the LH of Galanin-Cre mice with a cell-type specific anterograde virus (AAV-DJ-hSyn-FLEX-mGFP-2A-Synaptophysin-mRuby) and evaluated axonal projections and presynaptic bouton expression patterns in other brain regions. To determine inputs to LH galanin neurons, first we stereotaxically injected the LH of Galanin-Cre mice with a cell-type specific helper virus (AAV9-hSyn-FLEX-TVA-P2A-eGFP-2A-oG), three weeks later they were injected in the same location with a retrograde virus (EnvA-G-Deleted-Rabies-mCherry). Immunohistochemical analysis of brain sections from these mice revealed multiple circuits, which adds to the existing literature about the complex nature of the LH. Our results show that LH galanin neurons project to the lateral septum (LS), lateral preoptic area (LPOA), parabrachial nucleus (PB), ventral tegmental area (VTA) and locus coeruleus (LC), while strong inputs to the LH were observed from the basolateral amygdala (BLA), paraventricular nucleus (PVN), and bed nucleus of stria terminalis (BNST). While previous behavioral studies have looked at the independent roles of these brain regions in feeding, stress, and emotion, our data suggest that LH galanin associated circuits may be relevant neural substrates that encode the integration between stress, emotion and feeding behaviors in mice. Additionally, they may be potential druggable targets for stress, emotional, and even metabolic disorders.

Disclosures: A.T. Attah: None. **A. Li:** None. **R. Townsend:** None. **A. Juneau:** None. **H. Münzberg:** None. **E. Qualls-Creekmore:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.23

Topic: F.08. Food and Water Intake and Energy Balance

Support: DK 121117

Title: Cerebrospinal Fluid Flow Extends from the Central to Peripheral Nervous System

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Abstract: Cerebrospinal fluid (CSF) is the aqueous fluid that bathes central nervous system (CNS) tissues: the brain and spinal cord. It functions as a physical cushion, delivers nutrients, and removes waste. CSF flow, however, has not been described within peripheral nerves. Surgeons have described a clear fluid "weeping" when nerves are severed. The fluid is located in the innermost meningeal layer, the endoneurium, of peripheral nerves, but the origin of this "endoneurial fluid" is unknown. Further, we have observed that saline, when injected into CSF spaces with high pressure, caused swelling of peripheral nerves. Studies by our lab on human cadavers revealed channels on peripheral nerves within the outermost meningeal layer (i.e., epineurium) that neither stained for lymphatic nor hematopoietic markers. Although studying CSF flow is limited in post-mortem studies, our observations led us to hypothesize that CSF flow extends beyond the central nervous system reaching to distal peripheral nerves. To address this hypothesis, an *in vivo* model was needed. For this, a small tracer was infused into the CSF of healthy adult C57BL/6 and CD1 mice under physiological pressure. The distribution of the tracer was then determined by light and transmission electron microscopy (TEM) in the trigeminal nerve, spinal nerve roots and sciatic nerve. The results of this study indicate the existence of a contiguous system supplying continuous CSF flow to distal peripheral nerves. Given the importance of CSF in the CNS, we anticipate that CSF is critical for the maintenance of the peripheral nervous system. Thus, the identification of CSF flow to peripheral nerves could provide new insights into peripheral nerve disorders.

Disclosures: A.P. Ligocki: None. **A. Vinson:** None. **J. Pessa:** None. **E. Scott:** None.

Poster

727. Mapping and Organization of Feeding: Related Systems

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 727.24

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH Grant R01DK114279
Russell and Diana Hawkins Family Foundation Discovery Fellowship

Title: A basal forebrain to midbrain neurocircuit in inhibiting appetite by increasing responses to anxiogenic environment

Authors: *J. CAI[1], Y. XU[1], Z. JIANG[1], Y. JIANG[1], B. R. ARENKIEL[2], Q. TONG[1];
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Abstract: Nearly 1 in every 10 Americans are estimated to develop eating disorders in their lifetime. Yet, neuronal causes for eating disorders remain unclear. Stress impacts eating behaviors and reduces appetite in both animals and human beings. Understanding the brain mechanism underlying the disrupted balance between internal energy need and responses to anxiogenic environment is key to understanding eating disorders. The diagonal band of broca (DBB) is a basal forebrain region known for sensing environment stimuli to regulate higher order brain functions. Our recent study has shown that DBB glutamate neurons inhibit appetite by modulating the sensory perception such as olfactory inputs to induce food avoidance. Yet, the detailed mechanisms and downstream targets for the DBB in regulating feeding behaviors are unknown. Adeno-associated viruses (AAVs) based tracing results showed that DBB glutamate neurons send abundant projections to ventral tegmental area (VTA) glutamate neurons, which are vital for reward consumption and aversive responses. In addition, fiber photometry recordings indicated that these two groups of neurons increased neuronal responses simultaneously toward aversive stimuli. Optogenetic activation of the DBB to VTA circuit blunted fasting-induced refeeding by inducing aversive responses, which can be blocked by applying glutamate receptor antagonists. Consistently, acute activation of VTA glutamate neurons using the designer receptors exclusively activated by designer drugs (DREADD) based chemogenetic method reduced food intake as well as motivation for feeding. Importantly, chronic activation of VTA glutamate neurons led to reduced body weight and complete resistance to high fat diet-induced obesity mainly due to decreased food intake. These results demonstrate that VTA glutamate neurons are sufficient to inhibit feeding, reduce body weight and induce resistance to diet induced obesity, which at least partly mediates the aversive and anorexigenic effects from DBB glutamate neuron projections. In the future, more experiments will be conducted to test the functional relationship between the DBB to VTA circuit and the VTA dopamine system in modulating reward/food consumption.

Disclosures: J. Cai: None. **Y. Xu:** None. **Z. Jiang:** None. **Y. Jiang:** None. **B.R. Arenkiel:** None. **Q. Tong:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.01

Topic: F.08. Food and Water Intake and Energy Balance

Support: Dartmouth Women in Science Project

Title: Rat strain differences in the effects of exercise on diet choice

Authors: *E. YOUNG, A. ZENG, M. R. WEERASOORIYA, A. I. BYRD, A. S. CLARK;
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Abstract: Much of the emphasis in obesity treatment is placed on lifestyle modifications such as increasing physical activity or changing one's diet. However, genetic factors can also influence whether an individual is likely to become obese. The goal of the present study was to use a rodent model of obesity to explore the effects of exercise on diet choice in ovariectomized and intact female rats of two different strains, Long Evans (LE) and Sprague Dawley (SD). Rats were assigned to either an exercising or non-exercising condition. Exercising rats were housed in cages fitted with running wheels while non-exercising rats were housed in cages without running wheels. All rats were given ad libitum access to both standard chow and a palatable high-fat diet. Consistent with the literature, exercising SD rats initially preferred the standard chow diet but switched to preferring the high-fat diet days later. Surprisingly, exercising LE rats preferred the high-fat diet for the entire duration of the study. Ovariectomy did not influence these findings. As predicted, both non-exercising SD and LE rats consistently preferred the high-fat diet. Exercising SD rats consumed fewer total kilocalories of food per day and gained less body weight than non-exercising SD rats at the end of the study. Meanwhile, both exercising and non-exercising LE rats showed similar total food intake and body weight gain. Our data present a novel strain difference between SD and LE rats, supporting the view that lifestyle and genetic factors interact in obesity risk.

Disclosures: E. Young: None. **A. Zeng:** None. **M.R. Weerasooriya:** None. **A.I. Byrd:** None. **A.S. Clark:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.02

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH Grant P01-DK119130
Ruth L. Kirschstein National Research Service Award Individual Postdoctoral Fellowship, National Institute of Diabetes and Digestive and Kidney Diseases
Ruth L. Kirschstein Predoctoral Individual National Research Service Award, National Institute of Mental Health
Graduate Research Fellowship, National Science Foundation

Title: Ventromedial hypothalamic steroidogenic factor-1 neurons are potentiated by exercise training and underlie improvements in exercise performance

Authors: *R. J. POST, J. R. E. CARTY, N. GOLDSTEIN, M. KINDEL, R. VILLARI, M. TIMONEY, T. KELLARAKOS, H. KERN, B. SKELLY, J. BETLEY;
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Abstract: Exercise confers metabolic benefits that protect against obesity, including improvements in insulin sensitivity, glucose metabolism, and body composition. The ventromedial hypothalamus (VMH) is critical for the regulation of whole-body metabolism. The transcription factor steroidogenic factor-1 (SF1) that is necessary for the development of the VMH is also required for mice to receive the metabolic benefits of exercise training. This provocative observation suggested that SF1 neurons are essential for mice to improve performance and health following exercise. But are SF1 neurons activated during exercise? And can their activity alone serve as an exercise mimetic? To measure the activity of VMH SF1 neurons during exercise, 6-8 week-old male and female SF1-Cre mice were injected with AAV1-CAG-FLEX-GCaMP6s and a fiber optic was implanted over the VMH. A large, sustained increase in SF1 population neural activity was observed following the end of treadmill running sessions, including both 60 min training sessions ($n = 8$, $p < 0.01$) and endurance sessions in which mice run until exhaustion ($n = 8$, $p < 0.01$). Over a prolonged training paradigm in which mice run on the treadmill for 60 min per day for 5 consecutive days per week, the SF1 population neural response at the end of exercise becomes potentiated, increasing in magnitude over the course of the week ($n = 8$, $p < 0.05$). To determine if the magnitude of SF1 neural activity following exercise affects endurance capacity, SF1-Cre mice were engineered to express channelrhodopsin (ChR2) or a control virus, and a fiber optic was implanted over the VMH. Mice were run on a prolonged training paradigm of daily running sessions and 20 Hz stimulation was given at the end of each session to provide supplemental SF1 activation. The endurance capacity of mice was tested weekly over the course of training, and mice expressing ChR2 demonstrated a larger increase in endurance capacity than mice expressing the control virus over the course of training ($n = 12$, $p < 0.05$). Taken together, these results suggest that long-term changes in the activity of VMH SF1 neurons over the course of exercise training may underlie improvements in exercise performance.

Disclosures: **R.J. Post:** None. **J.R.E. Carty:** None. **N. Goldstein:** None. **M. Kindel:** None. **R. Villari:** None. **M. Timoney:** None. **T. Kellarakos:** None. **H. Kern:** None. **B. Skelly:** None. **J. Betley:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.03

Topic: F.08. Food and Water Intake and Energy Balance

Support: NRF- 2018R1A5A2025964
NRF-2020R1C1C1012399
NRF-2021R1A6A3A13042965)

Title: Neural Mechanism of Hunger-gated Food-seeking and Evaluating

Authors: *Y. LEE[1], Y. KIM[1], K. KIM[1], H. SONG[1], M. JANG[1], D.-S. HA[1], J. PARK[1], S.-H. JUNG[1], J. LEE[1], K. KIM[1], D.-H. CHEON[1], I. BAEK[1], M.-G. SHIN[2], E. LEE[2], S. KIM[3], H. CHOI[1];
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Abstract: The physiological need for energy evokes motivated feeding behaviours that help to ensure survival. However, the neural mechanisms underlying the generation of food motivation remain poorly understood. We investigated these mechanisms by subdividing feeding-related motivated behaviours into food-seeking, evaluating, and swallowing. Micro-endoscopic results indicated that neurons containing leptin receptors (LepRs) in the lateral hypothalamus (LH) are the major food-specific subpopulation of LH^{GABA} neurons. Optogenetic manipulation of LH^{LepR} neurons bidirectionally regulated both food-seeking and evaluating. Furthermore, micro-endoscope data revealed that distinct LH^{LepR} neurons encode seeking and evaluating. Computational modelling analysis demonstrated that LH^{LepR} neurons encode motivation, whereas neurons containing agouti-related peptide and neuropeptide Y (AgRP/NPY) encode the need for food. Additionally, slice studies revealed that NPY decreases inhibitory input to LH^{LepR} neurons via LH^{GABA} interneurons. This mechanism explains the permissive gate role of hunger (food need) in seeking/evaluating motivation. Together, the present study provides a comprehensive neural mechanism of how physiological needs drive distinct motivated behaviours.

Disclosures: Y. Lee: None. **Y. Kim:** None. **K. Kim:** None. **H. Song:** None. **M. Jang:** None. **D. Ha:** None. **J. Park:** None. **S. Jung:** None. **J. Lee:** None. **K. Kim:** None. **D. Cheon:** None. **I. Baek:** None. **M. Shin:** None. **E. Lee:** None. **S. Kim:** None. **H. Choi:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.04

Topic: F.08. Food and Water Intake and Energy Balance

Title: Role of Lateral Hypothalamus GABAergic Neurons on Goal-directed and Non-goal-directed Behaviors in Non-human Primates

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Abstract: **Introduction:** In recent years, the study of the role of LHA GABAergic neurons was vigorously executed in rodents. LHA GABAergic neuron activation in rodents is associated with

food-seeking and abnormal behavior. However, its role in the non-human primate is yet to be discovered. **Objective:** we dissected the behavior phenotype of goal-directed and non-goal-directed behavior. We also observed the role of LHA GABAergic neurons in Non-human primates. **Method:** we used three adult macaque monkeys in the experiment. We injected the AAV virus consisting of GABA specific promoter(hDlx) and chemo-genetics activation(hM3Dq). We developed the behavior indices and analyzed the assessment using manual and deep learning-based methods. **Results:** LHA GABAergic neuron activation in non-human primates was observed in goal-directed and non-goal-directed behavior. Goal-directed behavior for palatable food was significantly increased by LHA GABA neuron activation. Low speed with immobility to palatable food was increased by LHA GABA neuron activation connected to the meaning of compulsive food-seeking for palatable food. On the other hand, the vehicle-injected control monkey wandered with the palatable food and appeared to the stereotyped behavior as usual. No significant goal-directed behavior was observed with no object, toy, or water by LHA GABA neuron activation. In addition, non-goal-directed behavior of stereotyped and self-harming behavior was reduced in LHA GABAergic neuron activation. One monkey's vocalization relevant to stereotyped behavior was observed of reduced. **Conclusion:** LHA GABA neuron activation is presumed to increase food motivation and compulsive food-seeking for palatable food as a goal-directed behavior in non-human primates. In particular, as a non-goal-direct behavior, it is predicted to reduce the stereotyped and self-harming and eventually connected to the reduction in the vocalization of monkey B.

Disclosures: L.J. Ha: None. **H. Yeo:** None. **Y. Lee:** None. **J. Won:** None. **I. Baek:** None. **Y. Kim:** None. **Y. Jung:** None. **J. Min:** None. **K. Kim:** None. **J. Park:** None. **K. Lim:** None. **C. Jeon:** None. **W. Choi:** None. **S. Park:** None. **Y. Lee:** None. **H. Choi:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.05

Topic: F.08. Food and Water Intake and Energy Balance

Support: NWO-VICI grant 016.160.617
AMC PhD fellowship grant

Title: Consumption of a free-choice high-fat diet reduces lateral hypothalamic GABAergic neuronal activity in mice, while still responding to sugar drinking

Authors: *M. SLOMP[1,2], L. L. KOEKKOEK[1,2], M. MUTERSBAUGH[3], I. LINVILLE[3], S. H. LUQUET[4], S. E. LA FLEUR[1,2];
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Abstract: The lateral hypothalamus (LH) is crucial for regulating appetitive and consummatory behaviors. While it is known that overconsumption of high fat-sugary foods can lead to obesity, the precise mechanisms and circuits underlying these behaviors have yet to be determined. Previously, we have shown that glutamatergic LH neurons are responding to sugar drinking, and that this is disturbed by consumption of a free-choice high-fat diet (fcHFD). Whether the other major neuron population within the LH, the GABAergic neurons, also respond to sugar, and if a fcHFD affects LH GABAergic activity is yet unknown. Using *in vivo* two-photon microscopy, we analyzed activity changes in GABAergic LH neurons in chow or fcHFD-fed mice in response to water or sugar drinking. When looking at all responses, LH GABAergic neurons increase neuronal activity upon response to sugar compared to water irrespective of whether they are on a chow diet or fcHFD. This is driven by a greater number of LH GABAergic neurons that show a positive response to sugar drinking (13.31% sugar, 9.46% water), classifying individual neuronal traces as a response when showing a 20% change compared to baseline. A fcHFD decreased overall GABAergic neuronal activity, leading to a lower sugar response on fcHFD (7.71% positive responses) than on chow (13.31% positive responses). Thus, a fcHFD lowered overall LH GABAergic activity, but did not affect the response to sucrose specifically.Interestingly, when focusing on the response per unique, individual, neuron, a great variety in responses to subsequent trials of sugar drinking were observed, with the vast majority (95 % in chow-fed and 96% in fcHFD-fed animals) of neurons responding inconsistently over time. Consistent increased responses to sugar were only found in 2.6% of recorded neurons while animals were chow-fed, and 2.9% when fcHFD-fed. The remainder of neurons responded consistently decreasing, accounting for only 0.4% (chow) and 1.46% (fcHFD).In conclusion, a fcHFD dampens overall LH GABAergic activity , while it does not disturb the glucose sensing ability of GABAergic cells. The vast majority of neurons are responding inconsistently over time, suggesting it is not one specific subpopulation of LH GABAergic neurons that is driving this, but rather a network response from the population of neurons. To our knowledge, we are the first to describe the decreased network response of LH GABAergic neurons when fed a fcHFD. Further research should focus on determining how this dampening of LH GABAergic activity contributes to hyperphagia and the development of obesity.

Disclosures: M. Slomp: None. **L.L. Koekkoek:** None. **M. Mutersbaugh:** None. **I. Linville:** None. **S.H. Luquet:** None. **S.E. la Fleur:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.06

Topic: F.08. Food and Water Intake and Energy Balance

Support: DK118944

Title: Trapping a meal engram in the ventral hippocampus

Authors: *L. DECARIE-SPAIN[1], L. TIERNO LAUER[1], A. KAO[1], I. DENG[1], A. GALBOKKE HEWAGE[1], K. SUBRAMANIAN[1], A. BASHAW[1], A. CORTELLA[1], K. DONOHUE[1], R. CRIST[2], B. C. REINER[3], M. R. HAYES[4], S. E. KANOSKI[1];
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Abstract: The ventral subregion of the hippocampus (vHPC) has recently been identified as a key brain that integrates memory function and food intake control, yet the neural mechanisms mediating this integration have not been systematically evaluated. We set to illustrate the activity dynamics of vHPC neurons during appetitive and consummatory behaviors and characterize the profile and function of vHPC neurons engaged by eating in adult male Sprague-Dawley rats. [1] Fiber photometry-based recording of dynamic bulk vHPC calcium activity in awake behaving rats (n=6) revealed increased activity during a spatial memory-based foraging task, whereas vHPC activity was reduced during actual food consumption. [2] To evaluate a possible functional connection between vHPC neurons engaged by eating and foraging-related memory, rats received vHPC injections of a tamoxifen-inducible virus expressing Cre-recombinase driven by a Fos promoter, paired with a Cre-dependent virus expressing a diphteria toxin to ablate activated neurons. Recombination was induced by tamoxifen injection in 24h fasted rats given 30-minute access to food ('Fed'; n=11) or not ('Fasted'; n=10). Results show that ablation of food-responsive neurons in the Fed group increased spontaneous meal size and impaired performance in the spatial memory foraging task. [3] To identify the projection profile of vHPC food-responsive neurons, the use of the tamoxifen-inducible Fos-driven Cre-recombinase virus was paired with a Cre-dependent fluorescent tracer. Presence of axonal projections from the vHPC to the lateral hypothalamus (LHA) was specific to animals from the Fed (n=4) and not Fasted (n=5) group. [4] To confirm the relevance of this neural pathway to the function of vHPC food-responsive neurons, rats expressing inhibitory chemogenetic receptors (hM4Di) in vHPC-LHA neurons received intracerebroventricular infusion of clozapine-N-oxide (n=7) or its vehicle (n=6). Acute silencing of vHPC-LHA reduced spontaneous meal size and impaired performance in the spatial memory-based foraging task. [5] To characterize the genetic profile of vHPC food-responsive neurons, the vHPC was harvested in the Fed (n=6) or Fasted (n=6) state for single-nucleus RNA sequencing. Results identify that neurons active in the Fed state are enriched in the serotonin receptor type 2a, while those active in the Fasted state express the orexin type 2 and cannabinoid type 1 receptors. Together, these results identify and characterize a population of vHPC neurons that are engaged by eating and contribute functionally to both meal size control and foraging-related spatial memory.

Disclosures: L. Decarie-Spain: None. **L. Tierno Lauer:** None. **A. Kao:** None. **I. Deng:** None. **A. Galbokke Hewage:** None. **K. Subramanian:** None. **A. Bashaw:** None. **A. Cortella:** None. **K. Donohue:** None. **R. Crist:** None. **B.C. Reiner:** None. **M.R. Hayes:** None. **S.E. Kanoski:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.07

Topic: F.08. Food and Water Intake and Energy Balance

Support: Brown Foundation
NIH K08HL135275
ADA 1-16-INI-17
NIH P30 DK124723

Title: Nervous system reduction in branched-chain amino acid metabolism disrupts hippocampal neurogenesis and memory

Authors: *K. ABDI[1], R. RODRIGUIZ[1], W. C. WETSEL[2], M. ARLOTTO[1], R. W. MCGARRAH[1], P. WHITE[1];
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Abstract: A role for macronutrient metabolism in learning and memory is supported by numerous epidemiological studies. The *Ppm1k* gene encodes the branched-chain keto acid dehydrogenase (BCKDH) phosphatase that promotes the metabolism of branched-chain amino acids (BCAA). Here we show that nervous system deletion of *Ppm1k* in mice increases BCAA levels in brain tissue but not in plasma. These mice have significant impairments in working memory accompanied by a robust accumulation of DCX+/NeuroD1+ immature neurons within the dentate gyrus granule cell layer. Through single cell RNA sequencing and pathway analysis we identified substantial increases in transit-amplifying cells and immature neurons along with activated hedgehog signaling in *Ppm1k* deficient primary neural stem cells (NSCs). Inhibition of mTOR signaling reversed the effects of *Ppm1k* deletion on neuronal progenitor gene activation in primary NSCs. Together our findings uncover a new molecular link between BCAA metabolism, hippocampal neurogenesis, and cognitive performance.

Disclosures: K. Abdi: None. **R. Rodriguiz:** None. **W.C. Wetsel:** None. **M. Arlotto:** None. **R.W. McGarrah:** None. **P. White:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.08

Topic: F.08. Food and Water Intake and Energy Balance

Support: MOE Tier 2 (2019) / MOE2019-T2-2-024
NUSMed-FoS / NUHSRO/2018/075/NUSMed-FoS/01

Title: Loss of brain-specific RNA editing of the $Ca_V1.3$ channel promotes day hyperphagia and obesity.

Authors: *J. KOH, J. ZHAI, T. W. SOONG;
Physiol., Natl. Univ. of Singapore, Singapore, Singapore

Abstract: The $Ca_V1.3$ channel contributes to a variety of neural functions, from neurodevelopment, learning and memory to addiction, mood and circadian regulation. The discovery of brain-specific $Ca_V1.3$ IQ domain RNA editing wherein edited $Ca_V1.3$ channels have reduced Ca^{2+}-dependent inactivation, illuminated a novel modulatory mechanism of calcium signalling in the brain. To investigate the functional significance of RNA editing in $Ca_V1.3$ transcripts, we used a transgenic knockout mouse model of $Ca_V1.3$ IQ domain RNA editing ($Ca_V1.3^{\Delta ECS}$) and showed that $Ca_V1.3^{\Delta ECS}$ male mice had increased body weight (6 months: +3.36±1.46g, p=0.03; n>10mice). This was accompanied with reduced counts of anorexigenic pro-opiomelanocortin-expressing arcuate (ARC^{POMC}) neurons in the day (-25.45±9.63neurons, p=0.0458, n=3-4 mice) and increased day feeding (6 months:+0.16±0.06g, p=0.0144, n=11-12mice). $Ca_V1.3^{\Delta ECS}$ males also exhibited a slight trend of greater c-fos neuronal activation in the ARC and reduced c-fos activation in the bed nucleus of the stria terminalis compared to controls when fasted overnight (n=3-4 mice), which may suggest a greater hunger drive. Surprisingly, female $Ca_V1.3^{\Delta ECS}$ mice displayed no change to day feeding and only displayed significantly higher body weight at 12 months (+6.67±2.05g, p=0.0068, n=7mice). $Ca_V1.3^{\Delta ECS}$ males, but not females consequently developed higher levels of fasting plasma glucose (+2.06±0.7mmol/L, p=0.0065, n=15-16mice), fasting plasma insulin (+1.15±0.32ng/mL, p=0.0054, n=5-7mice) and glucose intolerance (males: area-under-curve:+467.1±173.7, p=0.0118, n=15-16mice). Body weight gain and the glucose dysregulation in $Ca_V1.3^{\Delta ECS}$ males could however be rescued with day fasting for 6 weeks (n=6-7 mice). When returned to 6 weeks of *ad libitum* feeding however, $Ca_V1.3^{\Delta ECS}$ males became heavier than their controls (+5.52±2.02g, p=0.0178) again but glucose tolerance did not deteriorate. These results highlight a novel functional significance of $Ca_V1.3$ channel editing in the modulation of feeding patterns that can result in metabolic dysregulation in the long run, and is subject to gender differences. The lack of feeding pattern change and metabolic disruption in female $Ca_V1.3^{\Delta ECS}$ mice suggests that gender differences in either the upstream regulation of $Ca_V1.3$ editing or other protective mechanisms downstream may protect female mice from calcium dysregulation. These findings beget further studies on the upstream regulation of $Ca_V1.3$ editing to better our understanding of age- and gender-differences in the regulation of feeding and obesity.

Disclosures: **J. Koh:** None. **J. Zhai:** None. **T.W. Soong:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.09

Topic: F.08. Food and Water Intake and Energy Balance

Support: FONDECYT Grant Nº 120–0474
DIUV-CI Grant N°01/2006

Title: Chronic exposure to an obesogenic diet only changes food preference in male Sprague Dawley rats, which is not reversed after dietary and pharmacological treatment for weight loss

Authors: *M. J. COVARRUBIAS[1,2], A. HENRIQUEZ[1], R. OLIVARES-BARRAZA[1,2], V. COLLIO[1,2], C. CRUZ-CARVAJAL[1], F. VALENZUELA-LAGOS[1], J. MARTINEZ-PINTO[1], R. SOTOMAYOR-ZARATE[1];
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Abstract: Obesity is defined as abnormal or excessive fat accumulation that may impair health. Currently it is considered a pandemic because its prevalence has increased in the world. An important cause that leads to overweight and obesity is the intake of highly caloric obesogenic foods (rich in fats and sugars), generating an energy imbalance between consumed and expended calories. Currently, the only therapeutic approach to treat obesity is based on changes in habits such as type of food and physical activity, and drugs that control hyperphagia such as phentermine.The aim of this work was to determine if chronic exposure to high fat diet (HFD) plus 5% sucrose (S) solution from postnatal day (PND) 21 to PND 62 modify food preference and whether it can be reversed by dietary and pharmacological treatment for weight loss. Parallel control groups were fed with standard chow food and water. At PND 62, a food intake test was performed to determine preference for HFD or chow. At PND 63, all the animals were fed with standard food for 10 days and during this period some rats were injected with phentermine (30 mg/kg i.p.) or vehicle (1 mL/kg i.p.). At PND 74 a new food intake test was made to determine the preference.The results show that the animals exposed to the obesogenic diet have greater weight gain and fat accumulation than the control group animals, which they are reversed after dietary and pharmacological treatment. At PND 62, the exposure to HFD for 6 weeks increased the preference for HFD in male compared with the control group. This preference was not observed in HFD female rats. Interestingly, at PND 74 male rats fed with HFD for 6 weeks and treated with phentermine and chow diet for the last 10 days, they show a higher preference for HFD than chow diet, despite phentermine-induced weight loss. These results indicate that chronic exposure to an obesogenic diet not only generates changes in weight and body fat, which can be reversed by an anorectic treatment, but also modifies food preference, which is not reversed by induction of weight loss. This may be due to changes in central hedonic and homeostatic control of feeding, which will be later evaluated by molecular biology techniques. Taken together, these results help to understand the neurobiology of obesity and its behavioral consequences.

Disclosures: M.J. Covarrubias: None. **A. Henriquez:** None. **R. Olivares-Barraza:** None. **V. Collio:** None. **C. Cruz-Carvajal:** None. **F. Valenzuela-Lagos:** None. **J. Martinez-Pinto:** None. **R. Sotomayor-Zarate:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.10

Topic: F.08. Food and Water Intake and Energy Balance

Title: Pacap 1-38 decrease the consumption of palatable food in a intermittent model of binge-intake.

Authors: *S. ORTEGA-TINOCO[1], J. GARDUÑO[2], J. BRAVO-MARTÍNEZ[3], S. HERNANDEZ-LOPEZ[4];
[1]UNAM, Ciudad de México, Mexico; [2]UNAM, Mexico, D.F., Mexico; [3]UNAM, CDMX, Mexico; [4]Univ. Nacional Autonoma De Mexico, Mexico City, Mexico

Abstract: According to the OMS, it has been reported that in all regions of the Americas, 62% of adults are overweight or obese. Overweight and obesity are mainly triggered by eating disorders such as binge-eating, which consists of an excessive consumption of palatable foods in a short period of time, approximately 2h. Food intake involves motivational and hedonic processes. The NAc is related to the modulation of the hedonic value assigned to palatable foods. Hurley and coworkers reported that microinjections of PACAP 1-38 into the NAc decreases the consumption of palatable feed. The objective of this work was to standardize the use of lunettes as a palatable food in the binge-like intake model proposed by Corwin and to evaluate the anorexigenic effect of PACAP in a different model of binge-type intake. Binge-type intake was evaluated using Corwin's model. The 24 subjects were separated as follows: control (n=6), binge-intake (n=6), binge intake, vehicle (n=6) and binge-intake, PACAP1-38 2 (n=7).Twenty-eight 2-month-old male Wistar strain rats weighing between 300 and 500 g were used.
For 28 days all subjects had *ad libitum* access to standard food and water. First, the use of M&Ms as palatable feed was tested. The experimental group with binge-intake had access to M&Ms 12 days (for 4 weeks).Second, microinjections of PACAP 1-38 were performed in the NAc with the Corwin binge-type intake model using M&Ms as palatable food. Both groups, with binge-intake) had access to M&Ms 12 days (for 4 weeks). On day 14 cannulas were placed bilaterally in the NAc with the following coordinates respect to Bregma: AP:1.20, ML: 2.01 and DV: 7.4. On days 21, 23 and 25, microinjections of saline and PACAP 1-38 (100 nM) were performed to the binge-intake groups, respectively. For the statistical analysis we used the Mann Whitney and Kruskal Wallis U tests. Significant differences were taken when $p < 0.05$.Our results indicate that M&Ms can be used as a palatable food in the binge-like intake model proposed by Corwin. We were able to observe that the groups with binge-intake had a high consumption of M&Ms. We observed that microinjections of PACAP 1-38 into the NAc decreased the intake of palatable food. The NAc is critical in mediating reward behaviors, including binge intake. In this study, we used a Corwin model. This model allowed us to confirm that microinjections of PACAP 1-38 promote an anorexigenic effect in the consumption of high-calorie food, as previously reported by Hurley in 2016. However, more research is needed on the molecular and signaling mechanisms by which PACAP 1-38 functions as an anorectic agent. On the other hand, PACAP 1-38 could be a therapeutic target for eating disorders such as binge-eating.

Disclosures: S. Ortega-Tinoco: None. **J. Garduño:** None. **J. Bravo-Martínez:** None. **S. Hernandez-Lopez:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.11

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH K08 DK118201
NYNORC
Whitehall foundation

Title: Mc4r activity in infralimbic cortex regulates food intake and food-seeking behavior

Authors: P. DAS[1], A. KIM[3], K. CALLAHAN[2], M. COOKE[2], Y. LI[4], V. Y. BOLSHAKOV[5], *R. ROSS[2];
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Abstract: The melanocortin-4-receptor (MC4R) is implicated in metabolism and energy expenditure, and mutations of the MC4R are strongly linked to obesity in humans and mice. Its activity is regulated by peptides released from arcuate feeding and satiety neurons, agouti related protein (AgRP) and pro-opiomelanocortin (POMC). The MC4R is highly expressed in the hypothalamus, but deletion of MC4R from this region does not recapitulate the obesity induced by global brain knockout, suggesting MC4Rs in other regions are involved. The MC4R is expressed in the infralimbic cortex (IL), an area of the brain involved in decision making and habitual activity. Human imaging data implicates this region in obesity-related food cue responses. Using an MC4R-cre mouse with a GFP reporter, we performed an immunohistochemical staining and found that projections from AgRP and POMC neurons converge onto the IL. **We hypothesized that MC4R activity in the IL (IL^{MC4R}) is regulated by peptides released from hypothalamic neurons, and also influences food intake and food-seeking behavior.** First we examined how pharmacologic manipulation of the MC4R affects neuronal dynamics in the IL using slice electrophysiology. MC4R agonists depolarized the membrane and increased excitability of IL^{MC4R} neurons, which we found are glutamatergic and project to areas associated with food-motivated behavior. Next, using optogenetic manipulation, we found that terminal stimulation of AgRP axons in the IL increases food intake. Lastly, we used viral-cre manipulation in male $MC4R^{lox/lox}$ mice to selectively delete IL^{MC4R} and observed an increase in food intake and body weight, as well as a delay in food-seeking and consuming behavior in an open field environment. Our data highlights a novel population of MC4R-expressing neurons in the IL that influences food intake and other food-seeking behavior. These findings contribute to our understanding of the mechanisms that govern food-seeking behavior, which is especially relevant in obesity, an illness in which food-related decision-making can be impaired.

Disclosures: P. Das: None. **A. Kim:** None. **K. Callahan:** None. **M. Cooke:** None. **Y. Li:** None. **V.Y. Bolshakov:** None. **R. Ross:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.12

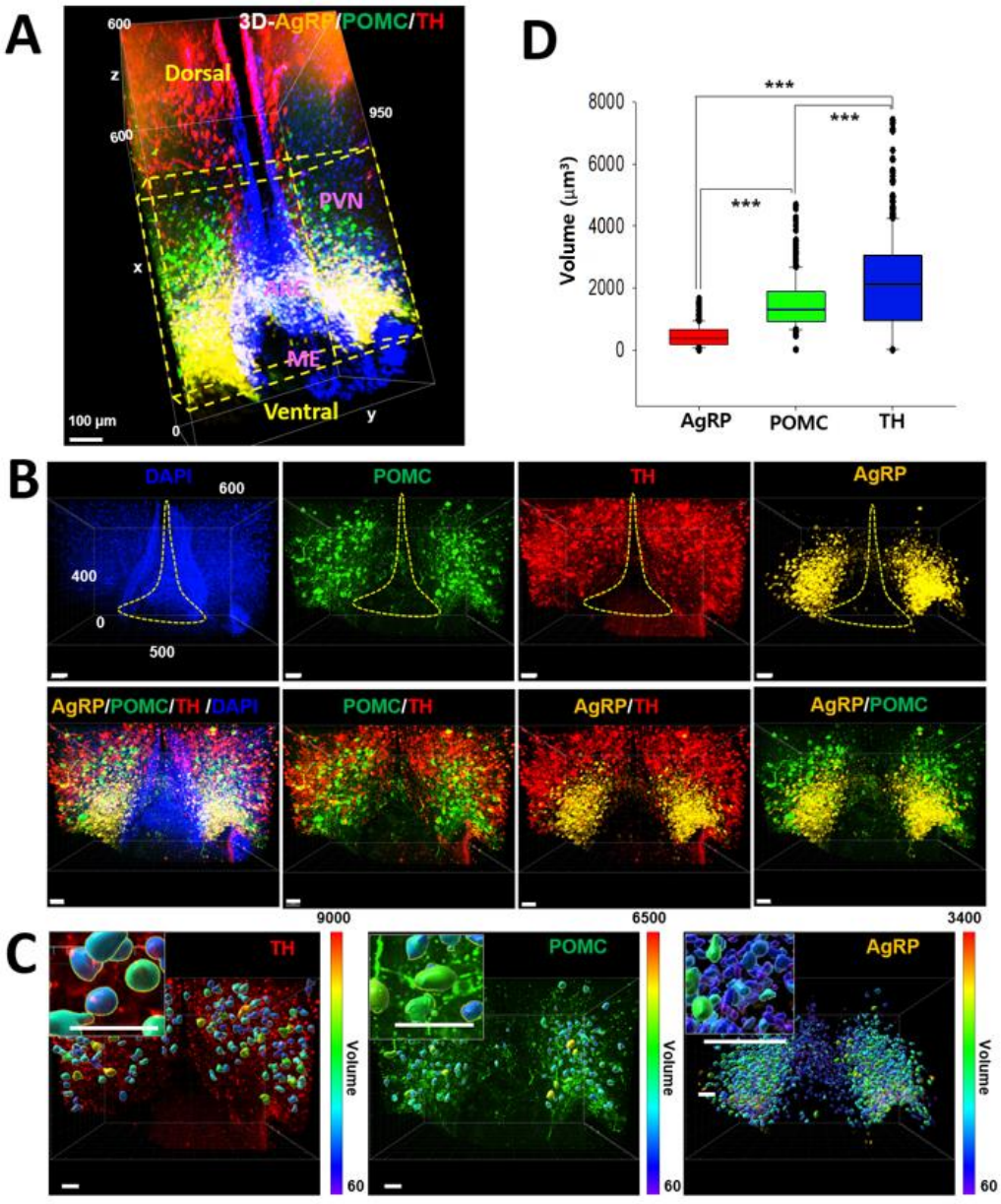
Topic: F.08. Food and Water Intake and Energy Balance

Support: NRF-2021R1C1C2005067

Title: Distinct firing activities of the hypothalamic arcuate nucleus neurons to appetite hormones

Authors: *J. NA[1], D. JANG[1], D. KIM[1], S. YANG[1], B. PARK[2], T. TU[2], J. KIM[2], Y. RYU[3], C. HA[3], M. KOCH[4], S. YANG[5];
[1]Nano-Bioengineering, [2]Life Sci., Incheon Natl. Univ., Incheon, Korea, Republic of; [3]Res. Div. and Brain Res. Core Facilities, Korea Brain Res. Inst., Daegu, Korea, Republic of; [4]Anat. and Cell. Biol., Inst. of Theoretical Medicine, Med. Faculty, Univ. of Augsburg, Augsburg, Germany; [5]Dept. of Neurosci., City Univ. of Hong Kong, Hong Kong, China

Abstract: The hypothalamic arcuate nucleus (Arc) is a central unit that controls the appetite through the integration of hormonal and neuronal afferent inputs. Agouti-related protein (AgRP), proopiomelanocortin (POMC), and dopaminergic neurons in Arc differentially regulate feeding behaviors in response to hunger, satiety, and appetite, respectively. Up to date, the anatomical and electrophysiological characterization of these three neurons has not yet been intensively explored. Here, we interrogated the overall characterization of AgRP, POMC, and dopaminergic neurons using genetic mouse models, immunohistochemistry, and whole-cell patch recordings. We iden-tified the distinct geographical location and intrinsic properties of each neuron in Arc with the transgenic lines labeled with cell-specific reporter proteins. Also, AgRP, POMC, and dopaminergic neurons had different firing activities to ghrelin and leptin treatments, showing the increased firing rate of dopaminergic / AgRP neurons to ghrelin and POMC neurons to leptin. These findings demonstrate the anatomical and physiological uniqueness of three hypothalamic Arc neurons to appetite control.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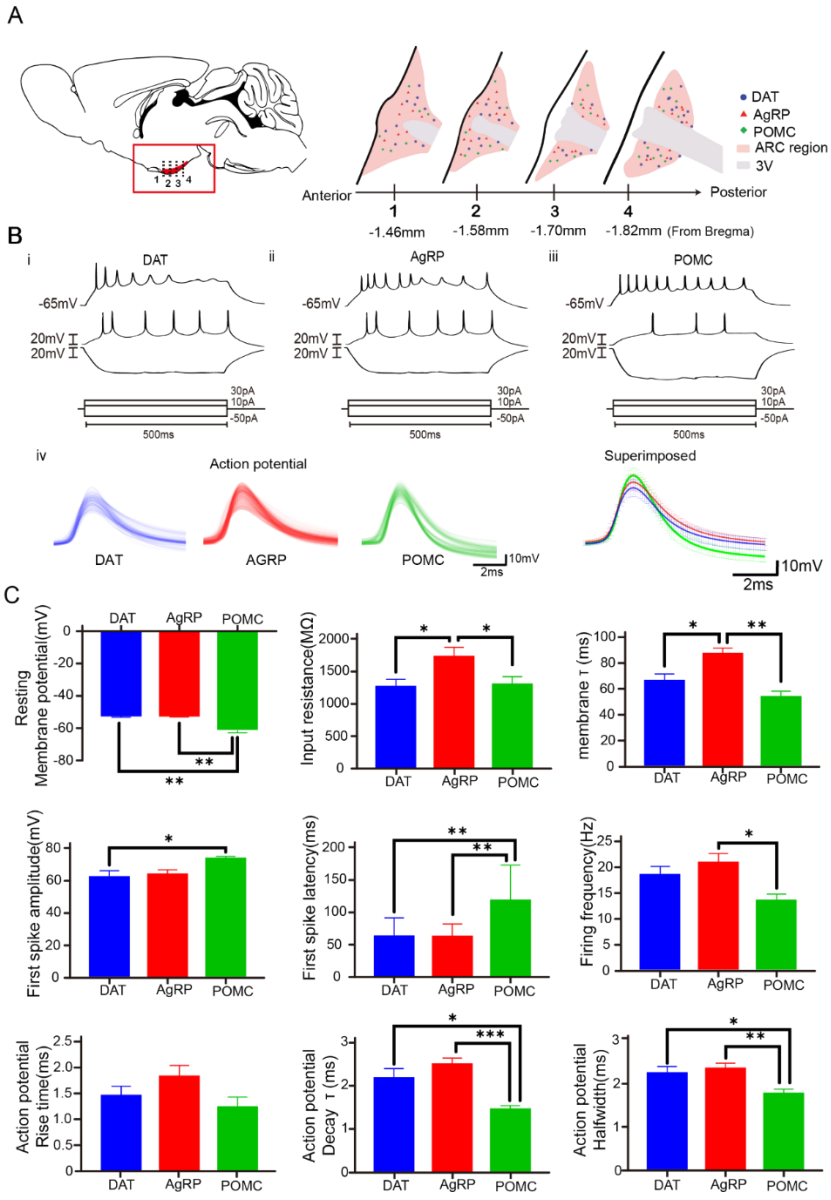

Disclosures: **J. Na:** None. **D. Jang:** None. **D. Kim:** None. **S. Yang:** None. **B. Park:** None. **T. Tu:** None. **J. Kim:** None. **Y. Ryu:** None. **C. Ha:** None. **M. Koch:** None. **S. Yang:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.13

Topic: F.08. Food and Water Intake and Energy Balance

Support: TWU Experiential Student Scholar Grant
TWU Center For Student Research Grant
TWU Startup funds and Research Enhancement Program Grant

Title: Pomc-specific mecp2 knockout alters preference for high fat diet and produces a depressive-like phenotype in mice.

Authors: *J. MEDRANO, E. NA, A. BAIRD, P. FRAYRE, M. RUIZ;
Texas Woman's Univ., Denton, TX

Abstract: Mutations in methyl-CP-G binding Protein 2 (MeCP2) gene function are implicated in neurodevelopmental disorders such as Rett syndrome, *MECP2* duplication syndrome, and Autism Spectrum Disorder, producing learning and memory deficits, as well as anxiety phenotypes. Past research demonstrates that knockout (KO) of *Mecp2* in hypothalamic pro-opiomelanocortin (POMC) neurons produces an overweight phenotype after prolonged high fat diet (HFD) exposure but it is not yet known if KO of *Mecp2* in POMC neurons might also affect other behaviors such as depression and anxiety. Given that obesity is highly co-morbid with mood disorders as well as anxiety, and that POMC is the precursor peptide to the stress hormone, adrenocorticotropin hormone (ACTH), we hypothesized that POMC-specific knockout of *Mecp2* may alter depressive-like or anxiety-like behaviors as a function of obesity. POMC-MeCP2 KO mice and wildtype (WT) controls were maintained on an obesogenic diet and then subjected to tests that assess depression and anxiety. Consistent with previous literature, we demonstrate that POMC-MeCP2 KO mice had increased body weight relative to WT controls despite comparable food intake. Interestingly, we show that POMC-MeCP2 KO mice spend significantly more time immobile in the forced swim test compared to WT controls, demonstrating a depressive-like phenotype. We, however, did not observe an anxiety-like phenotype in our KO mice. Plasma ACTH levels were also assessed between POMC-MeCP2 KO and WT mice given chronic HFD. Taken together, our data implicate POMC-specific loss-of-MeCP2 function may adversely impact depressive-like behaviors in mice which could recapitulate the depression observed in clinical cases of obesity.

Disclosures: J. Medrano: None. **E. Na:** None. **A. Baird:** None. **P. Frayre:** None. **M. Ruiz:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.14

Topic: F.08. Food and Water Intake and Energy Balance

Title: Characterization of orexin A effects on arcuate POMC neurons

Authors: *J. CHOI, J.-W. SOHN;
Biol. Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: Orexin A and orexin B (hypocretin 1 and hypocretin 2) are hypothalamic neuropeptides that promote feeding via the hypocretin receptor 1 (Hcrtr1) and hypocretin receptor 2 (Hcrtr2). Previous studies demonstrated that both Hcrtr1 and Hcrtr2 are expressed throughout the hypothalamus. Interestingly, Hcrtr2 is highly expressed by the pro-opiomelanocortin (POMC) neurons in fed state, but the role of Hcrtr2 expressed by POMC neurons remains unclear. In this study, we assessed the responses of POMC neurons to orexin A by multiple approaches including patch-clamp electrophysiology and immunohistochemistry. We found that applications of orexin directly altered a distinct subpopulation of POMC neurons. Our findings provide insight how orexin A controls feeding behaviors via the regulation of POMC neurons.

Disclosures: J. Choi: None. **J. Sohn:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.15

Topic: F.08. Food and Water Intake and Energy Balance

Title: Role of GIRK channels expressed by arcuate POMC neurons

Authors: *Y. CHOI, Y. OH, J.-W. SOHN;
Biol. Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: The pro-opioidmelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus have been regarded as key to regulate energy balance and glucose homeostasis. The G protein-gated inwardly rectifying (GIRK) channels are important to maintain resting membrane potential (RMP) and mediate slow responses to inhibitory signals. While there are some clues that the GIRK channel expressed by the POMC neurons may regulate homeostasis, we currently do not have direct evidence to support this idea. In this study, we found that GIRK1 subunits are responsible for the maintenance of RMP and mediating $GABA_B$-induced inhibition of POMC neurons. We also generated conditional knockout mice by breeding Pomc-Cre mice with $GIRK1^{flox/flox}$ mice to assess the metabolic function of GIRK1 subunits expressed by POMC neurons. Our results provide insight how GIRK channels expressed by POMC neurons regulate neuronal activity and metabolic function.

Disclosures: Y. Choi: None. **Y. Oh:** None. **J. Sohn:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.16

Topic: F.08. Food and Water Intake and Energy Balance

Support: Samgsung

Title: Role of GIRK channels in the hypothalamic NPY/AgRP neurons

Authors: *Y. OH, J.-W. SOHN;
Biol. Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: The neuropeptide Y(NPY)/agouti-related peptide (AgRP) neurons in the arcuate nucleus (ARC) of the hypothalamus is a central neuronal population to regulate energy homeostasis. NPY/AgRP neurons have been shown to release NPY, AgRP, and GABA, which directly or indirectly regulates feeding behavior and energy expenditure. Furthermore, short-term modulation of NPY/AgRP neuronal activity through genetically-modified constructs acutely regulated feeding behavior and energy expenditure in a reversible manner. However, we still lack knowledge about intrinsic regulatory factors in NPY/AgRP neurons that control energy homeostasis. Since it is well established that the G protein-gated inwardly rectifying K^+ (GIRK) channels play a key role to maintain resting membrane potential (RMP) of central neurons, we tested whether GIRK channels play a regulatory role in NPY/AgRP neurons. Specifically, we performed patch-clamp experiments in order to verify the role of GIRK channels in regulating NPY/AgRP neuronal activity, and found a key role of GIRK2 subunits. Next, we tested whether the deletion of GIRK2 channel subunits specifically in NPY/AgRP neurons induces changes in feeding behavior and energy expenditure. Our results suggested that GIRK channels expressed by the NPY/AgRP neurons serve as key intrinsic regulatory factors to control neuronal activity and energy

Disclosures: Y. Oh: None. **J. Sohn:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.17

Topic: F.08. Food and Water Intake and Energy Balance

Title: Central mechanisms of anorexia with a novel GLP-1 receptor agonist

Authors: *S. YOO, J.-W. SOHN;
Dept. of Biol. Sci., Korea Advanced Inst. in Sci. and Technol., Daejeon, Korea, Republic of

Abstract: Glucagon-like peptide-1 receptor (GLP-1R) is a widely investigated therapeutic target for obesity, and is well established for its potency in reducing food intake and body weight. GLP-1 suffers from a short half-life due to the degradative actions of dipeptidyl peptidase 4 (DPP-4) enzyme. One of the earlier forms of DPP-4 resistant GLP-1 analog, exenatide, has been

rearranged and modified to exendin-4 (1-32) K-capric acid (Ex-4c) for the maximal stability and efficacy in blood glucose and body weight regulation. Here, we investigated the cellular and ionic mechanisms of Ex-4c-induced food intake suppression via GLP-1R activation. We found that the central infusion of Ex-4c in C57BL/6J male mice at 6-12 weeks of age induced anorexia, and that the presence of pro-opiomelanocortin (POMC) neurons are essential in mediating the action. The ex vivo electrophysiological measurements indicate that the Ex-4c directly stimulates the POMC neurons in the arcuate nucleus of hypothalamus via the closure of ATP-sensitive potassium (K_{ATP}) channels, predominantly in a cAMP-dependent PKA pathway. We expect our findings to provide an insight into the central mechanisms of Ex-4c action and contribute to the development of novel GLP-1-based anti-obesity drugs.

Disclosures: S. Yoo: None. **J. Sohn:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.18

Topic: F.08. Food and Water Intake and Energy Balance

Support: RF1MH120144

Title: Using genetically-encoded optical sensors to detect GLP-1 release in vivo

Authors: *Y. LU, F. LUO, V. MIRABELLA, R. SAVANI, L. WANG, Z. PANG;
Neurosci., The Child Hlth. Inst. of New Jersey, New Brunswick, NJ

Abstract: Glucagon-like peptide 1 (GLP-1, encoded by Gcg gene) secreted by the L-cells of the intestine and a distinct subpopulation of hindbrain nucleus tractus solitarius (NTS) neurons is an incretin hormone that carries out essential functions in feeding and energy homeostasis. However, the temporal release patterns of endogenous GLP-1 in the brain and the correlation with animal behavior is still poorly understood. This is mainly due to the lack of molecular tools that can directly detect GLP-1 in real-time. Our lab has developed a novel, genetically encoded, highly sensitive and specific optical sensor, termed Reporter for Transmission mediated by G-protein-coupled Receptor (RTGR), for GLP-1. This unique tool allows real-time monitoring of GLP-1 release kinetics in intact mouse brains. Utilizing fiber photometry recording combined with optogenetic stimulation of the GLP-1 expression NTS neurons, we showed that GLP-1 RTGR could detect GLP-1 release with high sensitivity in mice. In free-moving mice, we found endogenous GLP-1 release was associated with food intake patterns in naturalistic feeding behavior in the paraventricular nucleus of the hypothalamus (PVN). Particularly, GLP-1 levels in the PVN were increased after each eating bout during the longitudinal recording overnight. Ongoing efforts are focused on further validating these findings and the delineation of the implication of GLP-1 release in food intake behavior. These results highlight the physiological role of central endogenous GLP-1 release in feeding and other naturalistic behaviors.

Disclosures: **Y. Lu:** None. **F. Luo:** None. **V. Mirabella:** None. **R. Savani:** None. **L. Wang:** None. **Z. Pang:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.19

Topic: F.08. Food and Water Intake and Energy Balance

Support: PO1DK117821

Title: Regulation of Glp-1 receptor and Gpr10-expressing neurons in the mouse area postrema

Authors: ***R. BHAGAT**[1], C. CONNAUGHTON[1], D. OLSON[2], P. GOFORTH[1];
[1]Pharmacol., [2]Mol. and Integrative Physiol. and Dept. of Pediatrics, Univ. Of Michigan, Ann Arbor, MI

Abstract: The area postrema (AP) contains multiple neuronal populations that sense nutritional status and aversive stimuli. AP populations include those expressing glucagon-like peptide-1 receptor ($Glp1R^{AP}$), a target for anti-obesogenic Glp1R agonist pharmacotherapies, which also produce nausea. A subset of $Glp1R^{AP}$ neurons express GPR10, the receptor for prolactin releasing peptide (PrRP), which suppresses food intake without aversion. We use ex vivo calcium imaging and electrophysiology to directly examine regulation of AP neurons by the Glp1R agonist, liraglutide, and the GPR10 agonist, PrRP. We demonstrate a heterogeneous population of $Glp1R^{AP}$ neurons, with $GPR10^{AP}$ neurons representing a functional subset, activated by both liraglutide and PrRP. We also examine regulation of AP neurons by the incretin, GIP. GIP receptor (GIPR) agonism promotes weight loss, with Glp1R and GIPR co-agonism producing synergistically larger reductions in body weight. The site and mechanisms of GIP action are poorly understood, yet data suggest that GIP acts via local AP GABAergic neurons to suppress Glp1R agonist-induced aversion. Our results showed both, GIP-induced inhibition, and activation of $Glp1R^{AP}$ and $GPR10^{AP}$ neurons. GIP inhibits $Glp1R^{AP}$ neurons indirectly by increasing the frequency of spontaneous inhibitory synaptic input and activating a hyperpolarizing current. In addition, GIP attenuates liraglutide-induced activation of $Glp\text{-}1R^{AP}$ neurons, consistent with reports that systemic administration of GIP ablates nausea associated with GLP1R agonists in vivo. u These data demonstrate functional subpopulations of $Glp1R^{AP}$ neurons that are indirectly and bidirectionally regulated by GIP.

Disclosures: **R. Bhagat:** None. **C. Connaughton:** None. **D. Olson:** None. **P. Goforth:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.20

Topic: F.08. Food and Water Intake and Energy Balance

Support: R01DK106476

Title: Postnatal high fat diet exposure alters the organization of convergent interosensory pathways and disrupts state-dependent GLP-1 network activity

Authors: *J. E. BIDDINGER[1], D. SRISAI[1], A. NANDA[2], M. RUBINOV[2], R. SIMERLY[1]; [1]Mol. Physiol. & Biophysics, [2]Biomed. Engg, Vanderbilt Univ., Nashville, TN

Abstract: Neural networks that integrate sensory information and coordinate physiological responses regulating homeostasis develop primarily during the first two weeks of postnatal life. Environmental conditions during this developmental critical period can profoundly influence the organization and activity of these pathways. For example, the adipocyte-derived hormone leptin influences development of convergent inputs to the paraventricular nucleus of the hypothalamus (PVH) by promoting axon outgrowth from AgRP neurons in the arcuate nucleus of the hypothalamus (ARH), while suppressing development of GLP-1 (Glucagon-like peptide-1) projections that arise from PPG (Preproglucagon) neurons in the nucleus of the solitary tract (NTS). Inputs from the ARH and NTS converge onto the PVH, an essential neuroendocrine integration site where a large proportion of neurons express GLP-1 receptors (GLP-1R). To explore further how the postnatal nutritional environment impacts the functional organization of PVH GLP-1R neuronal populations, we utilized genetically-targeted axonal labeling strategies and immunohistochemistry, together with chemogenetic assays, to visualize and manipulate GLP-1 circuitry in adult offspring that were exposed to maternal high fat diet during lactation (MHFD). The results suggest that MHFD impairs formation of these pathways in offspring, however, in contrast to the effects of postnatal leptin, both AgRP and GLP-1 inputs to the PVH are significantly reduced in adult mice derived from MHFD dams. Chemogenetic activation of PPG neurons reduces intake of high fat diet in control mice, an effect that is partially restored by silencing GLP-1R neurons in the PVH, but adult MHFD mice did not alter consumption upon PVH GLP-1R activation. In addition, calcium-imaging based microendoscopy was used to record population dynamics of PVH GLP1-R neuronal activity in response to metabolic stimuli in freely-behaving animals. Viscerosensory stimuli (e.g. i.p. CCK or gastric preload) activated numerous GLP-1R neurons in the PVH, with substantial heterogeneity in response profiles and temporal kinetics, effects that were blunted in MHFD mice. Correlational analyses of neural activity and network connectivity suggest that exposure to postnatal MHFD does not significantly alter acute activity of PVH GLP-1R neurons during periods of low energetic demand and minimal interoceptive stress. However, when physiological challenges require adaptive neural responses, an underlying instability of GLP-1 network connectivity leads to altered activity of PVH GLP-1R neural ensembles, which may contribute to the metabolic dysregulation observed in MHFD mice.

Disclosures: J.E. Biddinger: None. **D. Srisai:** None. **A. Nanda:** None. **M. Rubinov:** None. **R. Simerly:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.21

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH Grant T32DK20593
NIH Grant R01DK106476

Title: Microglia respond to maternal high fat diet during lactation and interact directly with developing AgRP projections in the hypothalamus.

Authors: *H. N. MENDOZA-ROMERO, R. B. SIMERLY;
Vanderbilt Univ., Vanderbilt Univ., Nashville, TN

Abstract: Environmental influences that occur early in life, such as nutrition, dictate adaptations of an organism that will affect susceptibility to weight gain and obesity later in life. Offspring that are subjected to overnutrition during the perinatal period are more likely to become obese. For example, maintaining dams on a high fat diet during the lactation period (MHFD-L) negatively affects body weight and the formation of hypothalamic feeding circuits in offspring. Agouti-related peptide (AgRP) neurons in the arcuate nucleus of the hypothalamus (ARH) react to changes in multiple metabolic signals and distribute neuroendocrine information to other brain regions, such as the paraventricular hypothalamic nucleus (PVH), which are known to regulate food intake. Development of neural projections from AgRP neurons to their targets occurs during the lactation period and these projections are reduced in MHFD-L offspring (Vogt et al. 2014), however, underlying developmental mechanisms remain largely unknown. Microglia are the resident immune cells of the central nervous system and are involved in refinement of neural connections and modulation of synaptic transmission. Because high fat diet exposure causes proliferation and activation of microglia in adults (Valdearcos et al. 2017), we hypothesized that they may be activated in offspring exposed to MHFD-L and play a role in development of hypothalamic feeding circuitry. Genetically targeted axonal labeling and immunohistochemistry were used to visualize AgRP axons and microglia in postnatal mice derived from MHFD-L dams. The morphology of microglia was quantified in the PVH and ARH of P16 mice by using confocal microscopy and an optimized 3D analysis pipeline (Imaris 9.8). The results suggest that MHFD-L results in larger microglia with enhanced process length and complexity in the PVH, but comparable changes do not occur in the ARH. These changes in microglial morphology correspond to reductions in AgRP terminals in the PVH and the presence of engulfed AgRP terminals within activated microglia. Together, these findings suggest that microglia are activated by exposure to MHFD-L and interact directly with AgRP axons during development to permanently decrease their density, with possible implications for developmental programming of metabolic phenotype.

Disclosures: H.N. Mendoza-Romero: None. **R.B. Simerly:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.22

Topic: F.08. Food and Water Intake and Energy Balance

Support: R01DK106476
F32DK123879
R01DA042475

Title: Melanocortin 3 receptor in the bed nuclei of the stria terminalis has sexually dimorphic effects on feeding and stress

Authors: *M. BEDENBAUGH, D. SRISAI, J. LUCHSINGER, D. G. WINDER, R. B. SIMERLY;
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Abstract: An inability to appropriately respond to stressors can lead to maladaptive feeding behaviors commonly observed with eating disorders and obesity. While there is substantial behavioral evidence that functional neural systems controlling feeding and stress responses are linked, the organization of underlying circuitry, and potential differences between males and females, remain poorly understood. Our recent work found the melanocortin 3 receptor (MC3R) is ideally positioned to mediate direct communication between feeding and anxiety circuits and may do so differently in males and females. To build upon our findings, the activity of MC3R neurons located in the bed nucleus of the stria terminalis (BST) during feeding behavioral paradigms and restraint stress was investigated. Using Fos as a marker for neuronal activation, 13.6 ± 1.6% of anteromedial BST^{MC3R} neurons were activated during refeeding after an 18 h fast with a significantly higher percentage of these neurons activated in males compared to females. While 26.8 ± 4.7% of anteromedial BST^{MC3R} neurons were also activated after 1 h of restraint stress, there was no difference between males and females. To investigate if activating BST^{MC3R} neurons influences feeding and anxiety-like behaviors, chemogenetic activation experiments were also conducted. Activating BST^{MC3R} neurons significantly decreases acute feeding in males; more modest effects were recorded in females. Moreover, activating BST^{MC3R} neurons significantly decreases refeeding after a fast in males, but not females. Next, we determined how activation of BST^{MC3R} neurons prior to restraint stress influences struggling during restraint and feeding following restraint stress. The results indicate that activating BST^{MC3R} neurons significantly decreases struggling bouts in both sexes during restraint, but increases food intake after restraint stress in males only. Additionally, the distribution of cells providing direct inputs to BST^{MC3R} neurons was mapped using rabies monosynaptic tracing, lightsheet imaging, and cell registration to the Allen Brain Atlas. Neurons that provide monosynaptic inputs to BST^{MC3R} neurons were identified in multiple areas known to convey autonomic, emotional and neuroendocrine signals, including the medial amygdala, subiculum, periaqueductal gray and prefrontal cortex. The results of brain-wide quantitative comparisons between the patterns of these inputs in male and female mice, together with the functional studies outlined above,

suggest BST^{MC3R} neurons play a key role in modulating feeding behaviors and responses to stressful events, and that they do so differently in males and females.

Disclosures: **M. Bedenbaugh:** None. **D. Srisai:** None. **J. Luchsinger:** None. **D.G. Winder:** None. **R.B. Simerly:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.23

Topic: F.08. Food and Water Intake and Energy Balance

Support: Canadian Institutes of Health Research (PJT-153173)
Canadian Institutes of Health Research Doctoral Research Award
Keith Griffiths Memorial Heart and Stroke Foundation Graduate Scholarship

Title: Prostaglandin E_2-EP2 receptors on melanin-concentrating hormone neurons contribute to diet-induced obesity

Authors: *L. Z. FANG, M. LICURSI, M. HIRASAWA;
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Abstract: Due to the increased availability of energy-dense, high-fat foods, the incidence of obesity and non-alcoholic fatty liver disease are on the rise. In male rodents, high-fat diet (HFD) consumption induces inflammation of the hypothalamus, a region critical in the control of energy homeostasis. This inflammation in turn induces further food intake and excess weight gain. Interestingly, female rodents are largely protected from this hypothalamic inflammation. The molecular mechanism by which inflammation promotes positive energy balance and whether these mechanisms differ between males and females remain poorly understood. Melanin-concentrating hormone (MCH) neurons within the lateral hypothalamus are a key orexigenic cell population known for its role in increasing food intake, fat accrual, and hepatic lipid accumulation. we have previously demonstrated that MCH neurons become activated after HFD consumption in males. Therefore, we hypothesized that MCH neurons mediate the hyperphagia and weight gain induced by HFD-induced hypothalamic inflammation in a sex dependent manner. To test this, rats and mice were fed a standard chow or a HFD for 4 to 14 weeks. Animals were then sacrificed, and in-vitro patch clamp electrophysiology was performed on MCH neurons. We found that in males, the HFD-induced depolarization of MCH neurons is blocked by a cyclooxygenase-2 inhibitor and mimicked by the inflammatory mediator prostaglandin E2 (PGE2). We further determined that this effect is mediated by the PGE2 EP2 receptor (EP2R) as the EP2R antagonist or genetic deletion of EP2R in MCH neurons (MCHEP2R KO) blocked the HFD-induced depolarization of MCH neurons. These KO mice were protected from HFD-induced obesity and liver steatosis compared to controls. In contrast, the excitability of MCH neurons in female mice was not affected by HFD consumption or PGE2

application. Accordingly, HFD-fed female KO mice were indistinguishable from their control counterparts in terms of body weight, food intake, adiposity, and liver steatosis. Together, our results suggest a sexually dimorphic role of PGE2-EP2R signalling in MCH neurons during diet-induced obesity. In males HFD-induced PGE2 activates MCH neurons, which contributes to obesity and related metabolic syndrome, while in females, PGE2-EP2R signalling appears to play no role in diet-induced obesity. Therefore, this mechanism may be part of the sexually dimorphic link between hypothalamic inflammation and obesity.

Disclosures: L.Z. Fang: None. **M. Licursi:** None. **M. Hirasawa:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.24

Topic: F.08. Food and Water Intake and Energy Balance

Support: CIHR
Mitacs RTA

Title: Chronic stress increases ghrelin entry into the arcuate nucleus of the hypothalamus

Authors: *A. SMITH[1], A. HUDAK[1], B. MACAULAY[1], J. SCHEUFEN[1], L. HYLAND[2], A. ABIZAID[2];
[2]Neurosci., [1]Carleton Univ., Ottawa, ON, Canada

Abstract: Ghrelin is a stomach-derived peptide hormone that increases food intake through central activation of the growth hormone secretagogue receptor (GHSR). Circulating ghrelin levels also rise in response to psychosocial stressors and this is associated with increased feeding and adiposity. The mechanisms by which ghrelin regulates such behaviors is still being elucidated, as ghrelin movement into and throughout the brain is extremely limited by the blood brain barrier. Notably, social stressors increase blood brain barrier permeability and therefore may facilitate the entry of hormones like ghrelin into the brain. To investigate if stress influences blood brain barrier permeability to ghrelin, male mice were subjected to 21-days of chronic social defeat stress then subcutaneously injected with 300pmol/g of fluorescently labelled ghrelin, Cy5-ghrelin. Mice were then sacrificed 7-, 15-, 30-, or 60-minutes following injection, to monitor ghrelin movement throughout the brain in comparison with control non-stressed mice. Results revealed that chronic stressed mice showed higher Cy5-ghrelin fluorescence in the arcuate nucleus of the hypothalamus, compared to non-stressed controls. This was accompanied by a decrease in astrocyte expression and end-feet branching, as determined by glial fibrillary acidic protein (GFAP) immunohistochemistry. These results suggest that increased food intake during stress may be due to the reduction in astrocyte coverage of the blood brain barrier, facilitating the entry of ghrelin through the median eminence and into the arcuate nucleus of the hypothalamus.

Disclosures: **A. Smith:** None. **A. Hudak:** None. **B. MacAulay:** None. **J. Scheufen:** None. **L. Hyland:** None. **A. Abizaid:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.25

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)
ARCS Foundation Scholarship

Title: Central Amygdala PKCδ+ neurons respond to food approach in a CCK-modulated manner

Authors: *M. SCHMIT[1], H. N. VU[3], C. JOHNSON[3], M. K. RIVERA[3], G. OZTURK[3], H. CAI[2];
[2]Neurosci., [1]Univ. of Arizona, Tucson, AZ; [3]Unviersity of Arizona, Tucson, AZ

Abstract: Recent research has demonstrated the Central Amygdala's role in eating, with different genetically defined subpopulations involved in either promoting or suppressing food intake. In the CeA, eating suppression appears to be mediated by a population expressing Protein Kinase C-Delta (PCKD+ neurons). For example, the satiety hormone cholecystokinin (CCK) reduces food intake. Silencing PKCD+ neurons attenuates this suppressive effect. As demonstrated by c*fos* studies, PKCD+ neurons are specifically activated by *i.p.* injection of CCK, but their dynamics in response to CCK or food cues were unknown. We approached this question using in-vivo calcium imaging, which allowed us to look at specific PKCD+ neurons across multiple conditions in freely behaving mice. We found that CCK injection activated 22% of PKCD+ neurons, and that the activity was sustained for at least 30 minutes. Surprisingly, in addition to this sustained activity, we discovered that PKCD+ neurons show a transient increase in their activity during the approach to food, and that approach responsive neurons make up 63% of the population. We found that the activity is specific to accessible food: non-food objects, the sight of food alone, or the smell of food alone did not activate PKCD+ neurons. Breaking down approaches into those that do and do not precede eating, we found that PKCD+ neurons responded much more strongly during approaches that preceded eating than those that did not. In addition, the percentage of the population recruited during an approach significantly correlated with the amount of time the mouse would eventually spend eating after that approach. We also found that approaches that preceded eating in a sated state induced by CCK injection recruited more of the population than approaches in a hungry state, although these two populations significantly overlapped. This suggests a role for the transient activation of PKCD+ neurons in the approach and initiation of food intake. Although PKCD+ neurons are activated by CCK injection for a sustained period, this population may also code for satiety in their transient

activity. We did not find a significant overlap between the CCK activated and approach activated populations. This data suggests that this subpopulation of neurons may be affecting food intake in two different ways, during food approach, and as part of sustained satiety-related activity. Answering these questions will help us understand the relationship between these transient and sustained changes in firing rate, as well as help us understand how and when this population may influence CeA neurons regulating other behaviors.

Disclosures: M. Schmit: None. **H.N. Vu:** None. **C. Johnson:** None. **M.K. Rivera:** None. **G. Ozturk:** None. **H. Cai:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.26

Topic: F.08. Food and Water Intake and Energy Balance

Support: Samsung Science & Technology Foundation SSTF-BA1901-11
KAIST Future Systems Health Care Project
KAIST Venture Research Program for Graduate and PhD students
American Heart Association 16SDG27260001
NIH R01 DK114036
NIH R01 DK100699
NIH R01 DK119169

Title: Disinhibition of sodium appetite by Htr2c in the lateral parabrachial nucleus

Authors: *S. PARK[1], K. W. WILLIAMS[2], C. LIU[3], J.-W. SOHN[1];
[1]Biol. Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; [2]Intrnl. Med., Univ. of Texas Southwestern Dept. of Intrnl. Med., Dallas, TX; [3]IM Hypothalamic Res., UTSW Med. Ctr. at Dallas, Dallas, TX

Abstract: Sodium appetite is a state that can drive animals to to ingest normally aversive concentrations of sodium. However, sodium appetite does not manifest itself normally in the absence of sodium depletion. Here we report a population of neurons in the lateral parabrachial nucleus that inhibit sodium appetite. These neurons are responsive to sodium content and can drive suppression of sodium intake. Inhibition of these neurons can also drive ingestion of sodium containing salts. Our results suggest that this population of LPBN neurons are normally involved in suppressing sodium appetite and that alleviation of this inhibition is required for full manifestation of sodium appetite.

Disclosures: S. Park: None. **K.W. Williams:** None. **C. Liu:** None. **J. Sohn:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.27

Topic: F.08. Food and Water Intake and Energy Balance

Support: CIHR FDN-143337
CONACyT (756608)

Title: Functional role of NaX channels in oxytocin and vasopressin releasing magnocellular neurosecretory cells of the rat supraoptic nucleus

Authors: *S. J. SALGADO MOZO[1,2], J. C. WYROSDIC[2], Z. S. THIROUIN[2], U. GARCIA[1], C. BOURQUE[2];
[1]Physiology, Biophysics and Neurosci., CINVESTAV, Mexico City, Mexico; [2]Physiol., Res. Inst. MUHC, Montreal, QC, Canada

Abstract: Body fluids are continuously monitored to regulate the electrolyte-water balance. The central monitoring of this process occurs at the circumventricular organs which lack blood-brain-barrier. Neurons in these structures are in contact with peripheral blood and cerebrospinal fluid, and they project to the magnocellular neurosecretory cells (MNCs) in the supraoptic (SON) and paraventricular nuclei (PVN). We hypothesized that MNCs can detect the extracellular sodium concentration ($[Na^+]_o$) through the sodium channel NaX. Although this channel is somewhat homologous to voltage-gated sodium channels (VGSCs), it differs from the other family members, including in key regions for voltage sensing and inactivation. Moreover, NaX channels are tetrodotoxin-resistant. In the present work, we demonstrated that both vasopressin and oxytocin, MNCs express NaX channels. Functionally, MNCs respond to a hypernatremic-isoosmotic stimulus with a depolarisation that increases their firing rate. This depolarisation temporally correlates with an inward current whose reversal potential corresponds to the equilibrium potential for sodium. In addition, the NaX current magnitude was dependent of the $[Na^+]_o$. The NaX current was isolated by blocking other sodium permeability pathways that are present in MNCs, such as VGSCs, epithelial sodium channels (ENaCs) and TRPV1 channels. Finally, we demonstrated that virally-mediated knockdown of NaX channels in MNCs reduced their electrophysiological response to physiological stimulus (hyperosmotic-hypernatremic) *in vitro*, as well as the sodium-mediated increase in c-fos expression *in vivo*. These data suggest a functional role for NaX channels in sodium detection by MNCs.

Disclosures: S.J. Salgado mozo: None. **J.C. Wyrosdic:** None. **Z.S. Thirouin:** None. **U. Garcia:** None. **C. Bourque:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.28

Topic: F.08. Food and Water Intake and Energy Balance

Title: Asta-ergic thirst neurons relay information to sex-specific circuits to drive water seeking

Authors: *B. P. WANG[1], N. FATIMA[2], F. W. WOLF[1];
[1]Quantitative and Systems Biol., [2]Dept. of Mol. and Cell Biol., Univ. of California, Merced, Merced, CA

Abstract: Drosophila continually senses both the external environment and internal bodily signals to drive behavioral choices to maximize fitness. Only a few of the many permutations of behavioral choices are optimal. It is unclear how different circuits are integrated in choice determination for complex situations. In Drosophila, AstA (galanin/kisspeptin/spexin) expressing Janu-AstA neurons are critical for promoting water seeking with positive valence, and reciprocally for inhibiting feeding behavior. Janu-AstA project from a ventral sensory processing brain region onto a higher order processing region called the superior medial protocerebrum (SMP). We hypothesize that the neural circuitry of thirst is integrated with other behavioral circuits through Janu-AstA. To test this, we identified all of Janu-AstA's postsynaptic partners in the SMP. We found that thirst is connected to both female egg-laying and male courtship circuits. Janu-AstA synapses onto GABAergic oviposition inhibitory neurons (OviINs) that inhibit female egg-laying behavior. Inhibiting the OviINs decreased water seeking. Janu-AstA in females may relay humidity information to the egg-laying circuit to restrict egg-laying to optimally humid environments. Janu-AstA also synapses onto specific Neuropeptide F (NPF, Drosophila NPY) neurons. Some of these NPF neurons are male-specific and inhibit male courtship behavior. Inhibiting these male-specific NPF neurons increased water seeking, the opposite function of the OviINs. The Janu-AstA/NPF-M connection may suppress courtship behavior when the fly is thirsty. Thus, Janu-AstA transmits the strongly motivated state of thirsty water seeking onto multiple behavioral circuits to drive task- and sex-appropriate responses.

Disclosures: B.P. Wang: None. **N. Fatima:** None. **F.W. Wolf:** None.

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.29

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIDDK: DK102529
NIDDK:DK118290

Title: The Cerebellum Modulates Thirst

Authors: *I. MISHRA[1], B. FENG[2], A. LANGSNER[1], C. POULTON[1], Y. XU[3], Y. HE[2], A. CHOPRA[1];
[1]Case Western Reserve Univ., Case Western Reserve Univ., Cleveland, OH; [2]Pennington Biomed. Res. Ctr., Louisiana, LA; [3]Baylor Col. of Med., Houston, TX

Abstract: We previously discovered the fasting-induced glucogenic and orexigenic protein hormone, asprosin, and its orexigenic receptor Protein Tyrosine Phosphatase Receptor δ (Ptprd). We now show that asprosin engages Ptprd for thirst stimulation, albeit via a neural circuitry distinct from hypothalamic $AgRP^{+}$ neurons. Asprosin competitively binds the molecular layer of the cerebellum, home to purkinje neuron cell bodies and projections. This cerebellar region also displays high *Ptprd* expression. Purkinje neuron-specific loss of *Ptprd* results in hypodipsia without an appetite or body weight deficit, while $AgRP^{+}$ neuron specific *Ptprd* loss results in an appetite and body weight deficit without hypodipsia. In contrast, plasma asprosin deficiency ($Fbn1^{Nps/+}$) and whole-body loss of *Ptprd* ($Ptprd^{-/-}$) results in both – hypodipsia and a deficit in appetite/body weight. Purkinje neurons are activated by recombinant asprosin in a Ptprd dependent manner, even with blockade of all synaptic input. In contrast, granule neurons, the predominant cerebellar cell type, are unresponsive to asprosin. Physiologically, plasma asprosin elevation induces thirst, again in a Ptprd dependent manner. Photogenetic and chemogenetic stimulation of purkinje neurons induces hyperdipsia in WT mice without appetite stimulation. This preponderance of evidence positions asprosin as a multifaceted protein hormone, that regulates two key aspects of homeostasis – energy accretion and water accretion. This work, for the first time, also shows that the cerebellum, previously linked to movement, coordination and cognition, modulates thirst.

Disclosures: I. Mishra: None. **B. Feng:** None. **A. Langsner:** None. **C. Poulton:** None. **Y. Xu:** None. **Y. He:** None. **A. Chopra:** A. Employment/Salary (full or part-time):; Associate Professor. 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.; DK102529, DK118290. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Atul Chopra has been awarded asprosin-related patents, and is a co-founder, director and officer of Vizigen, Inc., and Aceragen, Inc., and holds equity in both companies..

Poster

728. Neuromodulation of Food and Water Intake and Energy Balance

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 728.30

Topic: F.08. Food and Water Intake and Energy Balance

Support: NSF 2019346

Title: The dipsogenic effect of estradiol is mediated by estrogen receptor beta in ovariectomized adult female rats

Authors: *J. SANTOLLO, A. A. EDWARDS;
Univ. of Kentucky, Univ. of Kentucky, Lexington, KY

Abstract: We recently identified a dipsogenic effect of estradiol (E2) in female rats during states of low fluid intake, specifically water intake when food is unavailable. This is particularly novel given 50 years of research focused on the anti-dipsogenic effect of E2. To further characterize this phenomenon, we investigated whether E2 increases sodium intake, in addition to water intake, and examined the estrogen receptor (ER) subtype(s) underling the dipsogenic effect of E2. In Experiment 1, 24 h water and 1.5% saline intakes and bottle licks were measured, in the absence of food, in ovariectomized (OVX) rats treated with oil or 10 µg estradiol benzoate (EB) once a day for two days. In the presence of 1.5% saline, water intake was minimal and not influenced by EB treatment. Saline and total intake (water + saline) and licks for saline and total licks, however, were significantly increased after EB treatment, $p < 0.05$. In Experiment 2, 24 h water intake was measured, in the absence of food, in OVX rats treated centrally with DMSO control, 25, or 50 µg G1 (GPER1 agonist). Neither dose of G1 had any effect on 24 h water intake, p = n.s. In Experiment 3, 24 h water intake was measured, in the absence of food, in OVX rats treated with DMSO control, 200 µg PPT (ERalpha agonist) or 250 µg DPN (ERbeta agonist). Treatment with DPN significantly increased overnight water intake and licks in the absence of food, $p < 0.05$, mimicking the effects of EB. Surprisingly, treatment with PPT significantly decreased licks for water in the absence of food, $p < 0.05$, mimicking the effects of EB when food is available. To reconcile these discrepancies, we are currently testing the hypothesis that co-activation of ERalpha and ERbeta decreases water intake in the presence of food, while co-activation of ERalpha and ERbeta increases water intake in the absence of food. The results obtained here add to our understanding of how E2 bidirectionally controls fluid intake in the female rat. In the absence of food, E2 increases both water and saline intake. Activation of estrogen receptor beta underlies the dipsogenic effect of estradiol, but activation of estrogen receptor alpha appears to reduce water intake regardless of food availability.

Disclosures: J. Santollo: None. **A.A. Edwards:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.01

Topic: G.03. Motivation

Support: Project Grant CIHR

Title: Come for the Sugar, Stay for the Show: How Cues Impact Impulsivity and Risky Decision-Making in a Rodent Gambling Task

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Abstract: INTRO: The rodent Gambling Task (rGT), a rodent analogue of the Iowa Gambling Task, is used to assess probabilistic decision-making, and can be performed in the presence of cues. By modelling rodent gambling decisions as a function of experience, we can parse which choice outcomes lead to impulsive behaviour and risky decision-making. We aimed to understand how choice, reward magnitude, and experience winning or losing, predicted premature responding.**METHODS:** Long Evans adult male rats (N=280) performed the cued or un-cued versions of the rGT. We evaluated the occurrence of a premature response based on three scenarios: whether a win or loss preceded it, which intended choice was impulsively selected, and which choice was selected next. Winning or losing, audiovisual cue presence, and an animal's risk preference, were examined in each moment using a series of logistic mixed effects models applied to data from 117,898 total responses in the rGT. **RESULTS:** Premature responses were found to be slightly, but consistently, more likely to occur after experiencing a win than a loss (OR [95% CI] = 1.045 [1.002 – 1.092]). Unexpectedly, this positive urgency was predominantly observed among risk-averse rats (1.124 [1.076 – 1.175]) and not risk-preferring rats (0.972 [0.907 – 1.047]). Risk-preferring rats were found to be more impulsive on the uncued rGT (1.260 [1.117 – 1.403]), and less impulsive on the cued rGT (0.807 [0.733 – 0.881]), compared to risk-averse rats. Reward (0.885 [0.862 – 0.907] OR per sugar pellet obtained) and punishment (0.987 [0.984-0.989] OR per second time-out) magnitude experienced after making a choice were found to be negatively associated with premature response probability, however, risk-preferring rats were found to be less sensitive to time-out punishments than risk-averse rats (1.014 [1.009 – 1.019] OR per second time-out). When prematurely responding, and immediately afterwards, rats were more likely to choose a lower-risk option (during, OR [95% CI] = 2.104 [1.273 – 3.477]; after, OR [95% CI] = 4.048 [2.172 – 7.544]) on the uncued rGT and a higher risk option (during, OR [95% CI] = 2.618 [1.508 – 4.546]; after, OR [95% CI] = 3.002 [1.688 – 5.335]) on the cued rGT.**CONCLUSION:** In this study we dissociated impulsivity from risky decision-making on the rGT. In the uncued rGT, winning precipitates impulsivity in risk-averse rats. Audiovisual cues in the cued rGT reduce impulsivity yet exacerbate risky decision-making, enticing rats to choose high-risk option. Thus, the lack of cues leads to increased premature responding but not impaired decision-making, whereas the presence of cues leads to decreased premature responding and impaired decision-making.

Disclosures: M. Lysenko-Martin: None. **C. Hutton:** None. **C.A. Winstanley:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.02

Topic: G.03. Motivation

Support: CIHR Grant PJT-162312
CIHR Doctoral Award

Title: Modulating activity in the lateral orbitofrontal cortex differentially impacts risky decision making in the presence versus absence of reward-paired cues on a rat gambling task

Authors: *B. A. HATHAWAY, K. M. HRELJA, Y. Q. ZHAO, C. A. WINSTANLEY; Psychology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Reward-paired cues can enhance disadvantageous risky choice in both humans and rodents. The lateral orbitofrontal cortex (lOFC) may mediate this effect, as alterations to activity within this region can ameliorate cue-induced risky choice. However, the role of the lOFC in guiding risky decision making in the presence versus absence of reward-paired cues has not been thoroughly examined. Accordingly, the present experiments assessed whether altering activity within the lOFC during the learning phase of a risky decision-making task would differentially impact choice patterns in cued versus uncued versions of the task. Two cohorts of 48 male Long-Evans rats were trained on either the uncued or cued rat Gambling Task (rGT; *n* per task version = 48), a rodent analog of the human Iowa Gambling Task. Optimal performance on this task is attained by avoiding the two high-risk, high-reward options and instead favouring the options associated with lower per-trial gains and higher reward probability. The cued version of the task features the addition of reward-paired audiovisual cues that scale in magnitude and complexity with reward size. To assess the role of the lOFC, rats were infused with a viral vector carrying either an inhibitory DREADD, an excitatory DREADD, or an empty control vector into the lOFC prior to task training. Rats were then dosed with 1 mg/kg Clozapine-N-Oxide before each session of the rGT, until a statistically stable performance baseline was reached (~25-30 sessions). Rats trained on the uncued version of the rGT exhibited an increase in risky choice when lOFC activity was inhibited, particularly in the early training phase. These results corroborate the observed effects of lOFC lesions prior to training on the uncued rGT. Chronic activation of this region did not substantially alter decision making patterns. Conversely, early data suggest inhibiting lOFC activity during training on the cued rGT reduced risky choice. These results suggest that the lOFC is involved in guiding optimal choice when rats are learning to choose between options that vary in reward size and probability. However, the inclusion of reward-paired cues may alter the establishment of accurate action-outcome contingencies in the lOFC and thus impair decision making.

Disclosures: B.A. Hathaway: None. **K.M. Hrelja:** None. **Y.Q. Zhao:** None. **C.A. Winstanley:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.03

Topic: G.03. Motivation

Title: Acute corticosterone treatment alters risk-based decision making on a cued rat gambling task

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Abstract: Corticosteroid hormones, mainly released in response to stress, are known to affect decision making including risk-based decision making. Previous research has shown that corticosterone disrupts risk-based decision making in rats, preventing animals from learning to avoid suboptimal options. However, previous studies in rats utilized behavioural models of risk taking that lack the presence of salient reward cues, a major component in human gambling. A cued rat gambling task (crGT) has previously been developed, that pairs audiovisual cues with sucrose rewards when animals choose one of four options that differ in the magnitude and frequency of reward and the length of time-out punishments periods so that risky high-reward/high-punishment options are suboptimal compared to safer low-reward/low-punishment options over multiple trials. Here, we examine the effect of acute corticosterone injection on crGT choice behaviour in well-trained male Long-Evans rats. We found that corticosterone injections increased animals' preference for risky suboptimal options. These findings indicate that corticosterone biases risk-based decision making towards larger immediate rewards when they are accompanied by audiovisual cues.

Disclosures: L. Calderhead: None. **C.A. Winstanley:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.04

Topic: G.03. Motivation

Support: CIHR Grant F18-03649

Title: Histone deacetylase inhibitor sodium butyrate increases risk-taking during acquisition of the rat gambling task

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Abstract: Impaired decision-making is recognized as a diagnostic criterion for many psychiatric disorders, including gambling disorder and substance use disorders. The cued rat gambling task (rGT) is a translationally valuable task, as it incorporates salient audiovisual cues and complex schedules of reinforcement to closely model human gambling while accounting for factors like cost-benefit calculations and uncertainty of outcomes. The addition of cues to this task is known

to facilitate risky decision-making, as it causes animals to favour habitual rather than goal directed behaviour. Histone deacetylases (HDACs) are enzymes that negatively mediate gene expression, and inhibiting this process has been found to facilitate the formation of long term memories while further accelerating the rate of habit formation. To further investigate the role of HDACs in complex decision-making, we administered the non-specific class I HDAC inhibitor sodium butyrate (NaBut; 1000 mg/kg, subQ daily) to male Long Evans rats (N = 64) during the acquisition of the cued rGT. Animals were sacrificed at varying timepoints in order to measure molecular changes in the brain. We found that NaBut promotes habit formation, thereby accelerating the development of risky option preferences during acquisition of the cued rGT without impairing response latencies. This study lends insight into why some individuals develop habitual decision-making strategies, such as the ones that drive people to continue to engage in problematic gambling and/or drug use. Understanding mechanisms and timepoints at which individuals are most vulnerable to maladaptive decision making strategies will contribute to identifying targeted therapeutics for individuals suffering from gambling disorders and substance use disorders.

Disclosures: K.M. Hrelja: None. **S. Hipkin:** None. **C.A. Winstanley:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.05

Topic: G.03. Motivation

Support: CIHR project grant (PJT-162312)

Title: The effects of dopamine D2 and D3 receptors agonists on rodent decision-making

Authors: *B. RUSSELL[1], C. KWOK[1], S. ANSARY[2], T. CHANG[1], K. M. HRELJA[2], G. BETTS[3], C. A. WINSTANLEY[4], A. BAINS[1];
[2]Psychology, [3]Neurosci., [1]Univ. of British Columbia, Vancouver, BC, Canada; [4]Psychology, Univ. British Columbia, Vancouver, BC, Canada

Abstract: Dopamine D2/D3 receptor agonists, like ropinirole, are commonly prescribed to individuals with Parkinson's disease. Although these drugs are effective at alleviating Parkinsonian motor symptoms, they have also been found to induce gambling disorder, as well as other behavioural addictions and impulse control disorders, in a substantial minority of patients. However, the underlying mechanism by which these drugs induce these behaviours has been debated. There are findings to support the role of both the D2 receptor and D3 receptor in the development of iatrogenic gambling disorder, with some studies suggesting that activation of the D3 receptor, and not the D2 receptor, is precipitating these disorders. Previous research has shown that the administration of non-selective dopamine D2/D3 receptor agonists can increase preference for uncertainty and risky decision-making in healthy male rats. Thus, the purpose of

the current experiment was to examine whether the D2 receptor and/or the D3 receptor can independently induce risky decision-making in male rats on the cued rat gambling task (cued rGT), an adaptation of the Iowa Gambling Task. 104 Long Evans rats were trained on the cued rGT, in which rats choose between four options associated with distinct magnitudes and probabilities of reward (1-4 sugar pellets) or time-out penalties (5-40s). The optimal strategy is to favour options associated with smaller per trial gains, but shorter penalties. Following training to nose-poke for reward, male rats received two daily injections of the selective D2 agonist sumanirole (0.10 mg/kg) and the selective D3 agonist PD128907 (0.10 mg/kg; n=16), PD128907 and vehicle (n=8), sumanirole and vehicle (n=8), or vehicle and vehicle (n=8) prior to testing, and 32 female and 32 male rats were surgically implanted with an osmotic pump delivering either 5 mg/kg/day of ropinirole or saline. Drugs were administered for 28 days, including the acquisition phase of the cued rGT. We found that both ropinirole and the selective D2 agonist promoted risky decision-making on the cued rGT when compared to the control group. However, the selective D3 agonist and the combined administration of the D2 and D3 agonists did not have this effect and may instead promote optimal decision-making on this task. The results from this experiment will offer insight into the selective contribution of D2 and D3 receptor agonism on decision making and the development of both iatrogenic and idiopathic gambling disorder and other addictive disorders.

Disclosures: **B. Russell:** None. **C. Kwok:** None. **S. Ansary:** None. **T. Chang:** None. **K.M. Hrelja:** None. **G. Betts:** None. **C.A. Winstanley:** None. **A. Bains:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.06

Topic: G.03. Motivation

Support: CIHR Project Grant - Dr. C. A. Winstanley
NSERC CGS M - C. S. Chernoff

Title: Noradrenergic regulation of decision making and impulsivity is dissociable across frontal brain regions

Authors: *C. S. CHERNOFF[1], J. D. SCHUMACHER[1], S. RAMAIAH[1], T. J. HYNES[2], D. K. AVRAMIDIS[1], S. B. FLORESCO[3], C. A. WINSTANLEY[4];
[1]Psychology, [2]Univ. of British Columbia, Vancouver, BC, Canada; [4]Psychology, [3]Univ. British Columbia, Vancouver, BC, Canada

Abstract: The captivating lights and sounds of the modern casino environment are thought to drive problematic gambling, as such stimuli can arouse the urge to play and may facilitate trance-like game immersion. Consistently, adding reward-contingent audiovisual cues to human and rodent gambling tasks increases the proportion of subjects that develop risky strategies. Given

that noradrenaline critically regulates cognition, arousal and attention, noradrenergic activity may mediate the ability of cues to promote pathological gambling behaviour. We previously demonstrated that atomoxetine, a noradrenaline reuptake inhibitor, and guanfacine, a selective α2 adrenergic receptor agonist, reduced risk preference in the cued rat gambling task (crGT) when given systemically. The central mechanisms by which noradrenaline signaling may enhance cost-benefit decision making, however, are largely unknown. We therefore sought to locally manipulate noradrenaline action to probe the brain regions which may be involved in this effect. Male and female rats were trained on the crGT, during which animals choose between options of varying probabilities and magnitudes of sugar pellet wins and time out punishments. Cannulae were then bilaterally implanted into either the lateral orbitofrontal cortex (lOFC) or prelimbic cortex (PrL). Each animal received microinfusions of a high dose and low dose of both atomoxetine and guanfacine, plus the respective vehicle, during performance on the crGT following a counterbalanced Latin square design. We find that atomoxetine improved choice score when delivered into the lOFC, recapitulating our previous systemic findings, albeit only in males. Conversely, intra-PrL atomoxetine did not influence decision making but selectively improved motor inhibition in risk preferring rats, as indicated by fewer premature responses made during the intertrial interval. Guanfacine infused into the lOFC did not significantly alter crGT performance, yet intra-PrL infusions of the α2 agonist increased motor impulsivity. These data suggest that noradrenaline signaling importantly guides risk taking and response inhibition in the presence of cues. Our findings further indicate that noradrenergic signaling in the lOFC may be more critically involved in higher order decision making processes, while noradrenaline action in the PrL may be a stronger regulator of motor impulsivity.

Disclosures: C.S. Chernoff: None. **J.D. Schumacher:** None. **S. Ramaiah:** None. **T.J. Hynes:** None. **S.B. Floresco:** None. **C.A. Winstanley:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.07

Topic: G.03. Motivation

Support: NIH Grant MH063649
NIH Grant DA015188
NIH Grant T32DA007268

Title: Central amygdala role in addiction-like pursuit of reward and pain

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Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Under normal conditions, motivational ‘wanting’ and pleasure ‘liking’ often arise together, such that we ‘want’ what we ‘like’. However, they can also come apart in some

conditions, because their neural mechanisms are separable. Separation can produce intense 'wants' that don't cohere with how much something is 'liked', such as in addictions. In the present study, we examined individual neuronal subpopulations in the central amygdala (CeA) as potential mechanisms for 'wanting' that is independent of 'liking'. Laboratory rats were tested in a shock rod task in which they were presented with an electrified metal rod that they can voluntarily interact with and self-inflict shocks. Shock rod interactions were paired with optogenetic ChR2 activation of D1, D2(A2), or CRF neurons in the CeA. In another group, CeA neurons were targeted non-selectively in wild-type rats using the hSyn promoter. Over multiple test days, hSyn and D1 ChR2-activated rats displayed intense attraction for the shock rod, repeatedly self-inflicting shocks and even overcoming an occluding barrier to do so, as well as displaying neuron-specific phenotypical behaviors. Our findings provide a proof of principle that 'wanting' can indeed occur independently of 'liking', which has implications towards understanding why individuals with addiction pursue the addicted target despite knowing well that negative consequences will follow. Another key feature of addiction is that the individual will pursue the addicted target at the expense of life's other rewards. In a separate set of experiments, we examined the role of the CeA in producing similar narrowly focused pursuits. Rats were tested in a choice-test scenario for remifentanil versus sucrose rewards, with only one of the two rewards paired with CeA ChR2 activation. The results revealed that rats consistently pursued the laser-paired reward at the expense of not receiving the alternative reward. We conclude that CeA activation is capable of producing narrowly focused 'wants', and can even make a harmful object attractive and desired. Our findings suggest important implications for understanding brain mechanisms of addiction and other maladaptive conditions.

Disclosures: D. Nguyen: None. **I. Morales:** None. **K.C. Berridge:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.08

Topic: G.03. Motivation

Support: NIDA015188
NIMH63649

Title: The role of CRF neurons and of CRF neurotransmitter in generating positively valenced incentive motivation

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Abstract: Corticotropin releasing factor (CRF) neurons are traditionally assumed to help generate aversive stress states (George, et al. 2012). However, conflicting evidence shows that

CRF neurons in nucleus accumbens (NAc) and central amygdala (CeA) can oppositely generate positively-valenced incentive motivation to pursue and consume rewards (Lemos, et al. 2012; Peciña 2006). For example, optogenetic laser stimulation of CRF neurons in the CeA and NAc of *crh*-Cre rats can intensify pursuit and focus motivation on a laser-paired sucrose or cocaine reward over an equal reward earned without laser stimulation (Baumgartner et al. 2021; Baumgartner et al. 2022). These rats will also optogenetically self-stimulate for CRF neuron activation in the CeA and NAc, indicating positive valence of CRF neuronal excitation (Baumgartner et al 2021; Baumgartner et al. 2022). However, CRF neurons co-release several other neurotransmitters besides CRF peptide, and it is unknown whether CRF itself versus other neurotransmitters mediate the motivated behavior induced by optogenetic stimulation of CRF neurons in CeA or NAc. To specifically test the role of CRF peptide, we administered i.c.v. microinjections of a nonspecific CRF antagonist or of vehicle prior to laser self-stimulation sessions to stimulate CRF neurons, or prior to 2-choice tasks in which rats could earn either laser-paired sucrose reward or identical sucrose reward without laser. Preliminary results suggest that CRF neurotransmitter signaling may contribute to the incentive motivation effects induced by optogenetic stimulation of CRF neurons in CeA and NAc.

Disclosures: K. Emery: None. **L. Tittle:** None. **K.C. Berridge:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.09

Topic: G.03. Motivation

Support: NIH MH063649
NIH DA015188
NIH MH125613
NIH NS124176
NIH DC000011

Title: Identification of optogenetic hedonic hotspots in orbitofrontal cortex, insula, ventral pallidum, and anterior cingulate cortex that control liking and wanting for sweet reward

Authors: *I. MORALES[1], J. A. KRAVCHENKO[1], D. C. CASTRO[2], J. J. OLNEY[1], K. URSTADT[3], A. JAIN[1], M. GRANILLO[1], K. C. BERRIDGE[1];
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Abstract: Reward consists of distinct learning, ‘wanting’, and ‘liking’ components, but ‘liking’ remains the least understood. ‘Liking’, or hedonic function is causally amplified by distinct brain hedonic hotspots in the nucleus accumbens, ventral pallidum, orbitofrontal cortex, and insula

cortex when neurochemically activated by opioid and orexin receptor agonists during the taste reactivity test. This test categorizes affective orofacial expressions to various tastes into positive 'liking' and aversive 'disgust' components. Previous studies have primarily used local microinjections to study hedonic hotspot function, and the question remains whether hedonic hotspots are neurochemical artifacts or robust hedonic entities. Here we present novel data showing that optogenetic stimulation to control neuronal activity in the insula, OFC, and ventral pallidum hedonic hotspots doubles the number of hedonic 'liking' reactions elicited by sweet sucrose taste. Hedonic enhancement was anatomically restricted to the hedonic hotspots as the same manipulations within the same brain structure, but outside of the hedonic hotspots failed to increase 'liking' and may even oppositely suppress 'liking' despite still generate robust increases in 'wanting'. Furthermore, we identify a novel hedonic hotspot in caudal anterior cingulate cortex (pACC) never previously described and find that ChR2 stimulation of pACC neurons increases hedonic 'liking' as well as incentive motivation or 'wanting' for sucrose. Subcortically, we show that VP neurons bidirectionally control hedonic impact, as optogenetic inhibitions of the VP hotspot decreased hedonic 'liking' reactions to sweet sucrose and replaced them with aversive 'disgust'. We further study VP control of 'liking' and 'wanting' by selectively targeting VP^{GABA} neurons using transgenic GAD1-cre rats. We show that optogenetic activation of VP^{GABA} neurons within the posterior VP hotspot doubles hedonic 'liking' reactions to sucrose, while rostral VP^{GABA} activations fail to increase hedonic reactions. In comparison to our localized hedonic effects, optogenetic activation of VP^{GABA} neurons throughout the rostral-caudal extent increase 'wanting' for sucrose and elicit robust laser self-stimulation and can even elicit maladaptive attractions to a painful electric shock. Overall, our findings suggest that hedonic hotspots in the brain are robust hedonic entities in brain corticolimbic sites, whether stimulated pharmacologically or optogenetically, that form a functional hedonic circuit to enhance 'liking'.

Disclosures: I. Morales: None. **J.A. Kravchenko:** None. **D.C. Castro:** None. **J.J. Olney:** None. **K. Urstadt:** None. **A. Jain:** None. **M. Granillo:** None. **K.C. Berridge:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.10

Topic: G.03. Motivation

Support: S0254-22-1002
NRF-2021M3E5D9025026
NRF-2019M3C7A1032262

Title: Dispositional resilience is related to inferior frontal gyrus and superior longitudinal fasciculus in healthy individual: a multimodal T1 and DTI study

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Abstract: Background: Some people with high resilience to emotional regulation and high social cognition do not develop psychiatric disorders, even after extreme psychological distress. The purpose of this study is to investigate the neural correlates of dispositional resilience in healthy individuals using both T1 and diffuse tensor imaging simultaneously.**Methods:** A total of 92 healthy individuals participated in this study. The Korean version of the Connor-Davidson Resilience Scale (K-CD-RISC) and other psychological measures were used to evaluate dispositional resilience and other psychological characteristics. The gray matter volumes (GMVs), cortical thickness, and white matter (WM) of the whole brain of all participants were analyzed using voxel-based morphometry image analyses and tract-based spatial statistics, respectively. Additionally, we performed voxel-wise correlation analyses between the total scores of the K-CD-RISC and GMVs, cortical thickness, or mean fractional anisotropy (FA) values of whole-brain regions. **Results:** Healthy participants with higher resilience showed significantly higher GMVs in the inferior frontal gyrus (IFG) and lower mean FA values in the right second branch of the superior longitudinal fasciculus (SLF II). Furthermore, high GMVs in the right IFG regions were associated with low maladaptive coping strategies and high physical function among healthy individuals. Furthermore, the low mean FA values in the right SLF II correlated with low trait anxiety and low depression in healthy individuals.**Conclusions:** We found that GMVs in the social cognition-related IFG and WM microstructures in the DMN-related regions, including SLF II can be associated with dispositional resilience that contributes to emotional regulation and social cognition among healthy individuals. Therefore, these findings suggest that neural changes in these dispositional resilience-related brain structures may be associated with the capacity to overcome stressful life events and quality of life in healthy individuals.

Disclosures: H. Kim: None. **J. Seo:** None. **S. Lee:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.11

Topic: G.03. Motivation

Support: NIH intramural funding ZIAMH002784

Title: Hippocampal neurogenesis mediates decision making under conflict

Authors: A. P. SWIERCZ, H. R. MARTIN, R.-M. KARLSSON, *H. A. CAMERON;
NIMH, NIH, Bethesda, MD

Abstract: Approach-avoidance conflicts occur when an animal encounters stimuli associated with both positive and negative outcomes. These conflicts are resolved in part by the hippocampus, which acts to modulate the inhibition of prepotent behaviors. Here we examined the behavior of rats lacking neurogenesis in a platform mediated avoidance (PMA) task to determine whether adult-born neurons influence behavior when animals have the option to either avoid footshocks, obtain rewards, or attempt to do both. In the PMA task, animals can choose to avoid each footshock, but avoidance comes at the cost of being unable to lever-press for sucrose rewards. The simultaneous presentation of an auditory conditioned stimulus (CS) that reliably predicts a footshock, and a light cue signaling reward availability, creates an approach-avoidance conflict where the animal must balance threat avoidance with food-seeking behavior. Neurogenesis was eliminated by 8 weeks of treatment with valganciclovir in male transgenic Long Evans rats expressing the herpes simplex virus thymidine kinase (TK) under control of the glial fibrillary acidic protein (GFAP) promoter. Ablation of adult-born neurons was followed by three phases of behavioral training. During the avoidance training phase, animals learned to avoid CS-associated footshocks by stepping onto a small platform. In reward training, pellets were dispensed after each lever press, only while a chamber light was illuminated. During conflict training, auditory and light cues were presented simultaneously. The total time spent on the platform during CS presentation was similar between genotypes throughout avoidance training. Both groups also learned to increase lever pressing in response to the light during reward training. In the conflict phase, however, there was a significant reduction of avoidance behavior in TK animals relative to wild-type controls. The TK group also pressed for rewards at a higher rate and exhibited less freezing behavior in response to the cues. The loss of new neurons was associated with decreased avoidance and increased lever pressing during the presentation of conflicting stimuli, suggesting that neurogenesis plays an important role in regulating approach and avoidance behavior during high-conflict situations.

Disclosures: A.P. Swiercz: None. **H.R. Martin:** None. **R. Karlsson:** None. **H.A. Cameron:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.12

Topic: G.03. Motivation

Support: NIH Center for Compulsive Behavior Fellowship
NIH Postdoctoral Research Training Award

Title: Threat predictability drives divergent approach-avoidance conflict resolution strategies

Authors: R. FLORES GARCIA, M. A. AWANYAI, H. A. TEJEDA;
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Abstract: Effective approach-avoidance conflict resolution, such as foraging and predator avoidance, is vital for survival. The ability to predict threats may shape approach-avoidance action selection allowing animals to manage conflict. To date, the mechanisms underlying approach-avoidance behaviors during motivational conflict remain unclear. Here, we examined how mice adapt approach-avoidance behaviors in response to changes in the predictability of future punishments. To this end, we used a modified version of the platform-mediated avoidance task wherein mice nose poke for sucrose reward while avoiding shocks by mounting a platform away from the reward port. During reward training, mice learned to nose poke for sucrose when the reward port was illuminated. Next, a group of mice underwent conflict training involving the presentation of reward-predicting cues and shock-predicting tones that were randomly presented throughout the session. This resulted in different trial types where the tone-shock had complete, partial or no overlap with the light cue signaling reward. Throughout the training, mice displayed increased nose poking during light-only trials and avoidance during tone-only trials, and the ability to select approach/avoidance actions in response to rapid changes in reward and punishment contingencies in trials where the tone and light overlapped partially. Mice in the unpredictable group were presented with the same trial types, but the tone did not predict the shock. Instead, shocks were delivered during the intertrial intervals or the middle/end of a reward cue. Mice in the unpredictable group failed to attain rewards and avoid shocks to similar levels as mice in the predictable group, suggesting that unpredictable threats toggle conflict resolution to more passive defensive behaviors at the cost of reward attainment. To determine whether unpredictable threats during conflict resolution drove generalized motivational or reward-seeking deficits, we examined the preference for safe rewards in the presence and absence of conflict in both groups. While both groups showed a similar preference for safe rewards without conflict, mice in the unpredictable group displayed a higher preference for safe rewards, indicating that contexts associated with unpredictable threats bias behavioral states that favor risk-averse foraging strategies. On-going studies are examining the mechanisms underlying conflict resolution in predictable and unpredictable threat contexts, which will advance our understanding of motivation and emotional circuits implicated in psychiatric disorders involving maladaptive reward-seeking or avoidance.

Disclosures: **R. Flores Garcia:** None. **M.A. Awanyai:** None. **H.A. Tejeda:** None.

Poster

729. Decision Making, Impulsivity, Compulsivity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 729.13

Topic: G.03. Motivation

Support: NIDA R21 DA052594
T32DA07268

Title: Role of glucocorticoid receptors in corticostriatal projections in incentive learning and sign-tracking behavior

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Abstract: Through Pavlovian conditioning, environmental cues become predictors of biologically relevant stimuli. For some individuals, the cue also becomes an incentive stimulus, drawing them to approach and interact with the irresistible cue. Individuals who rely on incentive learning strategies are more prone to develop aberrant and maladaptive behavior characteristic of psychopathologies, such as substance use disorder. The sign-tracker/goal-tracker animal model can be used to capture individual differences in incentive learning via a Pavlovian conditioned approach procedure. When a lever-cue is repeatedly paired with food delivery, some rats (sign-trackers) direct their behavior towards the lever upon its presentation, while other rats (goal-trackers) direct their behavior towards the food-cup. For both sign-trackers and goal-trackers, the lever becomes a predictor, but only for sign-trackers does the lever also become an incentive stimulus. This model, therefore, allows us to probe the neural mechanisms underlying predictive versus incentive learning. We have previously reported that the prelimbic cortex exerts top-down control over subcortical regions to regulate incentive learning; and this incentive learning and the propensity to sign-track are dependent on dopamine signaling in the nucleus accumbens. Nucleus accumbens dopamine signaling has been shown to interact with glucocorticoids via their action at glucocorticoid receptors (GR) to mediate individual differences in reward-seeking behaviors. Here, we investigate whether GR in a top-down corticostriatal circuit mediate dopamine-dependent incentive learning. We used a combinatorial viral vector approach in GR-CRISPR transgenic rats of both sexes to knockdown GR in projections from the prelimbic cortex to the nucleus accumbens core. We assessed the effect of this circuit-specific GR knockdown on the acquisition of sign- and goal-tracking behaviors. GR knockdown in corticostriatal projections biased behavior in a sex-specific manner. In males, GR knockdown decreased response bias (i.e., pushed behavior towards goal-tracking) compared to wild-type controls. In females, GR knockdown had the opposite effect (i.e., pushed behavior towards sign-tracking). These findings suggest that GR function in a top-down cortical control circuit plays a critical role in incentive learning in a sex-dependent fashion.

Disclosures: S.R. Westbrook: None. **H.E. Davies:** None. **P. Felix:** None. **S.E. Chang:** None. **J.P. Herman:** None. **S.B. Flagel:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.01

Topic: G.03. Motivation

Support: NIMH Grant R01MH121350
University of Connecticut Research Foundation

Title: Exploring possible sex differences in the effort-related motivational effects of dopamine antagonists and dopamine depletion with tetrabenazine

Authors: *J. D. SALAMONE[1], S. SRYNATH[1], A. ECEVITOGLU[1], G. A. EDELSTEIN[1], N. MEKA[1], D. PIETRORAZIO[1], C. J. DWY[1], M. CORREA[2];
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Abstract: Dopamine (DA) plays an important role in regulating activational and effort-related aspects of motivation. Extensive evidence shows that DA antagonism, neurotoxic depletion of accumbens DA, and the DA-depleting agent tetrabenazine (TBZ), produce a low-effort bias in rats and mice, shifting choice behavior from high-effort to low-effort alternatives. These tasks also have been used for animal models of motivational symptoms in psychiatric disorders. However, a limitation of these studies is that the vast majority were done in male rodents. Additional research is needed to characterize the effort-related effects of DAergic drugs in females as well as males. The present studies investigated the effects of IP injections of three drugs that are commonly used to manipulate DA transmission (the D1 receptor antagonist ecopipam, the D2 receptor antagonist haloperidol, and the vesicular monoamine transport (VMAT-2) inhibitor TBZ, which blocks vesicular storage) in both male and female rats. TBZ was selected because this drug produces depressive symptoms and motivational dysfunctions in humans, and animal studies use TBZ to model these dysfunctions. This research was conducted employing the concurrent fixed ratio 5 (FR5)/chow feeding choice task. Under baseline or control conditions, males typically lever pressed more than females. All three drugs have previously been shown to shift effort-based choice in male rats tested on the FR5/chow choice task, decreasing lever pressing and increasing chow intake. In the present studies, ecopipam (0.05-0.2 mg/kg) and haloperidol (0.05-0.15 mg/kg) decreased lever pressing and increased chow intake in both males and females. With lever pressing, there was no significant dose x sex interaction after administration of haloperidol. There was a significant interaction after ecopipam injection, with the effect in females being slightly less potent than in males. In the first study with TBZ (0.25-1.0 mg/kg), there was a robust dose x sex interaction. TBZ produced a dose-related suppression of lever pressing and an increase in chow intake in male rats, but was ineffective in females. In a second experiment, a 2.0 mg/kg dose was shown to affect choice behavior in both males and females. Across both studies, lever pressing in males was more affected by TBZ than in females. Co-administration of the DA transport inhibitor methylphenidate reversed the effects of TBZ in males injected with 1.0 mg/kg and females injected with the 2.0 mg/kg dose. Investigating sex differences in the pharmacology and neurochemistry of effort-based choice may lead to a greater understanding of the role of sex in motivational dysfunctions in humans.

Disclosures: J.D. Salamone: None. **S. Srynath:** None. **A. Ecevitoglu:** None. **G.A. Edelstein:** None. **N. Meka:** None. **D. Pietrorazio:** None. **C.J. Dwy:** None. **M. Correa:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.02

Topic: G.03. Motivation

Support: NIHM Grant R01MH121350

Title: Potential therapeutics for effort-related motivational dysfunction: Assessing novel atypical dopamine transport inhibitors

Authors: *A. ECEVITOGLU[1], N. MEKA[1], G. EDELSTEIN[1], S. SRINATH[1], K. BEARD[1], R. A. ROTOLO[1], C. CARRATALÁ-ROS[2], R. PRESBY[3], J. CAO[4], A. OKOROM[4], A. H. NEWMAN[5], M. CORREA[6], J. D. SALAMONE[1];
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Abstract: People with depression, schizophrenia, Parkinsonism, and other disorders have motivational dysfunctions such as anergia, avolition, and fatigue, which are relatively treatment-resistant. Animal models have been established to measure effort-related motivational dysfunctions, and are used for developing new treatments. In studies of effort-based choice, rats are given the option of high effort/high reward vs low effort/low reward activities. By using the vesicular monoamine transport-2 inhibitor tetrabenazine (TBZ), a low effort bias that is thought to mimic motivational dysfunction in humans can be induced in rats tested on a fixed-ratio 5 (FR5)/chow feeding choice task. Preclinical data indicate that the TBZ-induced shift from lever pressing to chow intake can be reversed by dopamine transport (DAT) inhibitors, including lisdexamfetamine and methylphenidate, but not by drugs that selectively increase serotonin or norepinephrine transmission. Other animal tests using a progressive ratio (PROG)/chow choice task also are employed for studying effort-related aspects of motivation. This task is sensitive to the ability of DAT inhibitors to increase selection of high-effort PROG lever pressing. Although classical DAT blockers such as cocaine can produce undesirable effects such as abuse liability, not all DAT inhibitors have the same neurochemical profile, and novel compounds with atypical binding characteristics are being developed. Ongoing studies are characterizing the effort-related effects of novel DAT inhibitors that are modafinil analogs with a range of binding profiles (JJC8-088, JJC8-089, and JJC8-091). In the present study, these novel atypical DAT blockers were assessed by using two different effort-related choice behavior tasks in male Sprague-Dawley rats. The dose range for each drug was selected based on data from the Newman Lab at NIDA and pilot studies from Salamone Lab. JJC8-088 and JJC8-089 significantly increased the selection of high-effort responding by reversing the lever-pressing suppression induced by TBZ. JJC8-088 (cocaine-like profile) also increased the selection of high-effort PROG responding. However, JJC8-091 failed to produce these outcomes, potentially due to its unique DAT binding profile and dopamine D2 receptor antagonism. These findings and the continuing study of modafinil analogs may help identify novel therapeutics for effort-related aspects of motivational

dysfunctions observed in numerous psychopathologies. Future studies are focusing on the effects of these novel atypical DAT blockers on effort-based choice behavior in females.

Disclosures: **A. Ecevitoglu:** None. **N. Meka:** None. **G. Edelstein:** None. **S. Srinath:** None. **K. Beard:** None. **R.A. Rotolo:** None. **C. Carratalá-Ros:** None. **R. Presby:** None. **J. Cao:** None. **A. Okorom:** None. **A.H. Newman:** None. **M. Correa:** None. **J.D. Salamone:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.03

Topic: G.03. Motivation

Support: RTI2018-101424-B-I00
PROMETEO/2020/032
POSDOC/2021/24

Title: Mild forced exercise in young mice prevents anergia induced by dopamine depletion in late adulthood: relation to CDNF and DARPP-32 phosphorylation patterns in nucleus accumbens

Authors: *R. OLIVARES-GARCÍA[1], L. LOPEZ-CRUZ[1,2], C. CARRATALA-ROS[1], J. D. SALAMONE[3], M. CORREA[1];
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Abstract: The mesolimbic dopamine (DA) system regulates behavioral activation and exertion of effort. DA antagonism or depletion induces anergia in effort-based-decision-making tasks. However, little is known about the neural mechanisms underlying decision-making processes that establish preferences for sedentary versus activity-based reinforcers. Physical activities have intrinsic motivational and reinforcing properties, but the choice to engage in voluntary physical activity is undertaken in relation to the selection of other sedentary alternatives. The present study assessed the impact of previous experience with forced exercise on reinforcer preference and DA-related postsynaptic markers (phosphorylation of DARPP32), as well as the impact of DA depletion via tetrabenazine (TBZ), a catecholamine depleting agent and vesicular transport inhibitor (VMAT-2), on choice behavior. It was also analyzed whether there was an increase in the neurotrophic factor most associated with DA; the Cerebral-Dopamine-Neurotrophic-Factor (CDNF), which has been shown to play an important role in promoting the survival of DA neurons. CD1 male mice were trained daily in programmed-automatic running wheels (RW) that forced animals to move. The control group had locked-RWs. After 9 weeks of training, animals were tested in a T-maze-3-choice task developed for the assessment of preference between physical activity (RW) vs. more sedentary reinforcers (sucrose pellets or a non-social odor). TBZ (2.0 mg/kg) was administered intraperitoneally 120 minutes before the T-maze-test. Both groups

(trained and controls) preferred to spent more time interacting with the RW versus the other reinforcers. TBZ produced a relative change in preference in the control group; it reduced the time they spent running, while increasing the time they spent eating. However, the forced-exercise group was insensitive to the effects of TBZ, both in behavior and in pDARPP32-Thr34 expression. In addition, a significant increase in CDNF was observed in nucleus accumbens core and shell in trained animals. These results suggest that DA regulates the intrinsic reinforcing characteristics of voluntary exercise, but not the primary reinforcing characteristics of sedentary reinforcers such as intake of sweet foods. Moreover, mild forced exercise could act on DA-related cellular mechanisms that prevent the anergia-inducing effects of DA depletion.

Disclosures: R. Olivares-García: None. **L. Lopez-Cruz:** None. **C. Carratala-Ros:** None. **J.D. Salamone:** None. **M. Correa:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.04

Topic: G.03. Motivation

Support: Ministerio de Ciencia Investigación y Universidades (RTI2018-101424-B-I00)
Conselleria d'Innovació, Universitats, Ciència i Societat Digital (PROMETEO/2020/032)
Universitat Jaume I (POSDOC/2021/24)
Universitat Jaume I (UJI-B2018-31)

Title: Behavioral and neural correlates of individual differences in effort-based decision making in rats. Could they help to understand factors underlying vulnerability to anergia in motivated behaviors?

Authors: *A. MARTÍNEZ VERDÚ[1], R. OLIVARES-GARCÍA[1], P. MATAS-NAVARRO[1], C. CARRATALÁ-ROS[1], P. IBÁÑEZ-MARÍN[1], N. SAN-MIGUEL[2], J. SALAMONE[3], M. CORREA[1];
[1]Psychobiology Unit, Univ. Jaume I, Castellón, Spain; [2]Univ. de València, Univ. de València, Valencia, Spain; [3]Psychological Sci., Univ. of Connecticut, Storrs, CT

Abstract: Motivated behavior is characterized by a high degree of vigor, persistence, effort and activity. Nucleus Accumbens (NAcb) dopamine (DA) plays an important role in behavioral activation and effort-related decision-making. Previous results showed that individual differences in selection of high effort activities for food are modulated by neural markers related to NAcb DA activity such as phosphorylation of pDARPP32-Thr34. In the present work, we studied individual differences in the selection of effortful responding for a preferred sucrose concentration versus approaching and consuming a less preferred freely available sucrose solution. We also assessed individual differences in markers of DA activity in the NAcb such as

the Cerebral Dopamine Neurotrophic Factor (CDNF) and its relation to effort expenditure. Non-water deprived male rats were assessed with a progressive ratio (PROG)/sucrose-drinking task, in which animals can either lever press on a PROG schedule to get access the high-sucrose (5%) solution, or approach and consume a less preferred (0.3%) solution that is freely accessible. Animals were divided evenly into three groups of responders: high, intermediate, and low. Lever pressing was significantly different for these three groups, and their performance in the PROG/choice task was correlated with responses in the PROG under no free choice conditions. Thus, low performers are also low when there was no free option. Although the three groups were not different in the amount of free 0.3% sucrose consumed, there was a significant negative correlation between lever pressing in the choice condition and free sucrose consumed. In addition, before and after the PROG/sucrose-drinking task, animals were tested for spontaneous two-bottle sucrose preference (0.3% vs 5%) and consumption, voluntary locomotion in a Running Wheel (RW), and novel exploration of an Open Field (OF). Preference for 5% sucrose or RW activity pre or post operant evaluation were not correlated with number of lever presses in the PROG/Choice operant task. However, rearing in the OF evaluated before the operant task showed a significant positive correlation with lever pressing. Neural correlates of NAcb function such as immunoreactivity for CDNF seem to be related to these individual differences, with number of positive cells higher in high responders. These results suggest that neural and behavioral characterization of individual differences that lead to differences in effort-based choice can help to understand the underlying factors of vulnerability for symptoms such as anergia, avolition or fatigue, which are important in some psychological and neurological pathologies.

Disclosures: **A. Martínez Verdú:** None. **R. Olivares-García:** None. **P. Matas-Navarro:** None. **C. Carratalá-Ros:** None. **P. Ibáñez-Marín:** None. **N. San-Miguel:** None. **J. Salamone:** None. **M. Correa:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.05

Topic: G.03. Motivation

Support: NIH/NIMH Grant MH121350

Title: Detailed Characterization of the Effects of the Vesicular Monoamine Transporter-2 Inhibitor Tetrabenazine on Effort-based Decision Making and Binge-like Eating: Exertion of Effort vs. “Anhedonia”

Authors: *G. EDELSTEIN[1], A. ECEVITOGLU[1], C. CARRATALA-ROS[2,1], R. A. ROTOLO[1], R. PRESBY[1], R. FLEEHER[1], J. MASTHAY[1], M. CORREA[2], J. SALAMONE[1];
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Abstract: Brain dopamine (DA) transmission regulates exertion of physical effort and effort-based choice. Tetrabenazine (TBZ), a VMAT-2 inhibitor that blocks vesicular storage and depletes DA, alters effort-based choice by inducing a low-effort bias. TBZ induces depressive symptoms and motivational impairments such as anergia, fatigue and apathy in humans, and is used in rodents to model motivational dysfunctions. Administration of TBZ produces a low-effort bias in rats tested for effort-based choice using the concurrent fixed ratio (FR) 5/chow feeding choice task. At baseline, rats show a preference for FR5 lever pressing for the more palatable food (high-carbohydrate pellets) and eat little of the concurrently available lab chow. Detailed analyses of the temporal characteristics of lever pressing show that TBZ-treated rats (1.0 mg/kg IP) shift away from lever pressing, with a reduction in the number of completed ratios, a slowing of local rate within ratios, and an increase in total time spent in pauses from lever pressing. TBZ-treated rats showed a significant and substantial increase in intake of the concurrently available chow, increasing total grams consumed, total time spent eating, and number of bouts of chow feeding. Detailed temporal analyses showed that TBZ did not alter the total combined time spent lever pressing for pellets and consuming chow, but instead shifted the allocation of time away from lever pressing and towards chow intake, leaving fundamental aspects of food reinforcement intact. Additional studies employed a binge-like eating model in non-food-restricted rats, in which they were randomly exposed to periods of chocolate access. This exposure induced a gradual increase in chocolate intake. Administration of 1.0 mg/kg TBZ did not reduce chocolate intake, indicating that TBZ did not impair “hedonic eating”. Together with previous studies showing that TBZ did not alter food preference or sucrose preference, and the effects of TBZ did not resemble those induced by reinforcer devaluation, this pattern of results demonstrates that TBZ produces a low-effort bias at doses that do not induce “anhedonia”. These results have implications for modeling the motivational impairments seen in psychiatric disorders such as depression and schizophrenia.

Disclosures: G. Edelstein: None. **A. Ecevitoglu:** None. **C. Carratala-Ros:** None. **R.A. Rotolo:** None. **R. Presby:** None. **R. Fleeher:** None. **J. Masthay:** None. **M. Correa:** None. **J. Salamone:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.06

Topic: G.03. Motivation

Support: R01MH048404
F32AA027935

Title: Adolescent alcohol exposure impairs response inhibition and alters orbitofrontal cortex-striatal dynamics in adult and adolescent rats

Authors: *A. MCCANE, L. KRONHEIM, B. MOGHADDAM;
Behavioral Neurosci., Oregon Hlth. & Sci. Univ. Behavioral Neurosci., Portland, OR

Abstract: Development of alcohol use disorder (AUD) is strongly associated with initiation of drinking during adolescence. A better understanding of the impact of alcohol exposure on the adolescent brain in the context of motivated behavior is fundamental for understanding the etiology and pathophysiology of AUD. Deficits in response inhibition are a critical feature of AUD and are a clinically relevant endophenotype of the disorder. However, little is known about the functional consequences of adolescent alcohol drinking on response inhibition and related cognitive measures in adulthood. Here, we used a voluntary adolescent drinking model combined with Cued Response Inhibition Task (CRIT) that assesses response inhibition, stimulus-response relationships and attentional processes. We simultaneously recorded single units and local field potentials (LFPs) from adolescent and adult rats in the orbitofrontal cortex (OFC) and dorsomedial striatum (DMS) while rats performed CRIT. We measured firing rates, performed spectral analyses and computed neural synchrony between the OFC and DMS. Adolescent alcohol drinking was associated with increased premature responding and decreased correct responding in adolescents and after animals reached adulthood. In adolescence, alcohol exposure was associated with decreased firing rate in the OFC but increased firing rate in the DMS during premature responding. In adults, adolescent alcohol exposure was associated with an attenuated response to the inhibitory cue but an augmented response to reward. Adolescent alcohol exposure was also associated with an increase in theta and gamma power during premature responding. In alcohol exposed adults and adolescents, OFC-DMS synchrony was higher during reward relative to sucrose drinking controls. Our analysis reveals that adolescent alcohol exposure produces several dynamic changes to cortical-striatal ensembles. Adult rats who drank alcohol as adolescents exhibit physiological similarities to adolescent control rats. Moreover, adolescents who were previously exposed to alcohol show physiological and behavioral differences relative to sucrose control adolescents. Together, these data suggest that alcohol drinking in adolescence induces changes that begin in adolescence, alter development of OFC-DMS circuits, and results in alterations in adult brain function. Because dysfunction of cortico-striatal circuits is a critical feature of AUD, these translational results enhance our mechanistic understanding of brain changes that occur in these circuits following adolescent ethanol exposure.

Disclosures: A. McCane: None. **L. Kronheim:** None. **B. Moghaddam:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.07

Topic: G.03. Motivation

Support: R01MH048404
F32AA027935

Title: Adolescents engage orbitofrontal cortex and dorsomedial striatal neurons differently during response inhibition

Authors: *L. KRONHEIM, A. M. MCCANE, B. MOGHADDAM;
Behavioral Neurosci., Oregon Hlth. & Sci. Univ. Behavioral Neurosci., Portland, OR

Abstract: Adolescence is a vulnerable developmental period. Neuronal underpinning of this vulnerability is poorly understood but has been attributed to an immature frontal cortex and its connections to striatal and other subcortical areas that modulate action selection. We have observed that action-guided reward (outcome) processing by lateral orbitofrontal cortex (OFC) and dorsomedial striatum (DMS) neurons differ between adolescents and adults. Here, we test the specific hypothesis that action-outcome associations and response inhibition are processed differently in DMS-OFC circuits in adolescents compared to adults. We used a Cued Response Inhibition Task (CRIT) in male and female rats to assess response inhibition and stimulus-response relationships in adolescents and adults. To characterize the role of OFC to DMS projections in adults and adolescents in CRIT, we injected a retrograde cre virus into the DMS and an inhibitory DREADD virus into the OFC to target striatum projecting OFC neurons. This was followed by administering clozapine-N-oxide (CNO) before each behavioral session to inhibit OFC->DMS projections. In a separate group of rats, we simultaneously recorded single units and local field potentials (LFPs) in the OFC and DMS from adolescent and adult rats performing CRIT. Cell types in both regions were classified based on waveform characteristics and firing rates for events of interest were computed.We find that inhibiting the OFC->DMS projections decreases correct responses and increases premature responses during CRIT, suggesting this pathway is necessary for successful execution of response inhibition in both age groups. Age differences in neural activity in individual regions and in OFC-DMS coordinated activity were observed in both brain regions. In particular, compared to adults, adolescents' OFC neurons had a lower phasic response to the inhibitory cue whereas adolescents' DMS neurons had a larger phasic response to reward. Adolescent OFC-DMS functional connectivity was stronger during reward but weaker during action execution. These results indicate that while the OFC-DMS circuit is critical for response inhibition in both adults and adolescent, adolescents engage this circuit differently by tuning stronger to reward and weaker to inhibitory cues and action. These data expand our knowledge of how the adolescent brain differently guides behavior relative to adults and highlights the importance of OFC-DMS circuits for mediating response inhibition in adolescents.

Disclosures: L. Kronheim: None. **A.M. McCane:** None. **B. Moghaddam:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.08

Topic: G.03. Motivation

Title: Somatostatin signaling in the prefrontal cortex of mice is necessary for motivationally-charged behavior

Authors: *M. ARENIVAR[1], H. A. TEJEDA[2];
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Abstract: The prefrontal cortex (PFC) is critical for decision making, goal-directed behavior, hedonic processing, and adaptive behavior. Somatostatin (SST) is a neuropeptide expressed in local circuit PFC interneurons and is hypothesized to modulate cells that express its' cognate SST receptor/s. Despite recent significant advances in understanding the role of SST-expressing interneurons in regulating PFC circuit function and behavior, little is known about the regulatory functions of SST as a peptide neurotransmitter. In this study, we used a combination of genetic/viral approaches, in-vivo recordings, and behavior to determine how motivation regulates PFC SST neuron activity and the role of SST peptidergic transmission in motivated behavior. We demonstrate that selective genetic ablation of SST neuropeptide expression in the PFC, reduced sucrose consumption (appetitive drive), impaired nesting (an index of self-care), and reduced time swimming in the forced swim test (active coping with threats to survival), suggesting that SST is critical in regulating motivationally-driven behaviors. Moreover, we found reward/motivation deficits in mice lacking SST in an operant task, wherein mice press a lever to obtain appetitive rewards under conditions requiring increased effort. Collectively, our findings suggest that the SST peptide is crucial for motivationally-charged behavior. Moreover, *in-vivo* monitoring of SST, using fiber-photometry, shows that SST activity is enhanced during the aforementioned motivational task. Other efforts include elucidating the different subtypes of neurons that express SST and SSTRs within the PFC to identify how SST transmission may be embedded within PFC microcircuits. In conclusion, uncovering the dynamics of SST activity and subsequent SST neuropeptide release and its' influence on PFC-dependent behavior, is a critical step in elucidating how this neuropeptide shapes cortical circuits. This is of relevance given that clinical studies have revealed decreased expression of SST in individuals suffering from mood-related disorders, suggesting SST is an important factor relevant to the clinical population. Understanding the SST neuropeptidergic system in PFC circuitry may reveal therapeutic targets to treat symptoms associated with the various neuropsychiatric disorders associated with motivational drive deficits.

Disclosures: M. Arenivar: None. **H.A. Tejeda:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.09

Topic: G.03. Motivation

Support: CONACYT Grant 720657

Title: Evaluation of the sensitivity to delay of reinforcement after exposure to a hypercaloric diet

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Abstract: Experimental evidence has shown that exposure to hypercaloric diets is related to impulsive choice in rodents. In temporal discounting tasks, subjects exposed to a high-fat diet show a stronger preference for the small, immediate reward than subjects fed with a standard diet. Although researchers frequently use temporal discounting tasks, such procedures do not distinguish whether impulsive choice is influenced by changes in the sensitivity to delay or in the sensitivity to magnitude, which are factors that affect the value of the reinforcer. Therefore, the objective of the present study was to evaluate changes in the sensitivity to delay after exposure to a high-fat, high-sugar choice (HFHSc) diet. Twenty-four male Wistar rats (250-300 g) were divided in two groups (control and experimental) according to their body weights, at the beginning of the experiment. The control group had ad libitum access to water and standard chow diet, while the experimental group had ad libitum access to edible fat (INCA®), a 10% sucrose solution, standard chow diet and water. Both groups were exposed to their respective diet for 12 weeks. At the end of this period, training in the behavioral task started. Subjects were habituated to the conditioning chamber and after level-press training, they were exposed to a concurrent-chains schedule. The concurrent-chains schedule employed non-independent variable-interval 15 s schedules (VI 15 s) in the initial links and fixed interval schedules in the terminal link. The duration of the fixed interval determined the delay to reinforcement. The delays employed were: 2-28, 6-24, 15-15, 24-6 and 28-2 s for left and right levers, delays were presented in a semi-random order and behavioral stability was required in each condition. Unexpectedly, we observed that subjects of the experimental group were less sensitive to the delay in comparison than control group. Our results indicate that, in subjects exposed to the HFHSc diet, the assigned value to the reinforcer is less affected by the delay. Therefore, the impulsive choice observed in other studies could be related to changes in the sensitivity to magnitude and factors such as food deprivation condition, time of exposure to the hypercaloric diet and type of diet.

Disclosures: W. Zepeda-Ruiz: None. **D. Velázquez Martínez:** None. **R. Escartín Pérez:** None. **M. Cerbón Cervantes:** None. **V. Orduña:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.10

Topic: G.03. Motivation

Title: Sexually-motivated male rats present a higher activation and EEG synchronization prefrontal-parietal in front a receptive female

Authors: *C. DOMÍNGUEZ-ESTRADA[1], M. HERNÁNDEZ-GONZÁLEZ[1], E. HERNÁNDEZ-ARTEAGA[2,3], M. ARTEAGA-SILVA[3], M. GUEVARA[1,2];
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Abstract: Sexual motivation (SM) is a physiological state generated by the adequate processing of sexually-relevant stimuli. Induction and maintenance of this state requires the coordinated functioning of various cortical and subcortical areas. The medial prefrontal (mPFC, the prelimbic area in rats) and posterior parietal cortices (pPC) form an attentional network involved in processing incentive stimuli. Given that the sexual incentive stimuli emitted by a receptive female are highly relevant for the male rat, it is probable that these cortices interact functionally in processing the sexual stimuli that produce SM. Thus, the objective of this study was to characterize the cortical activation and degree of electroencephalographic coupling (coherence, hEEG) between the mPFC and pPC during a sexually-motivated state in male rats. Only rats that reached this state after 1 intromission prior to EEG recording, presented a higher frequency and duration of nose pokes, and showed higher prefronto-parietal activation and EEG synchronization while close to an inaccessible receptive female. Results show that both cortices are activated and that they are functionally coupled during the processing of sexually-relevant stimuli mainly in the right hemisphere, a key condition for inducing SM. We conclude that the attentional network made up of the prefrontal and parietal cortices participates in the adequate attention to, and processing of, sexual incentive stimuli and, hence, in inducing SM in male rats.

Disclosures: C. Domínguez-Estrada: None. **M. Hernández-González:** None. **E. Hernández-Arteaga:** None. **M. Arteaga-Silva:** None. **M. Guevara:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.11

Topic: D.02. Somatosensation – Pain

Support: NIH R01 DK110669

Title: Chronic Pain Intensity and Affect Disassociate in Fronto-Parietal Networks

Authors: *M. S. YANI, J. J. KUTCH;
Div. of Biokinesiology and Physical Therapy, USC, Los Angeles, CA

Abstract: Chronic pain is often characterized by disturbances in mood, which often makes treatment more difficult. However, the neural link between processing of pain intensity and mood changes is not clear. Here we investigate brain activity associations with processing of pain and mood, using a chronic pain condition with known inter-individual variation in pain intensity and mood disturbances (Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)). Men with CP/CPPS (N=42) and age-matched control men (N=48) underwent resting state functional magnetic resonance imaging and completed pain, affect, anxiety and depression questionnaires. Men with CP/CPPS had significantly less local activity (fractional amplitude of low-frequency fluctuations (fALFF)) in prefrontal cortical regions compared to controls, while pain intensity correlated with more local activity in a distinct set of regions in parietal cortex. Multivariate linear regression revealed that local activity in prefrontal regions correlated with negative affect, but not pain intensity, while local activity in parietal regions correlated with pain intensity, but not negative affect. Network information flow quantified by multivariate Granger causality analysis suggested a prefrontal-to-parietal net flow in controls, but a parietal-to-prefrontal net flow in patients. Our findings suggest that prefrontal dysfunction in chronic pain may allow bottom-up flow of sensory information to influence mood, implicating fronto-parietal networks as a link between processing of pain intensity and mood changes in chronic pain conditions. Causal research to target local activity and information flow within fronto-parietal networks is warranted and may provide novel approaches to reduce the multifactorial burden of chronic pain.

Disclosures: M.S. Yani: None. **J.J. Kutch:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.12

Topic: G.03. Motivation

Title: A hippocampal circuit for physical activity regulation

Authors: *A. C. LETSINGER, J. J. WU, D. E. YOUNGSTROM, K. U. TANG, J. L. YAKEL; Neurobio. Lab., Natl. Inst. for Envrn. Hlth. Sci., Durham, NC

Abstract: Greater than 80% of US adults do not meet minimal physical activity guidelines despite widespread belief that physical inactivity is bad for health. As such, it is critical to understand the biological determinates that regulate physical activity behavior if we hope to increase participation. The hippocampus is one of the most active brain regions during physical activity, making it a prime region for investigation a potential causal role in regulating physical activity. Further, recent reports reveal dopamine receptor (i.e., DRD2) expressing neurons in the hilus of the dentate gyrus, which are primarily mossy cells, can influence components of motivated behavior such as locomotion and foraging memory. We hypothesized that hilar DRD2-expressing cells can modulate mouse wheel running behavior. We first utilized fiber

photometry to analyze wheel running-related fluctuations of dopamine ($GRAB_{DA}2.0$) and calcium (GCaMP8s) in DRD2-expressing neurons within the hilus of the dorsal and ventral dentate gyrus of male and female DRD2-cre mice. We then expressed either inhibitory or excitatory DREADDS on DRD2-expressing hilar cells throughout the hippocampus of DRD2-cre mice and placed them in metabolic chambers with running wheels. Mice were offered 100 µg/mL and 250 µg/mL of clozapine-*n*-oxide (CNO) in place of regular drinking water on the 10^{th} and 13^{th} day, respectively. We found significant phasic increases of dopamine at the onset of most wheel running bouts, followed by decreases throughout the bout. Calcium activity within DRD2-expressing hilar cells were less consistent but had higher likelihoods of firing during wheel running bouts. Both dosages of CNO significantly decreased levels of wheel running regardless of the DREADD type, while excitatory DREADDS increased and inhibitory DREADDS decreased cage locomotion. Our findings indicate that the hippocampus, which was previously believed to be only stimulated by exercise, can modulate the likelihood of engagement in physical activity via a presently unknown mossy cell-related mechanism. Additional studies are being done to understand the acute effect of DREADDs on mossy cell function *in vitro* and wheel running *in vivo*.

Disclosures: A.C. Letsinger: None. **J.J. Wu:** None. **D.E. Youngstrom:** None. **K.U. Tang:** None. **J.L. Yakel:** None.

Poster

730. Motivated Behavior, Mechanisms

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 730.13

Topic: I.03. Anatomical Methods

Support: NIH Grant NS108259
NIH Grant NS119847

Title: Afferent projections to the paratenial and paraventricular nuclei of the dorsal midline thalamus in the rat

Authors: *A. K. P. ROJAS[1], R. P. VERTES[1,2], S. B. LINLEY[1,2,3];
[1]Ctr. For Complex Systems & Brain Sci., [2]Dept. of Psychology, Florida Atlantic Univ., Boca Raton, FL; [3]Dept. of Psychological Sci., Univ. of North Georgia, Dahlonega, GA

Abstract: The midline nuclei of the thalamus consist of the paratenial (PT) and paraventricular (PV) nuclei, dorsally, and the reuniens and rhomboid nuclei, ventrally. The functional properties of PV have been extensively investigated showing a PV involvement in appetitive and aversive motivation states (McGinty and Otis, 2020). By contrast, little is known regarding the functional characteristics of PT. We previously examined the efferent projections of PT and PV (Vertes and Hoover, 2008) and showed, with some differences, that both nuclei distributed to several common sites, characterized as “affective-associated” structures of the forebrain. They included

the septum, bed nucleus of stria terminalis (BST), nucleus accumbens, amygdala, ventral subiculum of the hippocampus (HF) and the infralimbic (IL) and prelimbic (PL) cortices of the medial prefrontal cortex (mPFC). Afferents to PV have been examined in a single report in the rat (Li and Kirouac, 2012), but to our knowledge inputs to PT have not been described. We examined the afferent projections to PT and PV using the retrograde fluorescent tracer, Fluorogold (FG). FG was made up at 5-6% concentration and was injected via pressure or iontophoresis into PT or PV. Following a 7 day survival, rats were euthanized, brains removed, sectioned and then immunohistochemically reacted (rabbit anti-FG, biotinylated goat anti-rabbit IgG, ABC kit) to identify retrogradely labeled cells in structures throughout the brain. **PT**: The main sources of input to PT were from the hypothalamus, basal forebrain (BF) and the cortex - with (interestingly) relatively limited inputs from the brainstem. Specifically, significant numbers of labeled cells with PT injections were observed in the lateral (LHy), paraventricular and arcuate nuclei of the hypothalamus, the preoptic region (POR) and nuclei of the diagonal (NDB) of the BF and the orbitomedial PFC -- prominently including the medial and ventral orbital (ORB) cortices, and the IL, PL and anterior cingulate cortices of the mPFC. **PV:** The main sources of afferents to PV were from the hypothalamus, BF, mPFC and the subiculum of HF. The main hypothalamic inputs to PV were from the ventromedial and dorsomedial nuclei and densely from the suprachiasmatic nucleus. Inputs from BF primarily originated from BST, NBD and the medial POR. While PT received input from the mPFC, ORB and entorhinal cortices, cortical afferents to PV were predominantly restricted to IL and PL of the mPFC. In summary, while PV and PT share some inputs, each nucleus receive unique afferents from cortical and subcortical structures, indicating that PT and PV may participate in dissociable roles to emotion, cognition and motivation.

Disclosures: A.K.P. Rojas: None. **R.P. Vertes:** None. **S.B. Linley:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.01

Topic: G.05. Mood Disorders

Support: Greehey Family Foundation Endowment for Alzheimer's Research
Zachry Family Foundation Endowment for Alzheimer's Disease

Title: Approximation to a Precision Medicine using Dimensional characterization of brain volumetry and behavior expression in hospitalized patients by affective and/or anxiety symptoms.

Authors: *M. J. USCAMAYTA AYVAR[1], J. TORANZO[1], J. ARNEDO[2], G. F. POBLETE[3], M. S. ALOI[4], I. ZWIR[2], R. SALAS[5], G. A. DE ERAUSQUIN[1];
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Center, San Antonio, San Antonio, TX; [2]Univ. de Granada, Granada, Spain; [3]Menninger Clin., Houston, TX; [5]Psychiatry, [4]Baylor Col. of Med., Houston, TX

Abstract: 4 out of 6 leading causes of years lived with disability are the result of mental illness. Available treatments are ineffective in many patients. Precision medicine proposes the adaptation of treatment to the patient's individual characteristics, through the analysis and integration of imaging techniques, clinical and omic data. We hypothesize that use of dimensional measures of behavior and brain volume, associated with affective and anxious symptoms, allows an approach to Precision Medicine. We obtained clinical and brain imaging data from 455 patients with affective and anxious symptoms. The clinical variables were obtained through psychological scales. Brain volumes were obtained through high resolution structural T1 MRI, collected on a 3T Siemens Trio MR scanner. Structural, T1 weighted brain images were processed using Freesurfer v6.0. The analysis of relationships between the study variables was carried out using the Generalized Factorization Method, which generates biclusters (groups of individuals that share a maximum possible number of characteristic features, without limiting the number of groups, or number of individuals per group, or number of characteristic features). This method allows discovering as many individuals as possible, sharing as many characteristics as possible. The same method is applied independently to neuroimaging and behavioral data, obtaining 2 sets of biclusters that describe the same individuals from 2 different levels of analysis. We discovered 24 clusters, each reflecting different brain volumetric patterns shared by different subsets of the study subjects; 24 clusters containing different clinical profile characteristics shared by different subsets of subjects; the intersection of both sets of biclusters identified individuals who simultaneously share changes in regional brain volumes, as well as in clinical profiles. Thus, high level relationships identify alterations in specific brain volumes that are associated with specific clinical variables in given individuals, e.g Clusters: R19 shows variations in the Gyrus occ. Temp. medial Parahippocampal thickness (P.V 0.000049) related to a clinical profile of low level of social functioning (P.V 0.0000029). R5 shows variations in Gyrus and Sulcus cingulate Ant volume (P.V 0.000019) related to difficulties in emotion regulation (lack of emotional clarity) (P.V 0.00008). The individuals defined by these characteristics are statistically different from other individuals, this allows us to classify them with more precision than the DSM. We have obtained encouraging results of improved precision diagnosis, using an unbiased machine learning approach.

Disclosures: M.J. Uscamayta Ayvar: None. **J. Toranzo:** None. **J. Arnedo:** None. **G.F. Poblete:** None. **M.S. Aloi:** None. **I. Zwir:** None. **R. Salas:** None. **G.A. De Erausquin:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.02

Topic: G.05. Mood Disorders

Support: James S. McDonnell Foundation
The McDonnell Center for Systems Neuroscience
National Institutes of Health Clinical and Translational Science Award (CTSA) program, TL1 TR002344

Title: A Comparison Study of Quiescence During Burst Suppression and Postictal Generalized EEG Suppression

Authors: *M. KAFASHAN[1,2], L. B. HICKMAN[1,9], A. LABONTE[1,3], E. HUELS[10,11], H. MAYBRIER[4], C. GUAY[1], S. SUBRAMANIAN[5], N. B. FARBER[5], S. CHING[12], R. E. HOGAN[6], M. B. KELZ[14], M. S. AVIDAN[1,5], G. A. MASHOUR[10], B. A. PALANCA[1,5,7,13,8]; [1]Dept. of Anesthesiol., [2]Ctr. on Biol. Rhythms and Sleep, [3]Neurosci. Grad. Program, [4]Psychological & Brain Sci. Dept., [5]Dept. of Psychiatry, [6]Dept. of Neurol., [7]Div. of Biol. and Biomed. Sci., Washington Univ. Sch. of Med. in St. Louis, St. Louis, MO; [8]Ctr. on Biol. Rhythms and Sleep, Washington Univ. Sch. of Med. in St. Louis, Saint Louis, MO; [9]Dept. of Neurol., David Geffen Sch. of Med. at Univ. of California, Los Angeles, Los Angeles, CA; [10]Dept. of Anesthesiol., [11]Neurosci. Grad. Program, Univ. of Michigan, Ann Arbor, MI; [12]Washington Univ. in St. Louis, Saint Louis, MO; [13]Dept. of Biomed. Engin., Washington Univ. in St. Louis, St. Louis, MO; [14]Dept. of Anesthesiol. and Critical Care, Univ. of Pennsylvania Sch. of Med., Philadelphia, PA

Abstract: Introduction: Periods of electroencephalographic (EEG) quiescence—low amplitude EEG signals—are present during both anesthetic-induced burst suppression (BS) and postictal generalized electroencephalographic suppression (PGES). PGES following generalized seizures induced by electroconvulsive therapy (ECT) has been posited to be linked to antidepressant response. The commonality of quiescence during both BS and PGES motivated trials to recapitulate the antidepressant effects of ECT using high-dose anesthesia. However, there have not been any direct electrographic comparisons of these quiescent periods to address whether these are distinct patterns. **Methods:** In this study, we compared periods of EEG quiescence recorded from two human studies: BS induced in 29 healthy adult volunteers by isoflurane general anesthesia and PGES in 11 patients undergoing right unilateral ECT for treatment-resistant depression. An automated algorithm was utilized to detect EEG quiescence based on a 10-microvolt amplitude threshold. Spatial, spectral, and temporal analyses were performed to compare quiescent epochs during BS and PGES. **Results:** The voltage for quiescent periods during PGES (median = 1.81, interquartile range = 0.22 microvolts) was greater ($p < 0.001$) than during BS (median = 1.22 microvolts, interquartile range = 0.33 microvolts). Relative power was greater for quiescence during PGES than BS for the 1-4 Hz delta band ($p < 0.001$), at the expense of power in the theta (4-8 Hz, $p < 0.001$), beta (13-30 Hz, $p = 0.04$) and gamma (30-70 Hz, $p = 0.006$) frequency bands. Topographic analyses showed that amplitude across the scalp was consistently higher for quiescent periods during PGES than BS, whose voltage was within the noise floor. **Conclusions:** Quiescent epochs during PGES and BS, important neurophysiological markers for clinical outcomes, have distinct patterns of EEG signals across voltage, frequency, and spatial domains.

Disclosures: M. Kafashan: None. **L.B. Hickman:** None. **A. Labonte:** None. **E. Huels:** None. **H. Maybrier:** None. **C. Guay:** None. **S. Subramanian:** None. **N.B. Farber:** None. **S. Ching:** None. **R.E. Hogan:** None. **M.B. Kelz:** None. **M.S. Avidan:** None. **G.A. Mashour:** None. **B.A. Palanca:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.03

Topic: G.05. Mood Disorders

Title: Repetitive TMS Reverses a Novel Temporal Biomarker of Major Depressive Disorder

Authors: *A. MITRA[1], M. RAICHLE[2], N. WILLIAMS[1];
[1]Psychiatry, Stanford Univ. Sch. of Med., Palo Alto, CA; [2]Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Major depressive disorder (MDD) is the leading cause of disability worldwide. We now understand that MDD is not caused by a single lesion in the brain, but instead, likely arises due to aberrant communication patterns within brain-wide network. Several studies have specifically postulated that MDD may be caused by an imbalance in signaling between the anterior cingulate cortex (ACC) to other brain areas involved in emotional processing. Indeed, transcranial magnetic stimulation (TMS) treatments have been developed to modulate signaling between the ACC and other brain regions by stimulating the left dorsolateral prefrontal cortex (DLPFC). Yet progress in treating MDD remains hindered by our inability to reliably detect mechanistic biomarkers of MDD in the human brain. Here, we address these hurdles with a causal study to examine how directed [AM1] communication patterns in the human brain relate to the neurobiology of MDD. We accomplish this by combining recently developed analysis method for computing the directional flow of brain-wide resting state fMRI (rs-fMRI) activity with a recently reported novel repetitive TMS (rTMS) protocol. We find that active rTMS modulates the directional flow of rs-fMRI activity between the dorsal ACC and a set of regions in the salience network, which has previously been implicated in emotional processing. Moreover, by analyzing baseline differences between patients with MDD and healthy controls, we find that rTMS corrects a baseline aberrancy in neural flow patterns. Finally, we show that the baseline temporal structure of individual patients with MDD can predict treatment response, such that patients with aberrant ACC-based flow patterns respond strongly to rTMS treatment whereas patients with near normal ACC-based flow patterns have far weaker treatment responses.

Disclosures: A. Mitra: None. **M. Raichle:** None. **N. Williams:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.04

Topic: G.05. Mood Disorders

Support: UH3 NS103549

Title: Information Flow within the Prefrontal Cortex Decodes Depression Severity

Authors: *J. MYERS[1], J. XIAO[1], B. METZGER[1], J. ADKINSON[1], A. ALLAWALA[4], V. PIRTLE[1], R. MATHURA[1], A. ANAND[1], R. GADOT[2], R. NAJERA[1], H. G. REY[3], B. SHOFTY[1], N. PROVENZA[1], W. GOODMAN[1], S. J. MATHEW[3], N. POURATIAN[1], K. BIJANKI[1], S. SHETH[1];
[1]Baylor Col. of Med., HOUSTON, TX; [3]Baylor Col. of Med., [2]Baylor Col. of Med., Houston, TX; [4]Brown Univ., Brown Univ., Providence, RI

Abstract: Major depression involves large scale dysfunction across the limbic system and neocortical regions such as the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (dlPFC). As part of an ongoing NIH-funded trial using deep brain stimulation (DBS) for depression, we implanted 3 patients with DBS leads and intracranial EEG electrodes to measure neural oscillations in the dlPFC, OFC, and ACC. We hypothesized that directed connectivity, as measured by Granger Causality (GC), between these prefrontal regions would unveil key connectivity patterns underlying depression severity. We tested this hypothesis by exploring the relationship between depression severity and resting state GC between the OFC, dlPFC, and the ACC. We frequently measured depression severity throughout a 9-day inpatient monitoring period using a validated adaptive severity scale. We measured directed connectivity using multivariate vector autoregressive models that quantified information flow between the right dlPFC, OFC, and ACC during resting state. We then examined the relationship between depression severity and GC within the delta band (1 - 3 Hz). Directed connectivity was used as input in a support vector machine (SVM), showing that depression severity can be accurately decoded from complex directed connectivity patterns. Depression severity was accurately decoded by the SVM, ($p < 0.001$). Information flow within the delta band was positively correlated with depression severity in each patient ($p < 0.05$). Across all patients, directed connectivity from the OFC to the ACC predicted depression severity ($p < 0.05$). Higher OFC -> ACC connectivity may relate to increased self-appraisals of mood and diminished control of emotional state during major depressive episodes. Results indicate that information flow within the prefrontal cortex is intricately linked to depression severity.

Disclosures: J. Myers: None. **J. Xiao:** None. **B. Metzger:** None. **J. Adkinson:** None. **A. Allawala:** None. **V. Pirtle:** None. **R. Mathura:** None. **A. Anand:** None. **R. Gadot:** None. **R. Najera:** None. **H.G. Rey:** None. **B. Shofty:** None. **N. Provenza:** None. **W. Goodman:** None. **S.J. Mathew:** None. **N. Pouratian:** None. **K. Bijanki:** None. **S. Sheth:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.05

Topic: G.05. Mood Disorders

Support: Universidad de Guanajuato

Title: Moderate depressive symptoms are correlated with progesterone and resting-state electroencephalography in early postmenopausal stage

Authors: *M. SOLIS-ORTIZ;
Med. Sci., Univ. De Guanajuato, Leon, Mexico

Abstract: Depressive moods are frequent in early postmenopausal periods. Resting-state electroencephalography has been associated with depression in women. However, the correlation between these variables and ovarian hormones is not entirely understood. The aim of this study was to examine the effects of depressive symptoms on resting electroencephalography and their correlation with endogenous hormone levels in postmenopausal women without a diagnosis of major depression. Fifty postmenopausal women aged 48 to 60 years were assessed for depressive symptoms using the Beck Depression Inventory. Electroencephalography activity was recorded during rest with eyes closed in 23 postmenopausal women with minimal and 27 with moderate depressive symptoms. Relative power for delta, theta, alpha1, alpha2, beta1 and beta2 were analyzed and compared between women with minimal and moderate depressive symptoms. Hormonal levels of estrone, estradiol, progesterone, follicle-stimulating hormone and luteinizing hormone were obtained and correlated with the electroencephalography parameters. The women with moderate depressive symptoms showed more relative alpha1power and less relative beta2 power. Relative theta and alpha2 power, estradiol levels and menopausal years were predictors of depressive symptoms. Progesterone was negatively correlated with the theta band and positively correlated with the beta2 band in women with moderate depressive symptoms. Estrone was negatively correlated with the alpha2 band, and estradiol was positively correlated with the theta band and negatively correlated with the beta2 band in women with minimal depressive symptoms. These findings suggest that slow and fast electroencephalography relative power, menopausal status and estrogen levels predict depressive symptoms and that progesterone is related with moderate depression.

Disclosures: M. Solis-Ortiz: None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.06

Topic: G.05. Mood Disorders

Support: Intramural Research Program of the National Institute of Mental Health National Institutes of Health (NIH) (Grant No. ZIA-MH002957-01)
Intramural Research Project ZIAMH002782

Title: Validation of CBCL Depression Scores of Adolescents in Three Independent Datasets

Authors: *M. ZELENINA[1], A. STRINGARIS[2], D. S. PINE[1], D. M. NIELSON[1];
[1]NIH, Natl. Inst. of Mental Hlth. (NIMH), North Bethesda, MD; [2]Univ. Col. London, London, United Kingdom

Abstract: Large, open datasets with rich brain measurements are increasingly being used to examine the mechanisms of adolescent depression, a global public health problem; it is crucial that such datasets employ validated measures of the clinical phenotype. In our pre-registered analysis, we examined depression measurements in 3 adolescent datasets: the Adolescent Brain Development Study (ABCD), the Healthy Brain Network (HBN) and the Brazilian High Risk Cohort study (BHRC). We focused on a continuous measure - the Child Behaviour Checklist (CBCL) DSM-5 Depression Subscale, that is available in all three datasets. First, in ABCD, we compared the parent-report CBCL against the child- and the parent-report of the standard clinical interview Kiddie Schedule for Affective Disorders (K-SADS). We used the Area Under the Receiver Operator Curve (AUCROC) > 0.80 as a measure of "good" prediction. CBCL was a poor (AUCROC = 0.63) predictor of child-report K-SADS scores but a good (AUCROC = 0.93) predictor of parent-report K-SADS scores. Further, we established the specificity of the prediction. On the same dataset (ABCD), we tested CBCL as a differentiator of subjects with depression vs. without depression but with another form of psychopathology (anxiety or ADHD); and of subjects with depression but without any other form of psychopathology vs. without depression but with another form of psychopathology. Our results confirmed our initial findings: CBCL was a poor predictor of child-report K-SADS scores (AUCROC = 0.48, 0.46) but a good predictor of parent-report K-SADS scores (AUCROC = 0.86, 0.84). To resolve the discrepancy between children's and parents' reports, we turned to clinician diagnoses. The clinician diagnoses were available in the HBN and the BHRC (but not in the ABCD). We repeated the same analyses we did on ABCD on the HBN and the BHRC, but used clinician diagnoses as gold standard. The CBCL was good at differentiating depressed from healthy subjects (HBN AUCROC = 0.93; BHRC AUCROC = 0.89), but performed poorly at differentiating from other disorders: HBN AUCROC = 0.74, 0.78; BHRC AUCROC = 0.78. It was not possible to test the second specificity hypothesis on HBN due to insufficient data. Our results suggest that CBCL can be used to predict parent-report-based diagnosis of depression, but care should be taken when trying to predict parent- and child-report-based clinician diagnosis. Furthermore, our results highlight the problem of parent-child disagreement on depression evaluation.

Disclosures: **M. Zelenina:** None. **A. Stringaris:** None. **D.S. Pine:** None. **D.M. Nielson:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.07

Topic: G.05. Mood Disorders

Support: NRF-2020R1A4A1019623

Title: Increased in vivo translocator protein binding and its relationship with clinical characteristics in patients with drug-naive unipolar major depression

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Abstract: Some studies have shown that inflammation is significantly associated with major depressive disorder (MDD): elevated peripheral inflammatory biomarkers are shown in patients with MDD and patients treated with cytokines are at greater risk in the development of MDD. In the present study, between-group differences of translocator protein (TSPO) availability and its relationship with clinical variables in MDD patients were investigated. Twenty drug-naïve unipolar MDD patients (9 males and 11 females, median age: 25.15 years) and 24 healthy controls (15 males and 9 females, median age: 23.75 years) were scanned using positron emission tomography (PET) with [^{11}C]PK11195. For quantification of TSPO availability, the binding potential (BP_{ND}) of [^{11}C]PK11195 was calculated by a receptor parametric model (RPM2) with gray matter clusters as a reference region using the modified supervised cluster analysis (SVCA4). Clinical assessments were conducted using the Hamilton Rating Scale for Depression with 17 items (HAMD-17), Beck Depression Inventory (BDI), and Rosenberg Self-Esteem Scale (RSES). A voxel-based between-group comparison analysis was performed using two-sample *t*-test at a statistical threshold of uncorrected $p<0.001$ with cluster size of false discovery rate (FDR) $q<0.01$. In the patient group, a voxel-based correlation analysis was conducted between [^{11}C]PK11195 BP_{ND} and clinical variables at a significance threshold of uncorrected $p<0.005$ with cluster size of uncorrected $p<0.05$. The between-group comparison analysis showed that MDD patients had significantly higher [^{11}C]PK11195 BP_{ND} in the bilateral middle frontal gyrus, bilateral postcentral gyrus, left insula, bilateral anterior cingulate cortex, and the posterior part of the pons (raphe nucleus) compared to healthy controls. The correlation analysis showed that the posterior part of the pons (raphe nucleus) and right pulvinar nucleus were positively correlated with the BDI and HAMD-17 scores, respectively, and right precuneus was negatively correlated with the RSES score. Our study demonstrated that drug-naïve unipolar MDD patients had significantly higher [^{11}C]PK11195 BP_{ND} values in various cortical and limbic regions and in the posterior part of the pons compared with healthy controls. Especially, the posterior part of the pons was positively correlated with the BDI score, suggesting inflammation hypothesis of MDD in the serotonergic system. In conclusion, the neuroinflammatory reaction in the brain regions can alter emotional modulation and affect the disease progression.

Disclosures: H. Park: None. **G. Shin:** None. **J. Kim:** None. **J. Kim:** None. **Y. Son:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.08

Topic: G.05. Mood Disorders

Support: ONR Grant 00014-19-1-2149
The Pritzker Neuropsychiatric Disorders Research Consortium Fund, LLC
Hope for Depression Research Foundation (HDRF)

Title: How different methodologies in the construction of various Polygenic Risk Scores affects the ability to explain mood symptoms

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Abstract: Methods for generating Polygenic Risk Scores (PRS) fall into two broad categories based on methods for Linkage Disequilibrium (LD), namely clumping and beta shrinkage. Within these two broad categories, there are a number of smaller decision points which can also lead to very different results. In this study we aim to highlight how these decision points affect the final PRS values and what impact this has on understanding the role of genetics in partly explaining mood. We detail the construction of the PRS, from the quality control on our own data to the use of imputation (or not) and the choice of method to calculate the PRS. We have longitudinal data on a sample of University of Michigan freshmen, from 2015 to 2021. The freshmen were genotyped and characterized at baseline using clinical variables. This included anxiety (GAD-7) and depression (PHQ-9) symptoms, as well as measures of neuroticism, childhood trauma, resilience, social support / isolation, and positive and negative suicide ideation. Their daily physical activity was captured using Fitbits, and their mood levels were sampled at multiple timepoints throughout the freshmen year. The breadth and longitudinal nature of this data means that we can use it to test PRSs for impulsivity, neuroticism, anxiety, depression and circadian rhythm. We can also test how the methods for calculating the PRS changes its explanatory power. As a test case, the PRS for major depressive disorder (MDD-PRS) was calculated using clumping and thresholding. The PRS with no p-value thresholding and using imputed genetic data gave us the most explanatory power. Using our own data, we will show how much the explanatory power of a PRS changes given how it is generated and how this applies to different PRSs.

Disclosures: **H. Khalil:** Other; This work was supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. **C. Turner:** Other; This work was supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C.. **V. Murphy-Weinberg:** None. **L. Gates:** None. **R. Grysko:** None. **K. Arakawa:** None. **T. Dokas:** None. **Y. Fang:** None. **J. Lopez:** None. **S. Sen:** None. **S.J. Watson:** None. **H. Akil:** Other; This work was supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C..

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.09

Topic: G.05. Mood Disorders

Support: Greehey Family Foundation Endowment for Alzheimer's Research
Zachry Family Foundation Endowment for Alzheimer's Disease

Title: Dimensional characterization of white matter connectivity and behavior expression in hospitalized patients by affective and anxiety symptoms, their contribution to a precision medicine diagnosis in psychiatry.

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Abstract: Current nosological systems have shown not to be precise enough to determine an accurate diagnosis. Our work proposes using a precision medicine model with axes to deconstruct, analyze, and regroup.
Our Hypotheses is that the use of behavior dimensional measures (self-report, subjective symptoms) and structural connectivity, associated with affective and anxious symptoms, allows and approximation to precision diagnoses. We analyzed a sample of 455 hospitalized patients at Menninger clinic-Houston, who were assessed with psychological scales (PHQ-SADS, GAD 7, DERS, AAQII, SSRS, BHS, BSS, SCS, WHODAS, WHOF, WHOA, RQ, BFI). Structural and diffusion-weighted brain images were processed using Tracula. Using Matrix factorization techniques: NMF methodology to examine the data we searched for biclusters reflecting different tractography patterns shared by distinct subsets of patients. Cross-correlated the uncovered biclusters with collected descriptions of clinical features of patients including affective symptoms severity, and identified clusters of individuals with high level of sharing of multiple clinical traits and structural connectivity. We uncovered 23 clusters of subjects that differ significantly from the rest of the sample on the basis of their clinical features and changes in white matter connectivity. These clusters allow us to see specific relationships between alterations in clinical characteristics and alterations in white matter tracts. As examples, below are some of the relationships and their most statistically significant characteristics.
Relationship R9 has shown a specific combination of alterations between the clinical variable of alcohol consumption and the Fractional anisotropy of the right inferior longitudinal fasciculus. R34 has shown a specific combination of alterations between the clinical variable of suicidal ideation and the right radial diffusivity of the corticospinal tract. R52 has shown a specific combination of alterations between the clinical variable of anxiety and the mean diffusivity of the right corticospinal tract.

Group	Feature	Group.media	Others media	Corrected p value
R9	WHOAALCOHOLR	3	1.59556	9.00E-07
R9	rh.ilf_FA_Avg	0.52227	0.46832	1.00E-06
R34	SSRSIDEATIONMTH	21.25	9.23956	0.00059
R34	rh.cst_RD_Avg	0.00059	0.00053	0.0005539
R52	PHQANXIETY	19.8	11.53304	0.000722
R52	rh.cst_MD_Avg	0.00081	0.00075	0.0001136

Disclosures: **J.M. Toranzo:** None. **M.J. Uscamayta Ayvar:** None. **J. Arnedo:** None. **G. Poblete:** None. **M.S. Aloi:** None. **I. Zwir:** None. **R. Salas:** None. **G. de Erausquin:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.10

Topic: G.05. Mood Disorders

Support: CONACYT CVU: 863433

Title: Coping strategies in mexican population during the COVID-19 pandemic

Authors: *M. A. PEREZ HERNANDEZ[1], R. L. CASTILLO-LÓPEZ[3], J. FERNÁNDEZ-RUÍZ[4], R. TRIANA-DEL RÍO[5], I. T. CIBRIÁN-LLANDERAL[2];
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Abstract: The prevalence of mental disorders that the COVID-19 pandemic can trigger on the general population is unknown. The high spread of the virus and deaths worldwide are causing stress, anxiety, and depression to increase putting the mental health of the general population at risk. Although this scenario is difficult to predict accurately, the type of coping strategies (CS) has been reported to influence the psychological impact and mental health status of individuals in adverse situations. We aim to explore the type of coping strategies in Mexican population during the COVID-19 pandemic. From August 2020 to May 2021, a total of 809 participants from the general population over 18 years of age were collected. Beck anxiety and depression inventories, perceived stress, coping strategies and an online sociodemographic questionnaire were applied. Correlational structures were explored by means of Pearson's Chi-Square, establishing a significance level of $P \leq 0.05$. Of a total of 809 participants, 74% were women and 25% men; 0.1% preferred not to respond. We found that the prevalence of anxiety (moderate/severe) was 35.5% in women and 29% in men. 41.3% of the women suffered from moderate/severe depression and 28.5% of the men. 88.8% of the women and 80% of the men considered

themselves to be stressed. In terms of CS, the highest percentage corresponds to active strategies, 62% in women and 60% in men, while 35% of women and 37% of men employed passive strategies. Differences were found between the active and passive coping strategies group in relation to perceived stress, anxiety (moderate/severe) and depression (moderate/severe) (X^2= 48.8, *df*= 2, p= <0.01). The COVID-19 health contingency makes people more susceptible to experience mental disorders and the type of coping strategies that they used to face an adverse event will be a determining factor in the state of their mental health. We propose to emphasize the need to know the psychological characteristics of the general population to create optimal intervention plans.

Disclosures: M.A. Perez Hernandez: None. **R.L. Castillo-López:** None. **J. Fernández-Ruíz:** None. **R. Triana-Del Río:** None. **I.T. Cibrián-Llanderal:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.11

Topic: G.05. Mood Disorders

Support: R01MH129742
R01MH116147
Baszucki Brain Research Fund and the Milken Institute's Center for Strategic Philanthropy grant to advance the understanding of bipolar disorder, therapeutic discovery, and translational efforts

Title: Hippocampal volume and medication mode of action in 2,231 individuals worldwide from the ENIGMA Bipolar Disorder Working Group

Authors: E. FONTANA[1,2], S. KING[1], L. NABULSI[3], G. TRONCHIN[1], S. I. THOMOPOULOS[3], J. RADUA[4], P. M. THOMPSON[3], O. A. ANDREASSEN[5,6,7], *C. R. K. CHING[3], C. MCDONALD[1], .-. FOR THE ENIGMA BIPOLAR DISORDER WORKING GROUP[8];
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Abstract: Introduction: Individuals with bipolar disorder (BD) are often prescribed multiple drugs but their influence on brain structure is poorly understood. Most prior studies used indication-based medication categories (e.g. antipsychotic) instead of mode of action (e.g. dopamine antagonism). The Neuroscience based Nomenclature (NbN) for psychotropic drugs was developed based on contemporary pharmacological information including mode of action. The ENIGMA Bipolar Disorder Working Group's Medication and Clinical Phenotypes project is the largest ongoing study using individual level data to map polypharmacy effects in BD. Here we examine interactions between polypharmacy and brain structure through an NbN approach. Methods: Hippocampal volumes (HV) (derived from the ENIGMA-standardized pipeline) were computed from 2,231 BD individuals from 27 sites. Participants were taking lithium, antiepileptics, first and second generation antipsychotics, and antidepressants. Drug categories were recoded based on mechanism of action (Table 1). To study the moderating role of each NbN category on the association between lithium and HV, moderation analyses were carried out using PROCESS software in SPSS. Results were adjusted for multiple comparisons using the standard false discovery rate (FDR) procedure.
Results: In those with BD, after controlling for age, sex, head size, and scan site, the glutamate sodium channel blockers significantly moderated the association between lithium and HV (β = 221.01), resulting in smaller HV in those on both the sodium channel blockers and lithium compared to those just on lithium. Dopamine-serotonin-norepinephrine receptor antagonists acted in a similar way, also moderating the association between lithium and HV (β = 236.01).
Discussion: Modeling medication mode of action may provide further insights into how medication influence brain structure. Ongoing data analysis of a wider range of medication and clinical phenotype information may help to clarify associations between brain structure and treatment response.

Neuroscience Based Nomenclature (NBN) Variables

Traditional Categories	NbN Categories based on their mode of action and/or pharmacological domain
Antipsychotics	• Dopamine receptor antagonist • Dopamine-serotonin antagonism • Dopamine-serotonin-norepinephrine receptor antagonist • Dopamine partial agonist
Antidepressants	• Serotonin reuptake inhibitor • Serotonin- norepinephrine reuptake inhibitor
Antiepileptics	• Glutamate voltage-gated sodium channel blocker • Glutamate voltage-gated calcium channel blocker • Glutamate voltage-gated sodium and calcium channel blocker

Table 1. Most prior neuroimaging studies linking psychiatric medications to brain structure/function have used indication-based drug labels (left column). In this study from the ENIGMA Bipolar Working Group's Medications and Clinical Phenotypes project, we re-coded commonly prescribed medications based on the current understanding of mode of action and pharmacological domain to more finely map the link between drugs, their interactions, and brain structure. Medications were re-coded into the following variables: lithium (n=796), valproate (n=231), glutamate sodium and calcium channel blockers (n=51), glutamate calcium channel blockers (n=26), glutamate sodium channel blockers (n=162), dopamine receptor antagonists (n=77), dopamine serotonin receptor antagonists (157), dopamine serotonin norepinephrine receptor antagonists (308), dopamine serotonin partial agonists (n=37), serotonin reuptake inhibitors (n=216), serotonin-norepinephrine reuptake inhibitors (n=152).

Disclosures: **E. Fontana:** None. **S. King:** None. **L. Nabulsi:** None. **G. Tronchin:** None. **S.I. Thomopoulos:** Other; The ENIGMA Working Group acknowledges the NIH Big Data to Knowledge (BD2K) award for foundational support and consortium development (U54 EB020403 to Paul M. Thompson)., For a complete list of ENIGMA-related grant support please see here: http://enigma.ini.usc.edu/about-2/funding/.. **J. Radua:** None. **P.M. Thompson:** 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.; Biogen Inc. for work unrelated to this study. **O.A. Andreassen:** None. **C.R.K. Ching:** 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.; Biogen Inc. for work unrelated to this study. **C. McDonald:** None. **-. for the ENIGMA Bipolar Disorder Working Group:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.12

Topic: G.05. Mood Disorders

Support: NIH Grant R01MH111578
The Carver Foundation
NIH Grant S10OD025025
NIH Grant S10RR028821
NIH Grant UL1TR002537
NIH Grant 5T32MH019113-28
Merit Award from Department of Veterans Affairs

Title: Decreased cerebellar gray matter in bipolar type I

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Abstract: Bipolar Disorder (BD) is a severe and often debilitating psychiatric disorder characterized by extreme mood states that can disrupt personal, work-related, and social function. Despite its seriousness, the neural underpinnings of BD remain largely unknown. BD is thought to involve dysregulation of the brain's emotional control network. A potential modulator of the emotional control network is the cerebellum. Although the cerebellum is classically associated with fine motor control, the field increasingly recognizes the non-motor regulatory functions of the cerebellum, including effects on emotion. In studies of brain volumes and BD,

conflicting findings have been reported as to whether cerebellar volumes are affected. To examine this question, we imaged cerebellar volumes in participants with bipolar disorder type I (BD-I, N = 131) and control participants (N = 80). We found that both left and right cerebellar gray matter was reduced in BD-I, but no differences were detected in any white matter or vermal volumes. Interestingly, when we tested polygenic risk score instead of BD diagnosis, we did not see a significant relationship with any cerebellar volumes, suggesting that genetic loading may not explain the differences in cerebellar gray matter volume. To better understand these volume differences in the context of the whole brain, we performed exploratory brain-wide machine learning to classify cases versus controls. We found that the most important variable for classification across multiple models was the volume of the white matter of the right posterior cingulate. Post-hoc examination of the cingulum white matter found that most subregions of this bundle tended to be smaller in BD. Our findings suggest that the cerebellum as well as the emotional control network are abnormal in BD. Future work will explore how the cerebellum may impact function of nodes of the emotional control network, especially the anterior cingulate, in BD.

Disclosures: G. Harmata: None. **J. Barsotti:** None. **L. Casten:** None. **J. Fiedorowicz:** None. **A. Williams:** None. **G. Christensen:** None. **J. Xu:** None. **J. Shaffer:** None. **J. Long:** None. **J.G. Richards:** None. **L. Sathyaputri:** None. **J. Michaelson:** None. **J. Wemmie:** None. **V. Magnotta:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.13

Topic: G.05. Mood Disorders

Title: Changes in functional connectivity and self-compassion after mindfulness based cognitive therapy in bipolar disorder

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Abstract: Introduction Decreased self-compassion is one feature of bipolar depression that contributes to diminished treatment outcomes. Previous meta-analyses implicate the insula, dorsolateral prefrontal cortex (DLPFC), and dorsal anterior cingulate cortex (dACC) as brain regions involved in self-compassion as well as regions that are activated through mindfulness-based cognitive therapy (MBCT).
Method We randomized 15 patients with bipolar disorder to receive 12 weekly 120 minute group sessions of MBCT or supportive psychotherapy (SP). Participants completed the 26-item Self-Compassion Scale (SCS) and underwent an MRI scan before and after treatment.

Designating the insula as the seed region, resting-state functional connectivity (rsFC) analyses were performed between this seed region and ROIs (DLPFC: BA9 & BA46 and dACC: BA33) using SPM8. Pearson's r correlations examined changes in rsFC and changes in the SCS subscales.
Results Patients who received MBCT exhibited decreased self-judgement ($F(1,12)=7.739$, $p=.017$). This decrease had a trending relationship with increased connectivity between the insula and the dACC (Pearson's $r(10)=.569$, $p=.086$). Although the decrease in over-identification was not significant, this decrease also had a trending relationship with increased connectivity between the insula and the dACC (Pearson's $r(10)=.602$, $p=.065$). For patients who received SP, there was no change in self-judgement or over-identification, and rsFC was not related to these subscales.
Discussion Although the sample size was small, the effect sizes were large. This suggests MBCT can enhance the functional connectivity between the insula and the dorsal anterior cingulate cortex, which may provide improvements in specific self-compassion components for individuals with bipolar disorder. Future studies should explore these associations in larger samples.

Disclosures: A. Hayden: None. **D.D. Dougherty:** None. **A.A. Nierenberg:** None. **T. Deckersbach:** None. **T. Chou:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.14

Topic: G.05. Mood Disorders

Support: NSERC Grant (Canadian Graduate Scholarship-Master's)
CIHR Grant MOP-FDN-148418
Career Award from the Fonds de la Recherche du Québec-Santé

Title: Feasibility of structured and unstructured eye-tracking tasks to develop potential biomarkers for adolescent subthreshold depression

Authors: *B. K. NOYES[1], L. BOOIJ[2], H. C. RIEK[1], D. C. BRIEN[1], B. C. COE[1], B. J. WHITE[1], S. KHALID-KHAN[1], D. P. MUNOZ[1];
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Abstract: Subthreshold depression (subD)—characterized by depressive symptoms not meeting clinical criteria for major depressive disorder (MDD)—is a growing cause of significant and distressing functional impairment, affecting nearly one-third of adolescents (Noyes et al., 2022). Despite this growing incidence, the neural anatomy and networks implicated in subD remain largely understudied. Understanding the neurological underpinnings of subD is critical to being

able to develop early treatment interventions before these symptoms escalate to MDD. This may be achieved via quantitative analysis of eye tracking; a well-established technique to identify impairments in cognitive control, arousal, and attention. Our goal is to use video-based eye tracking to compare saccades, pupil size, and blinks in individuals with subD to those with MDD and healthy controls to investigate the neural underpinnings of subD. Prior to embarking on the full study, this pilot study aimed to evaluate the feasibility of using two eye-tracking tasks to measure eye-movements among healthy controls and patients with MDD. Healthy controls (age range 12-25 yrs; mean=19.5 yrs) and outpatients with MDD (mean=17 yrs) were enrolled. Participants completed two tasks: 1) the Interleaved Pro-Anti Saccade Task (IPAST) to investigate impairments in cognitive control; and 2) the unstructured Free-Viewing (FV) video task to investigate differences in attention and arousal. Each IPAST trial included a central fixation spot whose colour (green or red) indicated whether participants were to make a pro-saccade (look toward peripheral stimulus) or anti-saccade (look away from the stimulus), respectively. In the FV task, participants watched 10 min of neutral video clips (e.g., cityscapes, nature) and 10 min of clinical-oriented video clips (e.g., emotional faces, food/eating, alcohol/drinking). Finally, participants completed self-report questionnaires for psychiatric symptoms. Preliminary data suggests participants with MDD had slower saccadic reaction time and more errors than control participants during IPAST, and larger pupil dilation during emotional faces clips than controls during FV. Future analyses will seek to determine the effect of sex, gender, and age on these outcomes. Enrolment is now including controls, individuals with MDD, and individuals with subD. This study showed that eye tracking may be an easy, inexpensive, and useful tool for probing network functioning in youth with MDD and provides a rationale for using eye-tracking to study the neurological impairments among youth with subD.

Disclosures: B.K. Noyes: None. **L. Booij:** None. **H.C. Riek:** None. **D.C. Brien:** None. **B.C. Coe:** None. **B.J. White:** None. **S. Khalid-Khan:** None. **D.P. Munoz:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.15

Title: WITHDRAWN

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.16

Topic: G.05. Mood Disorders

Support: Medical Research Council, UK, grant reference MR/K022113/1
European Commission Horizon 2020 Health Programme, CoSTREAM, grant agreement 667375
National Health and Medical Research Council (NHMRC) Investigator Grant 2021/GNT2007718

Title: Structure-function decoupling in post-stroke depression

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Abstract: Depression is a common sequel of stroke, affecting approximately 30% of survivors. Decades of research have been unable to pinpoint brain areas most susceptible to the effects of ischemic events in the development of depression. The brain-based mechanisms leading to this neuropsychiatric complication therefore remain an enigma. In a recent study (doi.org/10.1101/2021.11.05.21265997) we observed an absence of mutual inhibition between functional resting-brain circuits involved in reward and self-referential processing in stroke patients with depression. Aberrant neural dynamics were accompanied by structural changes and were independent of lesion location. Here, we extend these findings by applying novel measures of network communication to the structural connectivity of the human brain. We explore the capacity of these measures to predict functional deficits in stroke patients with depression. Forty-four recent stroke patients (age: M = 69, SD = 8.6; 34 male) and 16 healthy volunteers (age: M = 71.5, SD = 10.6; 5 male) underwent 3T T1, diffusion and resting-state fMRI and completed the Geriatric Depression Scale. Matrices containing parcellations constituting a nucleus accumbens-seeded reward network and the default mode network were populated with functional connectivity (FC) and partial volume corrected fractional anisotropy (FA_T). The graph metrics *search information (log)* and *path transitivity* were calculated from the FA_T matrices to capture internodal communication from diffusion models as opposed to traditional models of neural information flow, based on shortest paths. Multiple linear regression analyses were performed with graph measure matrices as predictors and the corresponding FC matrices as outcome variables. In neurotypical adults, *search information* (t(15)= -2.61, r = -0.08, p = 0.009) and *path transitivity* (t(15)= 8.79, r = 0.27, p < 0.001) significantly predicted FC in the default mode network. *Path transitivity* (t(15)= 2.02, r = 0.03, p = 0.044) was also a significant predictor of FC in the reward network. In stroke patients free of depression, *path transitivity* (t(31)= 6.55, r = 0.14, p < 0.001) significantly predicted FC in the default mode network. In conclusion, structural network communication predicts resting-brain functional connectivity in systems linked to reward and self-referential processing in neurotypical individuals and stroke patients free of depression, but not stroke patients with depression. These results indicate that graph metrics derived from diffusion models may be a useful avenue to better understand mechanistic underpinnings of brain changes linked to depression after stroke.

Disclosures: L. Oestreich: None. **P. Wright:** None. **M.J. O'Sullivan:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.17

Topic: G.05. Mood Disorders

Support: Maurice and Phyllis Paykel Trust
Neurological Foundation
New Zealand Pharmacy Education and Research Foundation
Oakley Mental Health Research Foundation

Title: Detection of neuroinflammation using quantitative magnetization transfer imaging: a randomized crossover study

Authors: *J. PLANK[1], C. MORGAN[2], F. SUNDRAM[2], N. HOEH[2], S. D. MUTHUKUMARASWAMY[2], J. LIN[2];
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Abstract: Psychiatric disorders impact a significant proportion of individuals worldwide. These disorders are associated with reduced quality of life and greater economic burden, yet their pathophysiological mechanisms are not completely understood. Prior studies support the pathogenic role of neuroinflammation; however, there are no established methods that can reliably and non-invasively measure these inflammatory processes in living patients.
We examined the potential of quantitative magnetization transfer (qMT) imaging to detect low-level neuroinflammation in the brain. Typhoid vaccine induced inflammation in 20 healthy volunteers in a double-blind, placebo-controlled, crossover study. Magnetic resonance imaging (MRI) scans optimized for qMT were conducted before and 3h after vaccine/placebo administration. Mood was assessed at hourly intervals using the Profile of Mood States. The effects of treatment, mood, age, and sex on the qMT parametric maps were investigated using voxel-wise and region-of-interest analyses.
Significant effects of mood and sex were observed on the whole-brain and regional qMT parametric maps, however treatment effects were absent. Significant effects of age were observed only on the regional qMT maps. The present study did not detect neuroinflammation using qMT. Future studies may investigate use of different qMT sequences for detection of neuroinflammation and should consider including age and sex as covariates in analyses.

Disclosures: J. Plank: None. **C. Morgan:** None. **F. Sundram:** None. **N. Hoeh:** None. **S.D. Muthukumaraswamy:** None. **J. Lin:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.18

Topic: G.05. Mood Disorders

Support: NIH NCCIH UH2AT009145
NIH NCCIH UH3AT009145
NIH NCCIH T32AT000051

Title: Depression severity moderates the association between changes in body trusting and brain mechanisms of interoception following mindfulness training

Authors: *M. DATKO[1,2,3], J. LUTZ[1], R. GAWANDE[1,3], A. COMEAU[1], M. TO[1], T. DESEL[2], J. GAN[1], G. DESBORDES[4], V. NAPADOW[5,2,3], Z. SCHUMAN-OLIVIER[1,3];
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Abstract: Interoceptive brain mechanisms are often dysregulated in depression and anxiety. Mindfulness-based interventions may target these mechanisms, cultivating interoceptive awareness through practices such as breath meditation and body scan. We investigated the effects of an 8-week intervention, Mindfulness Training for Primary Care (MTPC), on brain mechanisms of interoception in patients with depression and/or anxiety. We hypothesized that fMRI BOLD response during an interoceptive attention task would increase following MTPC. Previous work links depression with lower Body Trust, a subscale of the Multidimensional Assessment of Interoceptive Awareness (MAIA), and we further hypothesized that changes in BOLD response would be associated with increased Body Trust. Adults (n=28) with depression and/or anxiety completed baseline and post-MTPC fMRI visits, including a 10-min task alternating between focusing on heartbeat (interoception, INT) or visual stimuli (exteroception, EXT). We modeled the INT-EXT contrast, and fit interaction models between insula response, symptom severity, and MAIA Body Trust. Following MTPC, we found increased MAIA total scores, reduced anxiety and depression symptom severity, and increased fMRI response in left anterior insula (**Fig 1A**). We found a two-way interaction effect in right anterior insula, with increased insula response associated with increased Body Trust among participants with anxiety+moderate/severe depression (n=13), but not among those with anxiety+no/mild depression (n=15)(**Fig 1B**). Patients with primarily anxiety symptoms are often hypersensitive to interoceptive sensations, leading to distress and panic, while depressed patients often tend to avoid focusing on interoceptive signals. We show that increased trust of one's bodily sensations may be a mechanism for positive responses to MBIs specifically among patients with anxiety+comorbid moderate/severe depression. Future work could optimize MBIs for patients with anxiety by facilitating greater engagement with and trust in interoceptive sensations.

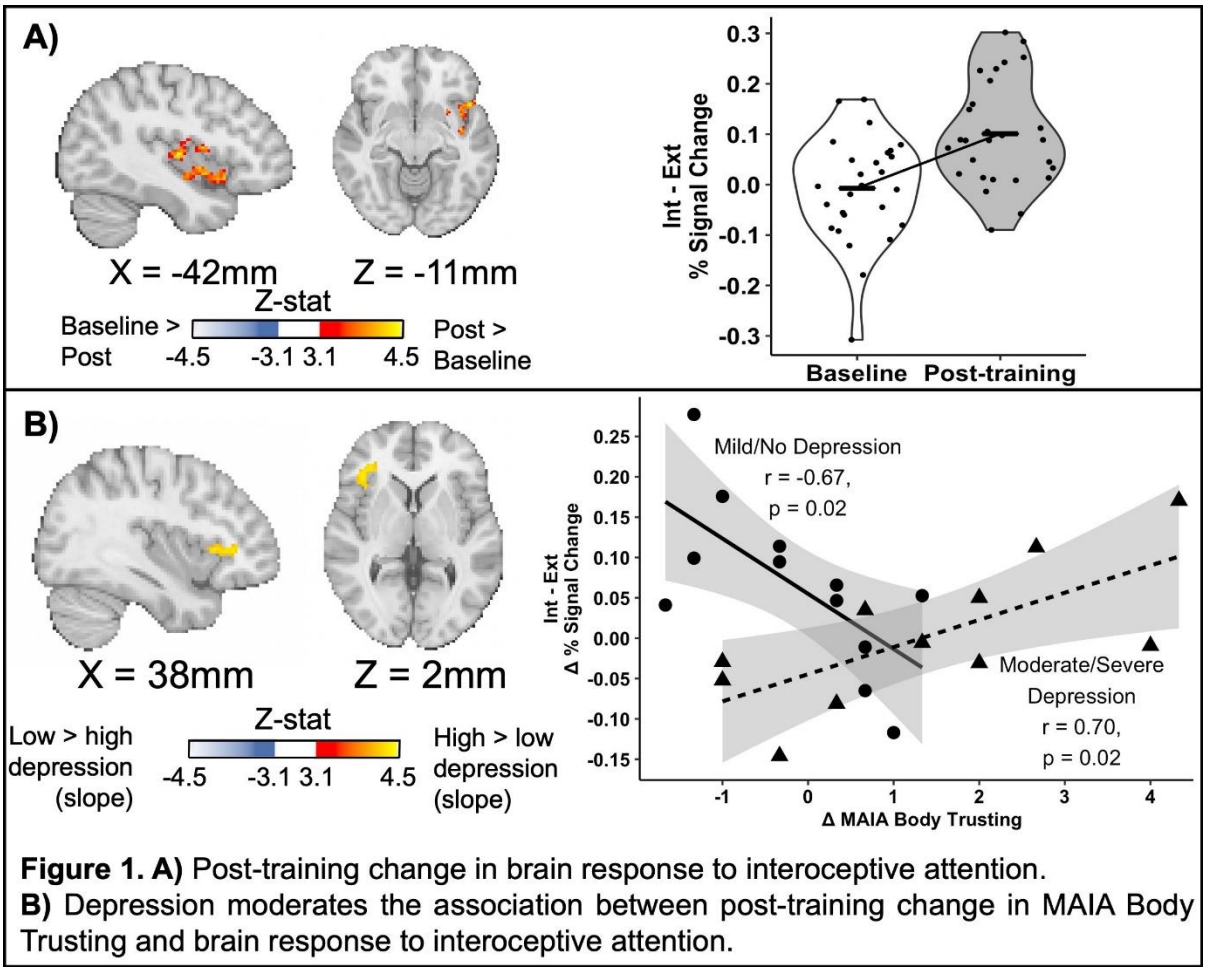

Figure 1. A) Post-training change in brain response to interoceptive attention. **B)** Depression moderates the association between post-training change in MAIA Body Trusting and brain response to interoceptive attention.

Disclosures: M. Datko: None. **J. Lutz:** None. **R. Gawande:** None. **A. Comeau:** None. **M. To:** None. **T. Desel:** None. **J. Gan:** None. **G. Desbordes:** None. **V. Napadow:** None. **Z. Schuman-Olivier:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.19

Topic: G.05. Mood Disorders

Title: Pre-treatment frontal EEG measured transient beta events are associated with depressive symptom improvement after repetitive transcranial magnetic stimulation

Authors: *Z. T. GEMELLI[1], B. C. KAVANAUGH[2], A. M. FUKUDA[3], E. TIRRELL[4], R. THORPE[5], S. R. JONES[5], L. L. CARPENTER[4];
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Abstract: Neocortical activity within the beta band (15-29 Hz) is one of the most well-defined indices of brain activity and associated to a range of behavioral and clinical variables. Although beta activity is traditionally measured via averaged power metrics, beta activity often emerges as transient, high-power burst-like events in non-averaged data. Novel approaches now characterize beta events by their power, duration, number, and frequency span (f-span). Beta event features have recently been observed to be associated with clinical improvements with repetitive transcranial magnetic stimulation (rTMS). The objective of this study was to examine whether features of frontal beta events, prior to a clinical course of clinical rTMS (predominantly 10 Hz to the left dorsolateral prefrontal cortex), is associated with treatment-related depressive symptom improvement. Thirty-four adults with depression completed: a) five minutes collection of eyes-closed resting electroencephalography (EEG) and, b) the self-report form of the Inventory of Depressive Symptomatology (IDS-SR) before and after a clinical course of rTMS for their primary depression. The rate, power, duration, and f-span of transient events in the beta band were calculated in frontal electrodes. The pre-post percent change in symptom was calculated for the IDS-SR. The association between IDS-SR pre-post change and pre-treatment frontal beta event features was calculated with and without control for age, sex, prior hospitalizations, prior electroconvulsive therapy, prior rTMS treatments, and total time between measurements. Correction for multiple comparisons was applied, as events at each individual electrode were calculated. Preliminary analysis shows that none of the pre-treatment beta events features were associated with pre-treatment IDS-SR. However, IDS-SR percent change was associated with the rate and power of pre-treatment beta events in multiple frontal electrodes. This association between pre-treatment beta events rates and IDS-SR percent change persisted after controlling for clinical variables. The direction of this association was positive, in that a higher rate and power of beta events was associated with a poorer rTMS treatment response. In this preliminary and retrospective study, a lower rate and power of frontal beta events prior to treatment predicted a stronger improvement in depressive symptoms after a course of rTMS treatment. This provides further evidence on the critical importance of transient beta events in depressive symptoms and suggests these events may reflect a pre-treatment predictor of treatment response likelihood.

Disclosures: Z.T. Gemelli: None. **B.C. Kavanaugh:** None. **A.M. Fukuda:** None. **E. Tirrell:** None. **R. Thorpe:** None. **S.R. Jones:** None. **L.L. Carpenter:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.20

Topic: G.05. Mood Disorders

Support: NIH Grant T32 MH064913
NSF Graduate Research Fellowship

Title: Relating state-trait anxiety to vigilance fluctuations derived from fMRI

Authors: *C. MARTIN[1], K. K. ROGGE-OBANDO[1], C. CHANG[1], J. ZHU[1], J. HOGEVEEN[2], S. GOODALE[1], R. YANG[1];
[1]Vanderbilt Univ., Nashville, TN; [2]Dept. of Psychology, The Univ. of New Mexico, Albuquerque, NM

Abstract: Untreated anxiety leads to significant impairments in functioning and quality of life. Prominent aspects of anxiety include sleep-wake disturbances and abnormal vigilance regulation. Typically, vigilance is measured through EEG brain waves, such as the ratio between alpha (8-12 Hz) and theta (4-8 Hz) spectral power[1]. More recently, however, methods have been introduced to derive a measure of vigilance from fMRI data alone. This approach enables studying vigilance states during fMRI scans, as concurrent EEG is typically unavailable. To explore whether this fMRI-based vigilance index could be used to model vigilance differences across a spectrum of anxiety severity, we compared the fMRI vigilance index with scores from the State-Trait Anxiety Inventory (STAI). Using methods described in Goodale et al., 2021, a continuous vigilance time course was extracted from each participant in a subset of resting-state fMRI data (n=175 men, 175 women) collected by the Nathan Kline Institute (NKI-Rockland Sample). We took the mean and standard deviation of this fMRI-based vigilance time course and correlated these metrics with the participants' STAI scores. As expected, our results showed a negative correlation between vigilance variation and state (present moment) anxiety ($r(348) = -.19$, $p = .0004$) as well as trait (general) anxiety ($r(348) = -.14$, $p = .009$). As a complementary approach for investigating vigilance by anxiety severity, we split the subjects into three groups based on state anxiety scores: low anxiety (threshold ≤ 38), moderate anxiety (threshold between 38-41), and high anxiety (threshold ≥ 53). Participants with higher anxiety scores showed a main effect of significantly lower variation in their fMRI-based vigilance measures [$F(2) = 4.99$, $p = .0265$]. Overall, our result suggests that the standard deviation of the fMRI-based vigilance index may be useful in identifying a biomarker of anxiety severity. This research aligns with the vigilance regulation model of affective disorders, follows the aims of the NIMH Research Domain Criteria, and contributes to the pursuit of precision psychiatry[3]. Additional research is needed to relate fMRI-derived vigilance markers with psychiatric symptomology and identify if these models match EEG vigilance findings.
References: [1] Liu, T.; et al, *Frontiers in Neuroscience,* 14 (2020)[2] Goodale, S.; et al. *ELife,* (2021)[3] Sander, S; et al, *Neuropsychobiology,* 72 (2015)

Disclosures: C. Martin: None. **K.K. Rogge-Obando:** None. **C. Chang:** None. **J. Zhu:** None. **J. Hogeveen:** None. **S. Goodale:** None. **R. Yang:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.21

Topic: G.05. Mood Disorders

Support: NIMH Grant K23-MH113793

Title: Hyperreactive Theta Activity to Loss as a Prospective Predictor of Depression in Women

Authors: *M. SHEENA[1], T. NGUYEN[1], K. L. BURKHOUSE[2,3];
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Abstract: Depression is a leading cause of mental health burden, affecting almost 300 million people worldwide, and prevalence is increasing. Across studies, there is increasing evidence that alterations in positive and negative emotion processing are implicated in the development and course of depression. For instance, a blunted response to reward has been shown to differentiate individuals with and without major depressive disorder (MDD), as well as prospectively predict future onset of MDD and depressive symptoms. Other work suggests depression is also characterized by a blunted response to loss of reward. These responses have commonly been measured with electroencephalogram (EEG) studies utilizing event-related potentials (ERPs) known as the Reward Positivity (RewP), a measure of initial response to reward, and the Feedback Negativity (FN), a measure of initial response to loss. However, novel research is beginning to show that the RewP and FN can be further extricated into delta (to reward) and theta (to loss) frequency bands, which may explain more variance than time-domain analyses alone. However, few prospective studies to date have evaluated whether these time frequency bands can be used to predict future profiles of depression. The current study sought to address this gap in the literature utilizing data from an ongoing study of the intergenerational transmission of depression including 94 adult women with (N=42) and without (N=52) a history of MDD. Participants completed the Doors Reward Task while EEG was recorded, and the Beck Depression inventory at baseline and 12 month follow up. Preliminary hierarchical regression analysis results indicate greater theta response to loss at baseline predicted increased depressive symptoms (BDI) at 12 months, controlling for baseline depressive symptoms, (t-value = 1.77, b = .416). Results revealed no significant effects for delta activity to gain. These findings may offer deeper insight into the neural mechanisms underlying the reward network, specifically in relation to dysfunctional reactivity to loss as a predictor of future depression risk in women.

Disclosures: M. Sheena: None. **T. Nguyen:** None. **K.L. Burkhouse:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.22

Topic: G.05. Mood Disorders

Support: Deutsche Forschungsgemeinschaft DFG; Forschungsgruppe/Research Unit FOR2107: KI 588/14-1, KI 588/14-2, KI 588/15-1, KI 588/17-1
Deutsche Forschungsgemeinschaft DFG; Forschungsgruppe/Research Unit FOR2107: DA 1151/5-1, DA 1151/5-2, DA 1151/6-1
Deutsche Forschungsgemeinschaft DFG; Forschungsgruppe/Research Unit FOR2107: KR 3822/5-1, KR 3822/7-2
Deutsche Forschungsgemeinschaft DFG; Forschungsgruppe/Research Unit FOR2107: NE 2254/1-2
Deutsche Forschungsgemeinschaft DFG; Forschungsgruppe/Research Unit FOR2107: HA 7070/2-2
Deutsche Forschungsgemeinschaft DFG; Forschungsgruppe/Research Unit FOR2107: JA1890/7-1, JA1890/7-2

Title: Hold me tight - Clinical and neural correlates of interpersonal resilience

Authors: *K. BROSCH[1], L. JÄGER[1], P. USEMANN[1], U. EVERMANN[1], J.-K. PFARR[1], K. G. RINGWALD[1], F. STEIN[1], F. THOMAS-ODENTHAL[1], A. WROBLEWSKI[1], L. WALTEMATE[2], H. LEMKE[2], S. MEINERT[2], A. WINTER[2], F. BREUER[2], K. THIEL[2], D. GROTEGERD[2], T. HAHN[2], A. JANSEN[1], U. DANNLOWSKI[2], A. KRUG[3], I. NENADIć[1], T. KIRCHER[1], N. ALEXANDER[1];
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Abstract: Childhood maltreatment (CM) is a traumatic interpersonal experience and individuals who have experienced it may have difficulty forming secure attachments even in adulthood. Hence, those individuals with CM and a secure attachment style can be described as interpersonally resilient. This study aims to investigate the clinical and neural correlates of interpersonal resilience as defined by a secure attachment style in adulthood despite having experiences of CM.We investigated gray matter volume in a sample of N=1317 healthy individuals and partially or fully remitted depressive patients aged 18-65. CM was assessed using the childhood trauma questionnaire (CTQ), attachment style was assessed using the relationship scales questionnaire (RSQ). Depressive symptoms were assessed both using the self-report Beck Depression inventory (BDI), and the rater-based Hamilton Depression Scale (HAMD). Brain structural data (3T magnetic resonance imaging) were analyzed using voxel-based morphometry (CAT12 toolbox). We applied a 2x2 design (CM x attachment style), including the covariates site, body coil change, age, sex, and total intracranial volume. Analysis of the interaction effect of CM x attachment style was conducted.On a phenotypic level, interpersonally resilient individuals showed significantly lower self-reported (BDI) and rater-based (HAMD) depressive scores compared to insecurely attached individuals with CM, even when controlling for magnitude of CM (BDI: $F(3,1189)=27.61$, $p<.001$, Bonferroni post-hoc group comparison $p<.001$; HAMD: $F(3,1183)= 12.46$, $p<.001$, Bonferroni post-hoc group comparison $p < .001$). On the brain level, we detected a significant interaction effect of CM x attachment in a cluster comprising the left supramarginal gyrus (T=4.55, x/y/z =-64/-39/26, k =951, p=.037 FWE-corrected at cluster level). Interpersonally resilient individuals presented with significantly larger gray matter volumes in this area. Our results shed light on the neural correlates of secure attachment despite CM. The supramarginal gyrus is part of the somatosensory association cortex

and further considered to be part of the mirror neuron system. Increased volume in the supramarginal gyrus might constitute a neural compensatory mechanism to CM and aid securely attached, maltreated individuals in more adaptively processing semantic information and tactile sensory integration. We further showed that securely attached individuals with CM had lower depressive scores when compared to insecurely attached individuals with CM, highlight the importance of secure attachment as a resilience factor in buffering the negative effects of CM.

Disclosures: **K. Brosch:** None. **L. Jäger:** None. **P. Usemann:** None. **U. Evermann:** None. **J. Pfarr:** None. **K.G. Ringwald:** None. **F. Stein:** None. **F. Thomas-Odenthal:** None. **A. Wroblewski:** None. **L. Waltemate:** None. **H. Lemke:** None. **S. Meinert:** None. **A. Winter:** None. **F. Breuer:** None. **K. Thiel:** None. **D. Grotegerd:** None. **T. Hahn:** None. **A. Jansen:** None. **U. Dannlowski:** None. **A. Krug:** None. **I. Nenadić:** None. **T. Kircher:** Other; Unrestricted educational grants from Servier, Janssen, Recordati, Aristo, Otsuka, and neuraxpharm. **N. Alexander:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.23

Title: WITHDRAWN

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.24

Topic: G.05. Mood Disorders

Support: NIH P20GM103645
NIH P20GM130452
NIH R01EY12793
NIH S10OD025181
Carney Institute for Brain Science Innovation Fund

Title: Seasonal affective disorder and major depressive disorder reduce light-induced responses in human prefrontal cortex

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Behavior, Brown Univ., Providence, RI; [5]Butler Hosp., Providence, RI; [6]Ctr. for Neurorestoration and Neurotechnology, Veterans Affairs Providence Healthcare Syst., Providence, RI

Abstract: Light intensity affects mood and cognition in humans and experimental animals. Reduced light levels during the winter months can trigger depressive symptoms in people identified with seasonal affective disorder (SAD), and phototherapy can be an effective therapy for SAD and other forms of depression, such as major depressive disorder (MDD). Mice exposed to unnaturally rapid light-dark cycles exhibit depression-like symptoms mediated by a neural pathway through which intrinsically photosensitive retinal ganglion cells transmit information about environmental light intensity to the prefrontal cortex (Fernandez et al. Cell 175: 71-84, 2018). We recently found, using functional MRI (fMRI), that several regions in the prefrontal cortex showed sustained modulation in response to different levels of diffuse illumination in healthy humans (Sabbah et al., PNAS 2022, in press). Here, we used BOLD fMRI at 3T to measure sustained brain responses to diffuse full-field illumination at different light levels (dark, dim and bright) in people diagnosed with SAD (N=20) or MDD (N=23) and in age-matched healthy controls (HC, N=22). We continuously acquired BOLD fMR images while participants wore light-diffusing goggles while viewing the three aforementioned light intensities, each for 30-sec, occurring in pseudorandom order across five 5-min runs. We statistically compared the brain responses for the dim and bright intensities using the dark condition as a baseline. The pattern of activation was broadly consistent with our prior results (Sabbah et al., 2022), with increased light levels associated with *increased* BOLD responses in posterior brain regions, such as the primary visual cortex, and with *decreased* BOLD responses in prefrontal regions, such as the orbital frontal cortex. Light-intensity-dependent modulation in prefrontal regions was attenuated in both the MDD and the SAD groups compared to HCs. The reduction in light-intensity related suppression in prefrontal regions was more pronounced and more widespread in the SAD group than in the MDD group. The regions for which we found a reduced response relative to HCs differed between those with SAD and MDD, and included the right inferior frontal gyrus for MDD and left inferior frontal gyrus and insula for SAD. Importantly, we found no differences in light-induced activation between either the MDD or SAD groups and HCs for occipital cortical regions associated with form vision. In conclusion, we found that people with depression-related disorders show reduced responsively to changes in illumination level in prefrontal cortex, which may underlie their clinical disorder.

Disclosures: M.S. Worden: None. **F. McEleney:** None. **M.A. Gonsalves:** None. **D.M. Berson:** None. **L.L. Carpenter:** None. **J.N. Sanes:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.25

Topic: G.05. Mood Disorders

Support: Fundación Carlos Slim N20200278

Title: Relationship between sex hormones, brain structure, and clinimetrics in women with depression

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Abstract: Major depression disorder (MDD) is one of the leading causes of disability worldwide and its prevalence is higher in women, with an estimated 1.7 cases for each case in men. Along with sociocultural factors, biology has been considered to account both for the pathogenesis of MDD and its different prevalence between sexes. Previous investigations have reported differences in brain structure and sex hormone levels (reduced testosterone) in MDD. However, the relationship between sex hormones and the brain morphometric features found in MDD is, so far, less clear.
In this study, we analyzed structural brain measures in 65 women (32 with MDD and 35 healthy controls) between 18 and 45 years with regular menstrual cycles. For this purpose, high resolution (1x1x1 mm^3) T1-weighted images were acquired using a 3.0 Tesla scanner (repetition time = 7.0 ms, echo time = 3.5 ms). Standard preprocessing was performed using FreeSurfer version 7 to estimate cortical thickness and cortical volume across a parcellation comprising the whole brain cortex. Blood samples were obtained for quantification and comparison between groups of total and free testosterone levels. Severity of MDD was assessed with the Hamilton Depression Rating Scale (HDRS). For statistical analysis, we used tools included in FreeSurfer, using age as a covariate to regress its effect. The brain structural measures were compared between groups, and we searched for correlations with levels of testosterone and with HDRS scores, using nonparametric statistics and multiple comparison correction with a cluster forming threshold of $p < 0.05$ and a cluster-wise p corrected value (CWP) of $p < 0.05$.
The group with MDD showed lower levels of free testosterone ($t = -2.04$, $p = 0.047$); smaller volume in the superior frontal (CWP < 0.01), rostral middle frontal (CWP = 0.034), and middle temporal (CWP = 0.015) gyri of the left hemisphere and superior frontal gyrus of the right hemisphere (CWP = 0.02). Total testosterone levels showed a significant correlation with the volume of the caudal middle frontal area of the right hemisphere (CWP = 0.004). Free testosterone levels showed a significant correlation with HDRS scores ($R=-0.29$, $p = 0.017$). No significant correlations were found between structural measures and HDRS scores.
This study found differences in brain structure and testosterone levels between women with MDD and healthy controls and provided information suggestig that these variables are interrelated, yielding potentially useful information towards a better understanding of MDD in women.
This work received support from Fundación Carlos Slim (N20200278).

Disclosures: S. Totxo: None. **S. Alcauter:** None. **M. López-Titla:** None. **M. Flores-Ramos:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.26

Topic: G.05. Mood Disorders

Support: R01-MH113929
P20GM130452
IK2 CX001824
The Hanlon Foundation
The Carney Institute for Brain Science
Brain Behavior Research Foundation
Canada Research Chair in Magnetic Resonance Spectroscopy in Brain Injury

Title: Cortical glutamate, Glx, and N-acetylaspartate: potential biomarkers of repetitive transcranial magnetic stimulation treatment response in major depression

Authors: *M. A. GONSALVES[1], T. L. WHITE[2], M. M. DEMAYO[4], A. D. HARRIS[4], J. L. BARREDO[3], L. L. CARPENTER[3];
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Abstract: Introduction: Repetitive transcranial magnetic stimulation (rTMS) is an FDA-approved treatment for major depressive disorder (MDD). rTMS is an effective treatment for some individuals with MDD who have not improved with standard therapies. However, only 30-60% of patients experience remission following rTMS, which is time and cost intensive treatment. Predicting expected response to modes of rTMS will benefit both patients and providers in terms of prescribing and targeting treatment for maximum efficacy and directing resources. Preliminary effectiveness of neuroimaging-based predictors of rTMS responsiveness has been demonstrated with proton magnetic resonance spectroscopy (MRS), with a small number of studies showing that baseline levels of glutamate (Glu) and Glx (Glu + glutamine) serve as biomarkers of rTMS treatment response, though more research is warranted regarding other metabolites. Methods: Metabolite data (Glu, Glx, and *N*-acetylaspartate (NAA)) was collected prior to a standard course of 10Hz rTMS (i.e., 6-week course of once daily sessions, 3000 pulses/session, 120% resting motor threshold) to the left dorsolateral prefrontal cortex in individuals with MDD (*N*=16; mean age 39.31(*SD* = 15.04); 50% female). The point resolved spectroscopy MRS voxel was placed in the right dorsal anterior cingulate cortex (dACC; 15x15x10mm^3). MDD symptoms were evaluated by total scores on the Inventory of Depression Symptomatology Self-Report (IDS-SR) prior to and following rTMS. Two-tailed bivariate Pearson correlations were calculated between baseline Glu, Glx, and NAA and IDS-SR percent change scores. Results: Baseline metabolite concentrations were significantly correlated with percent change in IDS-SR scores, demonstrating that lower levels of pre-rTMS Glu (r = -.58, p = .02, R^2 = .34), Glx (r = -.54, p = .03, R^2 = .29), and NAA (r = -.61, p = .01, R^2 = .37) in the right dACC were associated with greater MDD symptom improvement post-rTMS. Participants' scores on the IDS-SR decreased by an average of 48% (*SD* = 35%, range = -11.91% to 88.24%)

from pre- to post-rTMS, with 56.25% (n = 9) achieving remission. Discussion: Our results are the first to indicate that baseline NAA significantly correlates with MDD improvement after rTMS, aligning with the directionality of effects with glutamatergic compounds. This pattern suggests that the antidepressant effects of rTMS may arise from intracellular processes involving Glu, Glx, and NAA in the frontal lobe. Future work using machine learning tools and baseline metabolite levels may assist in a personalized medicine approach to determine which patients will most benefit from rTMS treatment for MDD.

Disclosures: M.A. Gonsalves: None. **T.L. White:** None. **M.M. DeMayo:** None. **A.D. Harris:** None. **J.L. Barredo:** None. **L.L. Carpenter:** 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.; Neuronetics Inc, Neosync Inc, Nexstim PLC, AffectNeuro Inc, Janssen Pharmaceuticals Inc. F. Consulting Fees (e.g., advisory boards); Neuronetics Inc, Nexstim PLC, AffectNeuro Inc, Neurolief LTD, Sage Therapeutics, Otsuka, Sunovion, Janssen Pharmaceuticals Inc.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.27

Topic: G.05. Mood Disorders

Support: Alzheimer Society of Canada
Weston Brain Institute
National Institute for Translational Neuroscience (INNT/Brazil)
Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)
Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ)

Title: Cerebrospinal fluid irisin, lipoxin A4 and BDNF are reduced in elderly individuals with depression: Insight into shared mechanisms between depression and dementia

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Abstract: Depression is frequent amongst older adults, and is closely associated with and a risk factor for dementia. Identifying molecular links between depression and dementia is necessary to shed light on shared disease mechanisms. Reduced brain-derived neurotrophic factor (BDNF) and neuroinflammation have been implicated in the pathophysiology of both depression and dementia. The exercise-induced hormone, irisin, increases BDNF and improves synaptic plasticity and cognition in animal models of Alzheimer's disease. Lipoxin A4 is a lipid mediator with anti-inflammatory activity. However, the roles of irisin and lipoxin A4 in individuals with depression remain to be determined. In the present study, blood and CSF samples were collected from 61 elderly subjects, including individuals with and without cognitive impairment. Screening for depression was performed using the 15-item Geriatric Depression Scale (GDS-15). Results show that CSF irisin, lipoxin A4 and BDNF are positively correlated and are reduced in elderly individuals with depression, similar to previous observations in patients with dementia. Our findings provide novel insight into shared molecular signatures connecting depression and dementia.

Disclosures: R.A. Goncalves: None. **F. K. Sudo:** None. **M.V. Lourenco:** None. **C. Drummond:** None. **N. Assunção:** None. **B. Vanderborght:** None. **D.D. Ferreira:** None. **F. Campos Ribeiro:** None. **F. A. Pamplona:** None. **F. Tovar-Moll:** None. **P. Mattos:** None. **S.T. Ferreira:** None. **F.G. De Felice:** None.

Poster

731. Human Imaging and Behavioral Studies of Mood Disorders

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 731.28

Topic: G.05. Mood Disorders

Title: Association between neurocognitive impairment and neutrophil lymphocyte ratio in post covid 19 mexican health care workers

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Abstract: COVID-19 is associated with long-term neuropsychiatric symptoms, called a post-COVID syndrome. Current studies describe SARS-CoV-2 with neurotropism, and possibly neurocognitive changes. On the other hand, the neutrophil-lymphocyte ratio (NLR) has been described as a biomarker of immunoinflammatory response. The design of this study was a

descriptive cross-sectional evaluation of health workers who survived COVID-19 disease. We recruited adult subjects from 18-65 years. We evaluated Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scales; then, we collected blood samples. The research was approved by the Ethics Committee of Mental Health Hospital "Villahermosa" in Mexico. This study was carried out from August to December 2021. Statistical analysis was performed using SPSS. Our study included 51 participants, females (*n*=29) and males (*n*=22). The mean age was 40.54±11.00 years. The most frequent acute symptoms presented were dysgeusia (*n*=20), anosmia (*n*=18), and headache (*n*=17). The most common chronic diseases included overweight (*n*=24), obesity (*n*=22), and hypertension (*n*=11). According to MoCA, we identified 76.4% (*n*=39) participants with mild impairment (score 22.86±3.34). While MMSE showed 7.84% (n=4) of workers with moderate-severe neurocognitive impairment. The most altered neurocognitive domains frequently for both scales were delayed recall (*n*=48), language (*n*=44), visuospatial (*n*=32) and language (*n*=50). We observed an association between NLR and neurocognitive impairment by MMSE (p=0.01). Another association (x^2 test) were rhinorrhea (*p*=<0.01), sudden onset (*p*=<0.01), arthralgia (*p*=0.05), and abdominal pain (*p*=0.02). We concluded that the health care workers presented neurocognitive impairment post-COVID-19 and highlight the importance of NLR levels in post-COVID-19 individuals because language domain and neurocognitive impairment were present and associated with NLR. This biomarker could be used as a biological marker to assess neurocognitive changes in post-COVID-19 subjects.

Disclosures: C. Alonso-García: None. **D. Hernández Martínez:** None. **G. Villar-Juarez:** None. **K. Jiménez López:** None. **D. Pérez Osorio:** None. **G. Nolasco-Rosales:** None. **M. Villar-Soto:** None. **I.E. Juarez-Rojop:** None.

Poster

732. Behavioral Models and Neural Mechanisms of Relevance to Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 732.01

Topic: G.05. Mood Disorders

Support: NIDA U01DA043098
Office of Naval Research (ONR) 00014-19-1-2149
The Hope for Depression Research Foundation (HDRF)
Pritzker Neuropsychiatric Research Consortium

Title: Transcriptional profiling of the hippocampus in an F2 cross of a genetic rat model of internalizing vs. externalizing behavior and addiction liability

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of Psychiatry, [4]Dept. of Psychiatry, Inst. for Genomic Med., Univ. of California San Diego, La Jolla, CA

Abstract: For 20 years, we have selectively bred two lines of rats (High Responders (bHR) and Low Responders (bLR)) that show contrasting extremes in affective behavior. These extremes map onto human temperamental differences underlying two paths to drug abuse—novelty seeking and reactivity to psychosocial stress. To elucidate the genes that underlie the divergent behavior of bHR/bLR rats, we created a bHRxbLR F0-F1-F2 cross and performed behavioral testing, transcriptional profiling, and whole genome sequencing (WGS). We used RNA-Seq to characterize hippocampal tissue in F0s (n=24, n=6 per phenotype /sex) and F2s (n=250, n=125 per sex) to identify differentially expressed (DE) genes related to bHR/bLR lineage and phenotypical behaviors: locomotor response to novelty, anxiety, and Pavlovian Conditioned Approach (PavCA). We found that bHR/bLR phenotypical behaviors remained correlated in the F2s, implying a shared genetic basis. We also found robust DE associated with bHR/bLR lineage in the F0s (217 genes with FDR<0.10). This surpassed the DE associated with sex and replicated many effects identified in our previous study using only males (Birt et al, 2021). The DE with bHR/bLR lineage was also predictive of DE associated with F2 bHR/bLR phenotypical behavior. Since many generations of selective breeding for a behavioral phenotype should produce an enrichment of alleles influencing that phenotype, we prioritized bHR/bLR DE genes identified in our current and previous studies (Birt et al, 2021) as candidates for mediating bHR/bLR phenotypical behaviors in F2s. Seventeen genes were DE (FDR<0.10) in association with locomotor response to novelty, many of which also had nominal relationships with PavCA (p<0.05, 7/17 genes). Seven of these genes were located nearby (+/-1MB) quantitative trait loci for bHR/bLR phenotypical behavior identified in our previous exome sequencing (Zhou et al, 2019) or WGS study (Chitre et al, in prep), including AABR07071904, Ucp2, Ttc30a1, Fzd6, Spg7, Vps9d1, and Afg3l1. We also identified 26 genes (including Tmem144 and Ucp2) that had been previously identified as DE in the hippocampus of other genetic rat models targeting internalizing behaviors (database: Birt et al, 2021) and which showed similar DE in association with bHR/bLR lineage (FDR<0.10) and F2 bHR/bLR-phenotypical behavior (p<0.05). Together, these genes provide strong candidates for mediating the influence of selective breeding on complex behavior, including exploration, anxiety, and reward learning.

Disclosures: **E.K. Hebda-Bauer:** None. **M.H. Hagenauer:** None. **P. Blandino:** None. **F. Meng:** None. **A.S. Chitre:** None. **A.B. Ozel:** None. **S.B. Flagel:** None. **S.J. Watson:** None. **A.A. Palmer:** None. **J. Li:** None. **H. Akil:** None.

Poster

732. Behavioral Models and Neural Mechanisms of Relevance to Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 732.02

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA U01DA043098
NIDA T32DA07268
Office of Naval Research (ONR) 00014-19-1-2149
The Hope for Depression Research Foundation (HDRF)
The Pritzker Neuropsychiatric Research Consortium

Title: Comparison of intravenous self-administration of psychostimulants vs. opioids and endogenous opioid system differences in an animal model of internalizing vs externalizing temperament

Authors: *M. EMERY[1], A. PARSEGIAN[1], S. KOONSE[1], S. CHANG[1], C. A. TURNER[1], E. K. HEBDA-BAUER[1], S. B. FLAGEL[1,2], S. J. WATSON, Jr.[1,2], H. AKIL[1,2];
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Abstract: In humans, only a small portion of those who experiment with recreational drug use transition to a substance use disorder (SUD). Multiple factors are thought to underlie this susceptibility, including differences in temperament. Those with externalizing temperaments are hypothesized to approach drugs of abuse from a sensation-seeking pathway, while those with internalizing temperaments appear less likely to approach drugs of abuse for recreational reasons but will in response to triggers such as psychosocial stress. Our lab has used a selective breeding strategy based on degree of exploratory locomotion in a novel environment to derive two lines of rats with distinct behavioral and neurobiological phenotypes, termed selectively-bred high-responders (bHRs) and low-responders (bLRs). We have previously shown that temperamental differences between these rats determines their propensity to seek and take psychostimulants, where sensation-seeking bHRs show a higher basal propensity to take drugs; while internalizing bLRs appear less susceptible at baseline but will seek and take drugs in response to psychosocial stress. However, we hypothesized these differences in baseline drug seeking may be partially drug-specific, where bLRs, who display a higher level of baseline anxiety than bHRs, would have higher preference for anxiolytic opioids than anxiogenic stimulants. Here, we used a free access self-administration paradigm of diacetylmorphine (heroin) or cocaine hydrochloride to determine whether these individual differences result in differential use patterns. For both drugs, we observed the expected phenotype differences, with bHRs seeking and taking more drug than bLRs. However, the differences were less pronounced for opioids than stimulants, implying increased preference for opioids in bLRs relative to stimulants. Interestingly, there appears to be a drug x sex x phenotype interaction where a line-specific (bHRs) effect of sex appears in heroin taking behavior, but not for cocaine. We additionally explored differences in opioid neurobiology between these lines, including opioid gene expression in key brain regions, finding differences in multiple opioid system components that likely contribute to line differences in drug-oriented behaviors. Future experiments will explore the impact of stress on drug preference in bHRs/bLRs, as well as the impact of differential expression of opioid system components to drive these differences. These findings contribute to our understanding of the impact of individual differences as well as a potential interaction between temperament, sex, and drug as antecedents of addiction development.

Disclosures: **M. Emery:** None. **A. Parsegian:** None. **S. Koonse:** None. **S. Chang:** None. **C.A. Turner:** None. **E.K. Hebda-Bauer:** None. **S.B. Flagel:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

732. Behavioral Models and Neural Mechanisms of Relevance to Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 732.03

Topic: G.09. Drugs of Abuse and Addiction

Support: U01DA043 (NIDA)

Title: Identification of individuals with resistant, mild, moderate, and severe cocaine addiction-like behaviors in over 500 heterogeneous stock rats

Authors: *M. BRENNAN[1], L. L. G. CARRETTE[1], G. DE GUGLIELMO[1], M. KALLUPI[1], L. MATURIN[1], B. BOOMHOWER[1], D. E. CONLISK[2], S. SEDIGHIM[1], L. TIEU[1], M. FANNON[1], N. VELARDE[1], J. KONONOFF[2], S. BONNET-ZAHEDI[1], K. SHANKAR[2], S. SIMPSON[1], A. J. AVELAR[1], L. C. SMITH[2], A. MARTINEZ[1], C. CROOK[1], A. J. KIMBROUGH[1], P. SCHWEITZER[1], L. C. SOLBERG[3], A. A. PALMER[1], O. GEORGE[1];
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Abstract: A key question for cocaine addiction research is why casual drug consumption escalates to problematic use in only some individuals. A better characterization of individual differences in the propensity to develop addiction-like behaviors could help identify new pharmacological targets for medication development. Most studies have used a small sample size (N < 8-20), limited access self-administration paradigms, or animal models with limited individual differences. Such limitations reduce the translational relevance and replicability. To address these issues, we characterized addiction-like behaviors using the state-of-the-art model of extended access to cocaine self-administration (6 h/daily for 14 days following an initial 10 days of short 2 h access) in large cohorts (N = 46-60 each, 567 total) of heterogeneous stock (HS) rats, a unique outbred strain of rats with large individual differences. Animals were also screened for motivation with progressive-ratio (PR) responding, responding despite adverse consequences (contingent foot shocks), and withdrawal-induced irritability-like behavior (bottlebrush test). All tests showed large inter-individual differences, with small intra-individual differences. Large sex differences were also observed, with females having a higher responding under fixed ratio (FR) (escalation, $p < 0.01$) and responding despite foot shock (compulsivity, $p < 0.001$) than males. However, there were considerably larger differences between individuals than just between sex. Final cocaine intake showed a bimodal distribution ($p < 0.001$), with 80% vulnerable rats escalating their cocaine intake over the extended access protocol and 20% resilient rats, who maintain low intake levels. These groups also showed significant differences in motivation ($p < 0.001$) and compulsivity ($p < 0.001$), but not in withdrawal-induced irritability. Principal component analysis of intake, motivation, compulsivity, and withdrawal showed escalation, motivation, and compulsivity clustering together on the first principal component (PC1), which explained 48% of the variance. Irritability-like behavior was orthogonal to PC1. Averaging the Z-scores of these three dependent variables into an addiction

index could be used as a proxy of PC1 to comprehensively score individual addiction-like behaviors. To our knowledge, this is the largest intravenous cocaine self-administration study characterizing individual differences of addiction-like behavior in rats. Biological samples were collected longitudinally and are available through the Cocaine Biobank to facilitate follow-up research for medication development purposes.

Disclosures: **M. Brennan:** None. **L.L.G. Carrette:** None. **G. De Guglielmo:** None. **M. Kallupi:** None. **L. Maturin:** None. **B. Boomhower:** None. **D.E. Conlisk:** None. **S. Sedighim:** None. **L. Tieu:** None. **M. Fannon:** None. **N. Velarde:** None. **J. Kononoff:** None. **S. Bonnet-Zahedi:** None. **K. Shankar:** None. **S. Simpson:** None. **A.J. Avelar:** None. **L.C. Smith:** None. **A. Martinez:** None. **C. Crook:** None. **A.J. Kimbrough:** None. **P. Schweitzer:** None. **L.C. Solberg:** None. **A.A. Palmer:** None. **O. George:** None.

Poster

732. Behavioral Models and Neural Mechanisms of Relevance to Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 732.04

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant AA024044

Title: Towards developing a mouse model of co-morbid binge-eating and -drinking.

Authors: *K. SZUMLINSKI, I. KAZERANI, L. MADORY, A. KHARWA, C. JIMENEZ CHAVEZ;
Univ. California-Santa Barbara, Santa Barbara, CA

Abstract: A high rate of co-morbidity exists between binge-eating and binge-drinking disorders, suggesting a common neuropathology. To test this hypothesis, we have worked to develop a mouse model of co-morbid binge-eating and -drinking, using C57BL/6NJ (B6NJ) mice. In our first study, *ad libitum*-fed and -watered female and male B6NJ mice underwent 1-h binge-eating sessions in the morning, every other day. Every afternoon, mice were offered 20 and 40% alcohol for 2 h. As expected, females binge-ate and binge-drank more than males. However, opposite our expectation, mice consuming either SPF or control Chow pellets both exhibited lower alcohol intake on binge-eating days, than on non-eating days. In a second experiment, mice underwent 10 days of binge-eating (5 days/week), followed by 10 days of binge-drinking. Under this “eat-first” procedure, females escalated their SPF intake more rapidly than males, and female-SPF mice also consumed the most alcohol on the first day of binge-drinking. Although males did not exhibit behavioral cross-sensitization on day 1 of drinking, both male and female SPF mice consumed more alcohol, overall, than no SPF controls and this observation was replicated in distinct cohort of mice. In contrast, 10 days of prior binge-drinking did not promote subsequent binge-eating in a fourth study. The unilateral cross-sensitization between binge-drinking and -eating indicate that binge-eating elicits neuroadaptations that facilitate the

manifestation of binge-drinking, with females being more sensitive to these neuroadaptations that underpin this cross-sensitization.

Disclosures: K. Szumlinski: None. **I. Kazerani:** None. **L. Madory:** None. **A. Kharwa:** None. **C. Jimenez Chavez:** None.

Poster

732. Behavioral Models and Neural Mechanisms of Relevance to Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 732.05

Topic: G.09. Drugs of Abuse and Addiction

Support: INBRE

Title: Investigating Drosophila melanogaster as a Model to Study Drug-Induced Behavior

Authors: *L. SA, C. LITIF, L. VACCARO, A. BOBADILLA;
Univ. of Wyoming, Laramie, WY

Abstract: Substance abuse is a highly prevalent disorder in the United States which has been shown to have a strong genetic basis underlying the habit of compulsive drug use. In our research, we used two methods to study drug-induced behavior within the *Drosophila melanogaster* model organism that is biomedically relevant due to the high genetic homology with humans. Administration of cocaine was carried out using either a capillary feeding system (CAFE) or a volatilized drug-delivery system which is connected to an activity monitor (DAM2) for observation of drug-induced behavior. The CAFE assay consisted of putting flies into individual tubes where they are exposed to a feeding tube of cocaine within a sucrose vehicle solution for 2 hours. Then, the activity of the cocaine-exposed flies as compared to non-exposed flies was measured using the DAM2 system. The flies that were exposed to cocaine had much higher activity measurements than the ones exposed to only sucrose. To prevent the bias of sucrose within the investigation, the flies were exposed to the drug within a different model that utilizes volatilizing cocaine without the need for a sucrose vehicle. After cocaine exposure via volatilizing, the activity was measured with the DAM2 system. Through our data that was collected, it was shown that exposing *Drosophila melanogaster* to volatized cocaine caused an increase in activity. The dose containing 100 ug of cocaine had a greater effect than the doses of 50 ug and 150 ug but a difference in activity compared to controls was seen with all doses. Therefore, we confirm that exposure to cocaine without a sucrose bias causes an altered activity in the *Drosophila melanogaster* and thus can serve as a relevant model for testing the underlying genetics of substance use disorder.

Disclosures: L. Sa: None. **C. Litif:** None. **L. Vaccaro:** None. **A. Bobadilla:** None.

Poster

732. Behavioral Models and Neural Mechanisms of Relevance to Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 732.06

Topic: G.09. Drugs of Abuse and Addiction

Support: R01DA052385

Title: Investigation of the role of prediction error in reconsolidation of cocaine-cue memories on cue-induced reinstatement of relapse-like behaviors in rats

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Abstract: Chronic use of addictive drugs results in maladaptive learning and memory processes, forming strong associations between the drug and cues. Exposure to these drug-associated cues can often trigger relapse even after long periods of abstinence. One potential method to reduce relapse is to disrupt drug-cues associated memories via alterations in memory reconsolidation. Reconsolidation is a process whereby reactivated memories become transiently destabilized and vulnerable to updating prior to being restabilized. Previous studies have indicated that induction of a prediction error (PE) during reactivation promotes memory destabilization, however, the role of PE in cocaine self-administration model has yet to be fully studied. Here, we focus on the investigation of the impact of a PE created by the unexpected magnitude of a cocaine unconditioned stimulus (US) during reactivation on subsequent cue-induced reinstatement of drug-seeking behaviors. Rats were trained to press the active lever for intravenous (IV) cocaine (0.5 mg/kg) infusion, each associated with a CS1 (light) or CS2 (tone) separately for 12-14 days followed by 8 days of lever extinction. The next day, rats underwent a reactivation session in which they were exposed to the CS1 presented with an unexpected magnitude of cocaine infusion to generate a PE. The control group of rats received CS1 with the expected dose of cocaine to produce no PE. Immediately after, the animals were systemically injected either with the amnestic agent anisomycin (a protein synthesis inhibitor) or vehicle. Twenty-four hr after the reactivation session, cue-induced reinstatement was assessed by presenting CS1 and CS2 in response to an active lever press but without any cocaine infusion. Each cue was tested for 30 min, two times each for a total of 2 hrs. Our results indicate that rats that received anisomycin with an unexpected magnitude of cocaine during reactivation showed a significant reduction in cue-induced reinstatement of cocaine-seeking behaviors, whereas vehicle treated animals did not. Together, the present findings suggest a role of PE-like processes in initiating memory destabilization to make them susceptible to amnestic agents, thereby reducing relapse-like behaviors. Ongoing studies aim to define the conditions whereby destabilization mechanisms can be used to make memories more susceptible to amnestic agents or targeted pharmacotherapies, in order to block reconsolidation of cocaine-cue memories and thereby reduce relapse behavior.

Disclosures: B. Cho: None. **H. Sanchez:** None. **J. Taylor:** None.

Poster

732. Behavioral Models and Neural Mechanisms of Relevance to Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 732.07

Topic: G.09. Drugs of Abuse and Addiction

Support: 20182MFDS422
20182MFDS425
2018R1A5A2025272
2019R1I1A1A01052581

Title: Impacts of isoflurane anesthesia on the reinforcing effects of cocaine in rats

Authors: *S. YOON[1], S. LEE[2], C. YANG[1];
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Abstract: Isoflurane anesthesia has been used in various studies related to substance abuse that require immobile animals. However, relatively little is known about the direct effect of isoflurane anesthesia on neurobehavioral activity induced by psychoactive substances. In this study, we investigated the influence of isoflurane exposure on cocaine-reinforced behavior using the self-administration paradigm. Male Sprague-Dawley rats were trained to self-administer cocaine (0.25 or 0.5 mg/kg/infusion) for approximately 2 weeks. Once stable self-administration behavior under a fixed-ratio 1 (FR1) schedule of reinforcement had been achieved, rats were exposed to 1% or 2% isoflurane for 10 min. After a 20-min recovery period, self-administration testing began. Additionally, the effect of isoflurane on motivation for cocaine was assessed under a progressive ratio (PR) schedule of reinforcement. To determine whether the effects of isoflurane were specific to cocaine under our experimental conditions, we conducted a nicotine (0.03 mg/kg/infusion) self-administration test similar to that used in the cocaine experiment. In another series of experiments, the effects of isoflurane on the locomotor activity induced by acute cocaine (15 mg/kg, intraperitoneal [IP]) were examined. The results showed that isoflurane exposure significantly suppressed cocaine- and nicotine-reinforced responses without affecting food consumption, and reduced breaking points under a PR schedule of reinforcement in a dose-dependent manner, indicating its efficacy in decreasing the incentive value of cocaine. Similarly, isoflurane also attenuated acute cocaine-induced hyperlocomotion. These results indicate that exposure to isoflurane attenuates the reinforcing and motivational effects of psychostimulants, including cocaine and nicotine, in the self-administration procedure. [Supported by a grant (20182MFDS422 and 20182MFDS425) from Ministry of Food and Drug Safety and National Research Foundation of Korea (NRF) grant funded by the Korea government MSIT (2018R1A5A2025272 and 2019R1I1A1A01052581)]

Disclosures: S. Yoon: None. **S. Lee:** None. **C. Yang:** None.

Poster

732. Behavioral Models and Neural Mechanisms of Relevance to Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 732.08

Topic: G.09. Drugs of Abuse and Addiction

Support: 1ZIADA000457
This work was supported by The National Institutes of Health and the National Institute on Drug Abuse Intramural Research Program

Title: Lateral habenula M_2 muscarinic receptor control of neuronal function and impulsive cocaine seeking in rats

Authors: C. I. C. WOLFE, E.-K. HWANG, E. C. IJOMOR, A. ZAPATA, *A. F. HOFFMAN, C. R. LUPICA;
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Abstract: The lateral habenula (LHb) balances reward and aversion by opposing activation of brain reward nuclei, and its dysfunction is implicated in psychiatric and substance use disorders. Using a rat model of impulsive cocaine seeking behavior, we previously reported that the withholding of responses for cocaine was prevented by LHb inactivation or by non-selective antagonism of LHb muscarinic acetylcholine receptors (mAChR; Zapata et al., 2017, Neuropsychopharm., 42: 1103). Here we define cellular mechanisms of mAChR control over LHb neuron activity and investigate mAChR subtypes mediating the effects of endogenous acetylcholine in impulsive cocaine seeking. Using whole-cell electrophysiology in male and female rat brain slices, we find that the nonselective cholinergic agonist carbachol (CCh) evoked depolarizing, hyperpolarizing, or biphasic currents in different subsets of neurons in the medial LHb. In contrast, the selective muscarinic agonist oxotremorine-M (Oxo-M) elicited inward currents in 89% of LHb neurons. The Oxo-M currents were blocked by the M_2-mAChR (M_2R) antagonist AFDX-116, but not by the M_1-mAChR (M_1R) antagonist pirenzepine (PZP), indicating that M_2Rs excite LHb neurons. We next examined effects of mAChR activation on synaptic integration be measuring evoked and spontaneous synaptic currents in LHb neurons. We found that CCh inhibited GABAergic and glutamatergic LHb afferents similarly in males and females, and that these synaptic effects were blocked by AFDX-116 and not by PZP, indicating M_2R control. Optogenetic experiments showed CCh inhibition of GABAergic currents arising from the ventral tegmental area, and reversal by AFDX, identifying one M_2R-sensitive LHb afferent. Finally, in behavioral Go/NoGo experiments in which rats had been trained to withhold responding for cocaine during its signaled absence, response inhibition for the drug was impaired by LHb infusion of AFDX-116, but not PZP. Our study demonstrates the involvement of the cholinergic system and M_2Rs in control of impulsive drug seeking and defines cellular mechanisms of M_2R receptors regulation of the LHb.

Disclosures: C.I.C. Wolfe: None. **E. Hwang:** None. **E.C. Ijomor:** None. **A. Zapata:** None. **A.F. Hoffman:** None. **C.R. Lupica:** None.

Poster

732. Behavioral Models and Neural Mechanisms of Relevance to Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 732.09

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH DA 040965
Good Samaritan Foundation of Legacy Health

Title: Perineuronal net removal in the rat medial prefrontal cortex attenuates prefrontal-hippocampal coupling during cocaine cue acquisition

Authors: *J. D. RAMOS[1], J. C. WINGERT[1], S. REYNOLDS[1], A. E. GONZALEZ[1,2], B. A. SORG[1,2];
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Abstract: Environmental stimuli become paired with exposure to drugs of abuse and play an important role in the maintenance of drug memories. In the medial prefrontal cortex (mPFC), parvalbumin (PV) interneurons regulate pyramidal cells critical for cocaine memory consolidation. Most PV neurons are coated with a perineuronal net (PNN), an extracellular matrix structure essential for supporting fast firing rates and precise spike timing of PV neurons. These qualities of PV cells help generate oscillations and mediate coupling within and between brain regions, which play an important role in memory consolidation. Removal of PNNs with chondroitinase ABC (Ch-ABC) disrupts acquisition of cocaine memories, but it is not known why this occurs. After microinjection of either saline (control) or Ch-ABC into the mPFC of male Sprague Dawley rats, tungsten electrodes were implanted into the mPFC and hippocampal dorsal CA1. Rats were given intravenous infusions of saline paired with one cue light or cocaine paired with a second cue light over eight alternating days. On the last day, rats were presented both cue lights in a pseudo-randomized order. Rats exhibited event-related phase resetting in response to cue presentation; however, both phase-amplitude coupling and phase-phase coupling between the mPFC and CA1 were vastly attenuated in Ch-ABC compared with control rats following cocaine cue presentation. Cocaine cue presentation also increased beta power in controls that was attenuated in Ch-ABC rats. Overall, PNN removal in the mPFC diminishes communication between the CA1 and mPFC, which may underlie the inability of these rats to consolidate drug-associated memories.

Disclosures: **J.D. Ramos:** None. **J.C. Wingert:** None. **S. Reynolds:** None. **A.E. Gonzalez:** None. **B.A. Sorg:** None.

Poster

732. Behavioral Models and Neural Mechanisms of Relevance to Addiction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 732.10

Topic: G.09. Drugs of Abuse and Addiction

Support: T34GM145384
P50 DA037844
U01DA051947

Title: Adolescent exposure to sucrose increases cocaine mediated behaviors in adulthood

Authors: T. SHWANI[1], R. PARMAR[2], M. COBB[2], M. KAUSCH[2], L. EVANS[2], C. WERNER[1], D. DIETZ[1], *A. GANCARZ-KAUSCH[2];
[1]Pharmacol. and Toxicology, State Univ. of New York, Univ. at Buffalo, Buffalo, NY;
[2]California State University, Bakersfield, Bakersfield, CA

Abstract: Adolescence is a critical period during which significant neurobiological changes occur. Drug experimentation co-occurs during this time, making it an important period of development to investigate its role in vulnerability to adult drug abuse. Here, we investigate how naturally rewarding stimuli, such as sucrose, a ubiquitously available stimulus in modern diets, can affect adult vulnerability to addicted-like behaviors.We show that juvenile sucrose leads to lifelong behavioral adaptations, which include increased susceptibility to drugs of abuse, as measured by enhanced sensitivity, motivation, and drug-taking in the face of negative consequences. To determine the neurobiological mechanisms leading to such behavioral adaptations, we investigated neuronal adaptations under naïve conditions following adolescent exposure to sucrose and found that the transcription factor Smad3 is upregulated in the NAc compared to water-exposed controls.To demonstrate functional significance, we utilized a transient viral-mediated system to block Smad3 signaling in the NAc following access to sucrose and tested while adults. Twenty-eight days later, adult animals were tested on a series of behavioral paradigms associated with addicted-like phenotypes. Overexpression of dominant-negative Smad3 (dnSmad3) following exposure to sucrose resulted in decreased self-administration of cocaine and less motivation to work for cocaine in adulthood. Moreover, using a within-session dose-response paradigm, dnSmad3 rats displayed a downward vertical shift compared to controls, indicating reduced vulnerability to cocaine.These data suggest that adolescent sucrose pre-exposure results in heightened motivation and reinforcing effects of cocaine, and identifies a role for Smad3 in mediating sucrose-induced vulnerability to cocaine. These findings have important implications for the human condition, suggesting juvenile sucrose may enhance vulnerability to drugs of abuse in adulthood and a molecular pathway for possible treatment.

Disclosures: T. Shwani: None. **R. Parmar:** None. **M. Cobb:** None. **M. Kausch:** None. **L. Evans:** None. **C. Werner:** None. **D. Dietz:** None. **A. Gancarz-Kausch:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.01

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01 DA046457

Title: C-fos activity in cortical and thalamic afferents to dorsomedial and dorsolateral striatum during punished cocaine seeking

Authors: *S. N. HANDEL[1], R. J. SMITH[2];
[2]Dept Psychological and Brain Sci., [1]Texas A&M Univ., College Station, TX

Abstract: One of the defining features of drug addiction is compulsive use despite negative consequences. In an animal model of compulsive drug seeking, a subset of animals will continue to self-administer cocaine despite footshock consequences (indicating punishment resistance), whereas other animals show greater punishment sensitivity. We hypothesize that punishment of cocaine seeking recruits goal-directed and/or habitual systems in the brain, including the dorsomedial striatum (DMS) and dorsolateral striatum (DLS). Here, we wanted to investigate punishment-induced c-Fos activity in cortical and thalamic afferents to DMS and DLS to determine the neural circuitry that may be guiding punishment behavior. Male Sprague Dawley rats were first injected with retrograde tracers (Fluoro-Gold or CTb) into DMS or DLS and then trained to self-administer cocaine on a seeking-taking chained schedule of reinforcement (2-hr daily sessions). Rats were given either 1 day of footshock punishment (0.7 mA, 0.3 sec, after completion of seeking on 1/3 of trials) or no punishment and then sacrificed 30 minutes later. c-Fos protein was quantified in retrograde-labeled cells in the prefrontal cortex and intralaminar thalamus. In the 1-day punishment group, we observed a range in punishment sensitivity with rats responding from 27-90% of their baseline and receiving 2-6 footshocks . In this group, we found that the number of footshocks received was correlated with c-Fos activity in cortical projections to DMS, but with thalamic projections to DLS. We found no correlation between c-Fos and cocaine infusions in the no-punishment group, indicating that c-Fos differences cannot be attributable to cocaine alone. These data indicate that footshock punishment drives activity in both the goal-directed and habitual systems, but via distinct inputs. Further studies involving manipulation of these brain circuits is necessary to determine whether increased activity in these circuits is driving punishment resistance or is reflective of progressive recruitment of these brain regions in response to footshock.

Disclosures: S.N. Handel: None. **R.J. Smith:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.02

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH/NIDA R01 grant DA046457

Title: Investigating the roles of the intralaminar thalamus and dorsal striatum in punished cocaine seeking in rats.

Authors: *A. M. CRUZ, S. N. HANDEL, R. J. SMITH;
Dept Psychological and Brain Sci., Texas A&M Univ., College Station, TX

Abstract: Compulsive drug seeking that continues despite negative consequences may result from a loss of behavioral flexibility, which is the ability to control or update behavior in response to changes in environmental conditions. The intralaminar thalamus (ILN) and dorsal striatum (DS) have been implicated in behavioral flexibility and regulation of compulsive behaviors. Recent work in our lab using an animal model of compulsive drug use found an association between punishment-resistant cocaine seeking and c-Fos expression in ILN afferents to dorsolateral striatum (DLS). Here, we wanted to further investigate the roles of ILN and DS in punishment-resistant cocaine seeking by examining c-Fos expression in ILN nuclei (parafascicular, PF; centromedial, CM; and paracentral thalamus, PC), as well as dorsomedial striatum (DMS) and DLS. Male Sprague Dawley rats were trained to self-administer cocaine on a seeking-taking chained schedule of reinforcement during daily 2-h sessions for ~3 wks. To assess c-Fos expression, rats were sacrificed and brains were collected 30 min after 1 or 2 sessions of footshock punishment (0.7 mA, 0.3 s, randomly 1/3 trials) or after a cocaine self-administration session with no punishment. We found correlations between the number of footshocks received during punishment and c-Fos in DMS and DLS ($p = 0.027, 0.052$). Within the ILN, we found increased c-Fos across PF, CM, and PC in the punishment groups. Given this increase, we tested the effects of post-training NMDA lesions of ILN in another group of rats receiving footshock punishment. These rats were given two types of punishment during cocaine self-administration: 4 sessions of footshock at 0.4 mA (0.3 s, randomly 1/3 of trials) and 3 sessions of footshock with ramped amplitude (0.32, 0.56, 1.0 mA, 0.3 s, every trial). Regardless of the type of punishment testing, we observed no difference in punishment sensitivity in rats that received ILN lesions as compared to rats with sham lesions. These data indicate that global inactivation of ILN does not affect punished cocaine seeking. However, future studies are necessary to test whether pathway-specific (e.g., PF-DLS) or temporally-specific manipulation of ILN has an effect on punishment-resistant cocaine seeking.

Disclosures: A.M. Cruz: None. **S.N. Handel:** None. **R.J. Smith:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.03

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH/NIDA R01 Grant DA046457

Title: Noncontingent footshock, unlike contingent footshock, does not reduce cocaine seeking in rats

Authors: *P. L. KAHANEK, A. M. CRUZ, A. N. STARNES, R. J. SMITH;
Psychological and Brain Sci., Texas A&M Univ., College Station, TX

Abstract: A defining characteristic of addiction is compulsive drug use, or continued drug use despite negative consequences. In an animal model of compulsive drug seeking, a subset of animals continue to seek cocaine despite receiving footshock (punishment resistance), while another subset reduces cocaine seeking to avoid footshock (punishment sensitive). Here, we wanted to investigate the effects of noncontingent footshock on cocaine seeking to determine what role footshock-induced stress might play in punishment sensitivity. Male Sprague Dawley rats were trained to self-administer intravenous cocaine via a seeking-taking chained schedule of reinforcement during daily 2-hour sessions. After ~3 weeks of self-administration, rats were given 4 days of testing with either contingent footshock (0.4 mA, 0.3 sec, randomly 1/3 trials, delivered after completion of seeking) or noncontingent footshock (similar parameters and number of shocks, but independent of behavior). We found that noncontingent footshock did not affect cocaine seeking and that rats self-administered cocaine at a similar rate to baseline. In contrast, contingent footshock resulted in reduced cocaine seeking on average, with some rats more sensitive than others. A proportion of rats then received ramped levels of footshock across days (0.32, 0.56, 1.0 mA). Surprisingly, even at the highest amplitude, noncontingent footshock did not reduce cocaine seeking. These data indicate that sensitivity to footshock punishment cannot be explained by footshock-induced stress and that contingency plays a key role. Further work is necessary to determine whether punishment resistance, therefore, may be related to a lack of awareness of the footshock contingency.

Disclosures: P.L. Kahanek: None. **A.M. Cruz:** None. **A.N. Starnes:** None. **R.J. Smith:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.04

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH/NIDA R01 Grant DA046457

Title: Random ratio and random interval schedules of reinforcement have a strong influence on the development of punishment resistance in cocaine-seeking rats

Authors: *B. JONES[1,3], A. CRUZ[2], R. J. SMITH[2,3];
[2]Dept Psychological and Brain Sci., [1]Texas A&M Univ., College Station, TX; [3]Inst. for Neurosci., College Station, TX

Abstract: Drug addiction is a debilitating brain disease characterized by compulsive drug use despite negative consequences. In an animal model of compulsive use, a subset of rats continue to seek cocaine despite footshock consequences and are considered punishment resistant. Given that random ratio (RR) and random interval (RI) schedules of reinforcement influence whether responding is goal-directed or habitual, we wanted to investigate the influence of these schedules on the development of punishment resistance. Male Sprague Dawley rats were trained to self-administer intravenous cocaine on a seeking-taking chained schedule of reinforcement, with the seeking lever requiring completion of either an RR20 or RI60 schedule. Punishment testing occurred for 4 sessions, with 0.4-mA footshock given at the completion of the seeking link of the chain (randomly on 1/3 of trials). RR20-trained rats showed higher rates of responding and more infusions per session as compared to RI60-trained rats, despite similar amounts of training. RR20-trained rats were also vastly more sensitive to punishment than RI60-trained rats, showing a greater reduction in responding from baseline. Using K-means clustering analysis, we identified two distinct groups of rats based on their response to punishment: punishment sensitive (responding <65% baseline) and punishment resistant (>65% baseline). Nearly all RR20-trained rats were sensitive to punishment (27/29), while the RI60-trained group had similar amounts of sensitive(n:21) and resistant rats (n:27). Therefore, responding under the RI60 schedule is more likely to be habitual and resistant to punishment. Interestingly, within the RI60-trained group, resistance to punishment was correlated with lower cocaine intake in early training (when reinforced on a fixed ratio 1 schedule), but higher cocaine intake in late training before punishment testing. For RR20-trained rats, there were no correlations between cocaine intake and punishment sensitivity. Altogether, these results show the profound influence that schedule of reinforcement can have in the development of compulsive behavior.

Disclosures: B. Jones: None. **A. Cruz:** None. **R.J. Smith:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.05

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH-NIGMS #2R25GM082406
Catalyzer- CRG-2020-00114
INBRE- P20 GM103475-19

Title: Effects of stress prior to cocaine self-administration in adult rats

Authors: *Y. A. PEREZ-PEREZ, R. J. MORALES-SILVA, J. PEREZ-TORRES, J. K. ALVARADO-TORRES, G. RODRIGUEZ-TORRES, M. SEPULVEDA-ORENGO;
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Abstract: Co-morbidity between cocaine use disorder (CUD) and trauma/stressor-related conditions such as PTSD has been recorded frequently, indicating a strong link between stress and cocaine use. Because of the unpredictable and often uncontrollable nature of stress, the ability of stressful life events to trigger drug use is particularly problematic for the management of cocaine relapse treatments. Therefore, this research aims to provide insight into how stress acts as a risk factor for developing cocaine use disorder and its influence on cocaine-seeking behavior and consumption in an animal model. We hypothesize that male rats exposed to stress will show an increased drug-seeking behavior and drug consumption compared to rats not exposed to stress. Male Sprague Dawley rats were subjected to acute stress in the form of a single session of fear conditioning, in which a total of 3 habituation tones (500 Hz) and 7-foot shocks (0.6 mA) paired with tones (500 Hz) will be presented. Following stress exposure, rats were subjected to 12 days of short-access cocaine self-administration (2-h/day), followed by 15 days of extinction training (2-h/day) and cue-induced reinstatement. Results show that the stress group had no difference in cocaine consumption and drug-seeking behavior during cocaine acquisition and extinction, respectively, compared to the non-stress group. Interestingly, the stress group had higher active lever presses in cue-induced reinstatement when compared to non-stressed cocaine rats. In conclusion, stress is an influential factor contributing to increased vulnerability to developing cocaine use disorder. Currently, we are performing experiments to investigate if stress prior to cocaine self-administration affects drug-seeking behavior in female rats as observed in male rats.

Disclosures: Y.A. Perez-Perez: None. **R.J. Morales-Silva:** None. **J. Perez-Torres:** None. **J.K. Alvarado-Torres:** None. **G. Rodriguez-Torres:** None. **M. Sepulveda-Orengo:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.06

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant 1F31DA053793-01

Title: Effects of chronic stress on cocaine seeking behavior after 15 day forced abstinence in male and female rats

Authors: *R. MORALES SILVA[1], M. MARTINEZ VELEZ[2], U. GELPI-DOMÍNGUEZ[3], J. PEREZ TORRES[2], Y. PEREZ PEREZ[2], G. RODRIGUEZ TORRES[2], M. T. SEPULVEDA

ORENGO[2];
[2]Basic Sci., [1]Ponce Hlth. Sci. University, Ponce Res. Inst., Ponce, Puerto Rico; [3]Psychology, Ponce Hlth. Sci. Univ., Ponce, Puerto Rico

Abstract: Generally, Post-Traumatic Stress Disorder (PTSD) and substance use disorder (SUD) are studied independently in preclinical studies. However, they can occur concurrently in patients, and PTSD patients exhibit higher rates of SUD. Moreover, stress has been associated with a higher probability of relapse. Previous studies have shown that modified single prolonged stress reduces cocaine self-administration in rats, as well as a reduced cue-induced reinstatement of cocaine-seeking behavior, without any effects on acquisition and extinction of cocaine self-administration. These studies used different models of PTSD in rodents and a short-access cocaine self-administration paradigm. However, the effects of chronic stress on extended-access cocaine self-administration have not been reported. In addition, no published results from our laboratory showed that chronic stress prior to cocaine acquisition increases cocaine-primed memory retrieval after 30 days of withdrawal in male and female rats. Interestingly, only female rats show an increase in cue reactivity in the stress group compared with the male group. A previous study suggested that male rats at withdrawal day 30 reached a plateau during cue reinstatement. To determine if this was the effect we saw in cue-reactivity at 30 days of force abstinence, we ran a different set of animals using a similar behavioral method but instead of 30-days of abstinence, we did 15 days. We hypothesize that chronic stress prior to cocaine self-administration with 15 days of force abstinence will increase cue-induced seeking behavior in both sexes. To test this hypothesis, we used unescapable footshocks for 5 days at an intensity of 0.50mA (presented randomly), followed by 6-hour sessions of extended-access cocaine self-administration for 10 days and a 15-days forced abstinence period. Subsequently, we examined cue- and cocaine-induced cocaine-seeking behavior. Our data show that chronic stress prior to cocaine acquisition decreases cue-reactivity after 15-day withdrawal in male rats without effect in cocaine induce memory retrieval. Like males, female rats show a tendency to a decreased cue-reactivity but no effect in cocaine-induced memory retrieval; however, this still needs to be addressed. These results suggest that the effects of chronic stress prior to cocaine exposure on cocaine-seeking behavior depend on the withdrawal period's length, indicating different phases of neurophysiological changes during incubation.

Disclosures: R. Morales Silva: None. **M. Martinez Velez:** None. **U. Gelpi-Domínguez:** None. **J. Perez Torres:** None. **Y. Perez Perez:** None. **G. Rodriguez Torres:** None. **M.T. Sepulveda Orengo:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.07

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA049930
OHSU Startup Funds
NIDA Training Grant 5T32DA007262-29

Title: Role of nucleus accumbens dopamine in incubation of cocaine craving

Authors: *S. J. WEBER, A. L. MOUTIER, A. B. KAWA, A. M. WUNSCH, M. E. WOLF; Oregon Hlth. and Sci. Univ., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Relapse represents a consistent clinical problem when treating individuals with Substance Use Disorder. We and others have studied this in rodents using the incubation of cocaine craving model. In this model rats undergo extended access drug self-administration where they learn to nose-poke in the active port for a cocaine infusion paired with a light cue. Next, they undergo a period of prolonged abstinence during which drug-craving increases (incubates) over time as measured by cue-induced drug seeking tests. Previous work in our lab and others have shown that strengthening of AMPAR transmission in the nucleus accumbens core (NAcc) is required for expression of incubated cocaine craving. However, it remains unknown whether dopamine plays a role. Dopamine is well-known for its role in motivation and salience, and would therefore be expected to contribute to a behavior reliant on increased cue reactivity. To investigate this, we expressed dLight1.3b or GRAB_DA1m and implanted a fiber optic cannula in the NAcc of male and female Long Evans rats prior to cocaine self-administration. The dopamine signal was recorded via fiber photometry during a 15-30 min cue-induced seeking test on forced abstinence day (FAD) 1 or FAD40-45. Initial results show a dopamine response following pokes into the active port. Furthermore, we observed a trend toward an increased dopamine response following active port responses in late abstinence compared to early abstinence. We are currently adding more rats, including saline controls. In addition, we are testing whether expression of incubation is reduced by intra-NAcc infusion of dopamine receptor antagonists.

Disclosures: S.J. Weber: None. **A.L. Moutier:** None. **A.B. Kawa:** None. **A.M. Wunsch:** None. **M.E. Wolf:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.08

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA050457
NIH Grant DA015835
NIH Grant DA049930

Title: Incubation of cocaine craving: Cell-type specific transciptomics in the nucleus accumbens core

Authors: *A. B. KAWA[1], J. G. HASHIMOTO[1], A. R. NECTOW[2], M. GUIZZETTI[1], M. E. WOLF[1];
[1]Oregon Hlth. & Sci. Univ., Portland, OR; [2]Med., Columbia Univ., New York, NY

Abstract: In the 'incubation of cocaine craving' model of relapse, rats self-administer cocaine using an extended access procedure, and then experience a prolonged abstinence period. During abstinence, rats exhibit a progressive intensification (incubation) of cue-induced craving. We have shown that Ca^{2+}-permeable AMPA receptors (CP-AMPAR), comprised exclusively of the GluA1 subunit, accumulate in the nucleus accumbens (NAc) core during abstinence and are required for the expression of incubated craving. Further, ongoing protein translation is required for the maintenance of synaptic CP-AMPARs and incubated craving after prolonged abstinence from cocaine self-administration. If general translation is blocked, synaptic CP-AMPARs are no longer detectable and seeking is reduced. We have previously found that *Gria1* mRNA (GluA1-subunit) translation is increased in incubation, but a broader and cell-type specific interrogation of translation in the NAc core after cocaine incubation is lacking. Here we used male and female rats that express Cre recombinase in either D1R or A2a/D2R medium spiny neurons to express a GFP-tagged ribosomal subunit in a cell-type specific manner. This enabled us to use Translating Ribosome Affinity Purification (TRAP) to isolate actively translating mRNAs from both neuronal subtypes for analysis by RNA-Seq. This analysis has revealed genes that are differentially expressed in these specific cell types in rats with a history of saline versus cocaine self-administration and in early versus late abstinence after cocaine self-administration. Additional analysis is underway to identify biological functions and cellular pathways implicated by our data and also to further interrogate any notable sex differences in our data set.

Disclosures: A.B. Kawa: None. **J.G. Hashimoto:** None. **A.R. Nectow:** None. **M. Guizzetti:** None. **M.E. Wolf:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.09

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA Grant K01DA045295 to JRM

Title: Changes in stress reactivity and stress-related behaviors following stress-induced escalation of cocaine intake in rats

Authors: *E. A. TEPE[1], A. D. GAULDEN[1], E. K. SIA[1], S. ROLLINS[1], H. MCARDLE[1], G. ALLEN[1], K. SHANNON[2], J. R. MANTSCH[3], J. R. MCREYNOLDS[1];

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Abstract: Stress is an important contributing factor to substance use disorder (SUD) and understanding the neurobiological mechanisms that underlie this contribution is critical. We have shown that repeated daily stress at the time of SA induces an escalation of cocaine intake. This is likely due to long-lasting neuroplastic changes that also increases susceptibility to reinstatement of drug-seeking behavior. This may be explained by changes in stress reactivity as increased stress reactivity is associated with the severity of relapse in humans. We hypothesize that repeated stress at the time of SA increases susceptibility to stress-induced reinstatement and produces long-lasting changes in stress-related behaviors and stress reactivity. Male SD rats were trained to SA cocaine (0.5 mg/kg/inf) on a FR4 schedule in 4 X 30 min SA sessions separated by 5-min drug-free periods. Some rats received intermittent footshock stress during the 5 min drug-free period over 14 days. Rats were then tested for reinstatement to cocaine, footshock, or yohimbine. Stress-escalated rats show increased reinstatement across the 3 modalities. Additional groups of rats, including saline SA rats, were tested for changes in stress reactivity and stress-related behaviors at reinstatement time points for changes in anxiety-related behaviors (elevated plus maze, open field, marble burying), social interaction, and cognition (object location memory) on different days. Finally, rats were subjected to a 30-min restraint stress and blood was sampled from the tail at various time points to measure changes in plasma corticosterone and brains were collected to examine stress-induced cFos activation in stress- and reward-related brain regions. Repeated stress or cocaine SA history results in long-lasting changes in anxiety-like behavior, cognition, and the HPA axis response to stress. While cocaine-experienced rats showed variable changes in passive anxiety-like behavior in the open field and EPM task, rats with a history of combined repeated stress and cocaine SA show increased anxiety-like behavior in more active anxiety-like responses as assessed by a marble burying task. Analysis of social interaction behavior and cFos expression is currently in progress. Combined stress and drug use increase susceptibility to reinstatement of drug-seeking behavior. Stress-induced neuroplastic changes influence the behavioral, hormonal, and neural responses to stress and changes in stress reactivity may be one factor in increased reinstatement behavior observed in stress-escalated rats.

Disclosures: E.A. Tepe: None. **A.D. Gaulden:** None. **E.K. Sia:** None. **S. Rollins:** None. **H. McArdle:** None. **G. Allen:** None. **K. Shannon:** None. **J.R. Mantsch:** None. **J.R. McReynolds:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.10

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA Grant R01 DA049837
NIDA Supplement DA049837

Title: Early life adversity promotes resilience to cocaine addiction-like behaviors in males and produces sex-specific transcriptional changes in the basolateral amygdala

Authors: *A. CUARENTA, R. KARBALAEI, M. DUPUIS, A. HEHN, A. INGRAM, C. DECKERS, S. FAMULARO, M. E. WIMMER, D. A. BANGASSER;
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Abstract: Early life adversity (ELA) is a well-known risk factor for the development of psychiatric disorders including substance use disorder (SUD). However, stress that is not overwhelming may promote resilience later in life. Therefore, ELA has the potential to produce behavioral and neurological changes that may be adaptive in some circumstances and maladaptive in others. In our laboratory, we use the limited bedding and nesting (LBN) paradigm in rats to model mild ELA. Our prior research shows LBN reduces morphine self-administration in adult male, but not female rats. We are now extending this to work to determine whether changes in reinforcing efficacy for morphine also apply to another class of drug: cocaine. The basolateral amygdala (BLA) is a region critical for behavioral responses to stress and is a key regulator of reward circuitry. We are beginning to investigate the molecular correlates induced by LBN. We used RNAseq to assess LBN-induced transcriptional changes in the BLA. Our preliminary behavioral analysis demonstrates that male rats exposed to LBN self-administer lower levels of cocaine (0.5 mg/kg/infusion) than control males. This behavioral change is not exhibited in female rats. We also find that LBN induces sex-specific changes in transcription. RNA sequencing was conducted to delineate the effect LBN had on the transcriptional profile of the BLA in adult rats (male control, $n = 4$; female control, $n = 5$; male LBN, $n = 5$; female LBN, $n = 4$). We used rank-rank hypergeometric overlap (RRHO) analysis to compare overall gene expression pattern in males and females induced by LBN. We found that LBN induces sex-specific changes in transcription. Specifically, we see significant distinction between genes upregulated in males and downregulated in females due to LBN. We narrowed our analysis to genes showing a significant difference (LogFC |0.58| and FDR 0.1) between control and LBN and found 209 differentially expressed genes (DEGs) in females and 149 DEGs in males. These changes in gene expression were predominantly sex specific as only 11 genes were altered by LBN in males and females. The transcriptional changes in males may promote resilience to drug taking behavior. Altogether these findings further our understanding of the effects of ELA on addiction-like traits and the transcriptome in adulthood. Opioids and psychostimulants produce divergent changes at the structural level, and the molecular signatures of each drug are distinct in most brain regions. Therefore, it is crucial to understand how ELA impacts molecular and behavioral outcomes in a sex-specific manner. Understanding these mechanisms may lead to novel therapeutical techniques relevant to SUD.

Disclosures: A. Cuarenta: None. **R. Karbalaei:** None. **M. Dupuis:** None. **A. Hehn:** None. **A. Ingram:** None. **C. Deckers:** None. **S. Famularo:** None. **M.E. Wimmer:** None. **D.A. Bangasser:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.11

Title: WITHDRAWN

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.12

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA14328

Title: Selective and intake-dependent plasticity in nucleus accumbens group 1 metabotropic glutamate receptors function following cocaine self-administration

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Abstract: Prolonged high level cocaine abuse leads to severe drug addiction in humans. This pattern of drug abuse leads to gradual increase in drug intake over time and produces persistent long-term drug craving during periods of abstinence. We can model this pattern of drug abuse by using extended-access cocaine self-administration in rats (LgA, 6hr daily session). A major obstacle in the treatment of addiction has been the propensity to relapse, often mediated by drug-associated cues, even after prolonged period of abstinence from drug use. Recent work suggests that glutamatergic signaling has an important role in cocaine addiction and particularly in drug seeking and relapse. In particular, group 1 metabotropic mGlu1/5 receptors have been shown to be important for both drug taking and drug seeking; and therefore, they have been pursued as promising targets for therapeutic development. Male Sprague-Dawley rats were trained to self-administer cocaine (FR1; 1.0 mg/kg/200 µl/inf) during either 2-hr (ShA) or 6-hr 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 mGlu1/5 receptor antagonist [JNJ16259685 (0.015 mg/kg, sc) or MTEP (3 mg/kg, ip)]. Following a short abstinence period (3 or 10 days), the systemic blockade of mGlu5 receptor reduced drug seeking only in ShA subjects without affecting the LgA animals, while mGlu1 receptor blockade was effective in reducing drug seeking in both cocaine treatment groups. However, after a long abstinence period (60 days), the

systemic blockade of either receptor significantly reduced drug seeking in both ShA and LgA rats. It has been demonstrated that intracerebral infusion of MTEP (3 µg/side) into either NAcore or NAshell after 10 days of abstinence leads to a decrease in drug seeking in ShA rats, whereas blockade of NAshell mGluR1 does not block drug seeking. However, our results in LgA cocaine treated rats suggest that blockade of mGluR5 in NAcore or NAshell after 10 days of abstinence was not effective in reducing drug seeking. These results suggest that high level cocaine use produce a transient intake dependent plasticity in mGluR5, but not in mGluR1, function in the brain. Moreover, our data point to nucleus accumbens core and shell as anatomical substrates contributing to the selective modulation of mGluR5 function in LgA rats. Our observations suggest that systemic activation of mGluR5, during early abstinent period may ameliorate the persistent drug craving present during prolonged periods of abstinence.

Disclosures: M. Ghasemzadeh: None. **D. Sharma:** None. **A. Qasem:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.13

Topic: G.09. Drugs of Abuse and Addiction

Support: DA049930
DA046141

Title: Retinoic acid-mediated homeostatic plasticity in the nucleus accumbens core contributes to incubation of cocaine craving

Authors: *A. L. MOUTIER[1], A. M. WUNSCH[1], E.-K. HWANG[1], T. A. GREEN[2], M. E. WOLF[1];
[1]Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR; [2]PharmTox, UT Med. Br., Galveston, TX

Abstract: Incubation of cocaine craving refers to the progressive intensification of cue-induced craving that occurs during forced abstinence from extended-access cocaine self-administration. We showed previously that Ca^{2+}-permeable AMPA receptors (CP-AMPAR) accumulate in excitatory synapses of nucleus accumbens (NAc) core medium spiny neurons (MSN) after ~1 month of abstinence and thereafter their activation is required for expression of incubation. We hypothesize that CP-AMPAR upregulation represents homeostatic plasticity (scaling up). One form of synaptic scaling involves activity-dependent regulation of dendritic protein translation by retinoic acid (RA). In hippocampal neurons, blockade of neuronal activity disinhibits RA synthesis, leading to GluA1 translation and CP-AMPAR synaptic insertion. We hypothesize that reduced activity in NAc circuits during cocaine abstinence increases RA synthesis in NAc core MSN, leading to increased CP-AMPAR levels. To test this hypothesis, we used viral vectors to

interfere with RA synthesis or degradation in the NAc core during incubation of cocaine craving. First, we increased RA by knocking down Cyp26b1, an enzyme required for degrading RA. Rats self-administered cocaine and then underwent cue-induced seeking tests on withdrawal day (WD) 1 and WD15 (a 'threshold' time for incubation). Rats expressing Cyp26b1 shRNA exhibited 'incubated' seeking on WD15 compared to WD1 whereas control rats did not. Using slice electrophysiology, we found synaptic CP-AMPARs in Cyp26b1 shRNA-expressing MSN (WD15-18) but not in MSN from scramble controls. Second, we reduced RA levels during forced abstinence by knocking down Aldh1a1, the main enzyme that synthesizes RA. In MSN expressing the Aldh1a1 shRNA, synaptic CP-AMPARs were reduced in late withdrawal compared to scrambled controls (WD42-60). However, we were unable to detect an effect of this manipulation on incubated cocaine seeking (WD40), probably because relatively few MSN were infected. Lastly, immunoblotting studies are underway exploring how chronic manipulation of RA synthesis and degradation alter levels of RARα, GluA1, and GluA2 in the NAc of rats expressing Cyp26b1 shRNA, Aldh1a1 shRNA, or scrambled viruses. The present findings, together with other work showing that manipulating RA levels in NAc slices bidirectionally regulates synaptic CP-AMPAR levels,support the hypothesis that an increase in RA signaling during abstinence contributes to the synaptic accumulation of CP-AMPARs that ultimately mediates incubation of cocaine craving.

Disclosures: A.L. Moutier: None. **A.M. Wunsch:** None. **E. Hwang:** None. **T.A. Green:** None. **M.E. Wolf:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.14

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH / NIDA IRP
DA000069
Howard Hughes Medical Institute

Title: Novel chemogenetic receptor activated by cocaine decreases cocaine self-administration in rats via negative feedback modulation of the lateral habenula.

Authors: *J. L. GOMEZ[1], C. J. MAGNUS[2], M. R. LEVINSTEIN[1], M. L. CARLTON[1], E. N. VENTRIGLIA[1], J. BONAVENTURA[3], M. MICHAELIDES[1], S. M. STERNSON[2];
[1]IRP, Natl. Inst. on Drug Abuse, Baltimore, MD; [2]Neurosciences, Janelia Res. Campus, HHMI, La Jolla, CA; [3]Univ. De Barcelona, Barcelona, Spain

Abstract: Behavioral and/or pharmacological therapies for substance use disorder (SUD) have varying success rates. Current pharmacological approaches have limitations such as compliance,

off target side-effects, and non-selectivity. To test the contributions of neural populations to SUD, precisely tied to the self-administered time course of addictive drugs, we have developed chemogenetic receptors that are directly responsive to cocaine. Chimeric ion channels, based on the ligand binding domain of the α7 nicotinic acetylcholine receptor and the ion pore transmembrane domain of the cation-selective serotonin 3a receptor, were engineered through ligand binding domain mutagenesis to bind cocaine (K_i : 0.033 μM). These receptors, called coca-5HT3, were gated by cocaine ($EC50_{cocaine}$: 1.5±0.3 μM) and elicited neuronal depolarization and increased action potential frequency at cocaine concentrations of 1-3 μM. We used coca-5HT3 to investigate the influence of cocaine-induced activation of lateral habenula (LHb), an anti-reward brain region, to produce negative-feedback regulation of intravenous cocaine self-administration (IVSA). Long-Evans rats were injected with AAV-hSyn-Coca5HT3-ires-mCherry into the LHb (Coca) or underwent sham surgery (Sham). After operant conditioning using food pellets, rats were switched to a fixed-ratio cocaine IVSA paradigm for 10 days. Rats were then tested using a dose response procedure for cocaine IVSA followed by euthanasia and immunohistochemistry to confirm mCherry expression. There was no significant difference in food self-administration between groups (Coca = Sham). Both Coca and Sham rats acquired cocaine IVSA and administered the same number of infusions per session during training. However, during dose response testing, Coca rats showed a downward shift in the cocaine unit dose response curve, indicating a depression of cocaine IVSA. These results demonstrate a closed-loop chemogenetic strategy based on ion channels engineered for agonism by commonly abused drugs. We found that that a cocaine-activated chemogenetic system targeted to anti-reward brain circuits creates an artificial negative feedback process that suppresses cocaine seeking selectively, without affecting natural rewards. This type of chemogenetic strategy may have potential as a novel therapeutic approach for individuals with serious SUDs who do not respond to traditional methods.

Disclosures: J.L. Gomez: None. **C.J. Magnus:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Redpin Therapeutics Inc.. **M.R. Levinstein:** None. **M.L. Carlton:** None. **E.N. Ventriglia:** None. **J. Bonaventura:** None. **M. Michaelides:** 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.; AstraZeneca, Redpin Therapeutics, Attune Neurosciences. **S.M. Sternson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Redpin Therapeutics Inc..

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.15

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA Grant K01DA045295 to JRM

Title: Stress-induced Escalation of Cocaine Self-Administration is Modulated by Sex and Endocannabinoid Signaling.

Authors: *A. D. GAULDEN, E. A. TEPE, E. SIA, S. S. ROLLINS, J. R. MCREYNOLDS; Pharmacol. and Systems Physiol., Univ. of Cincinnati Col. of Med., Cincinnati, OH

Abstract: Stress exacerbates the development, maintenance, and resurgence of substance use disorder (SUD). For many individuals, stress is an unavoidable part of life; yet, we do not fully understand how stress can interact with substance use, and treatments for cocaine use disorder remain elusive. There are known sex differences in both SUD and stress reactivity, therefore, we hypothesized that male and female rats may differ in stress-driven changes in cocaine self-administration (SA). Male and female SD rats were trained to SA cocaine in 4x30 min SA sessions separated by 5-min drug-free periods. Some rats received shock in the SA chamber during the 5 min drug-free period over 14 days. In both sexes, footshock stress induces a significant increase in cocaine intake though stress increased cocaine SA earlier and to a greater degree in female rats compared to male rats. Across sexes, a history of combined stress and cocaine SA resulted in delayed extinction of cocaine-seeking behavior, though this effect is greater in females. Stress-escalated rats show increased sensitivity to cocaine- and stress-induced reinstatement across sexes. This suggests that stress at the time of cocaine SA induces long-lasting neuroadaptations in signaling systems at the intersection of stress and reward, such as endocannabinoid (eCB) signaling. Therefore, we hypothesize that stress-induced escalation of cocaine SA may be regulated in part by eCB signaling in both sexes. Systemic administration of the cannabinoid receptor 1 (CB1R) antagonist Rimonabant attenuated cocaine intake in stress-escalated rats, and females showed a greater overall sensitivity to Rimonabant treatment. To understand potential circuit-specific contributions of eCB signaling, we are currently examining changes in cocaine-induced dopamine signaling, via *in vivo* fiber photometry in the nucleus accumbens shell, in rats with a history of stress and cocaine SA. Furthermore, we are investigating the role of prelimbic cortex (PLc) eCB signaling in enhanced cocaine -induced reinstatement in rats with a history of stress. Our preliminary data indicates that intra-PLc administration of rimonabant attenuates cocaine-induced reinstatement in stress-escalated rats. Together, our results indicate that sex and stress modulate the expression of cocaine taking and seeking in distinct ways. We propose eCB signaling as a candidate mechanism by which stress exacerbates addiction-like phenotypes. Our recent work outlines the distinct neurocircuitry by which stress and eCB signaling regulate cocaine taking and seeking, and advocates for a more detailed understanding of eCB involvement in substance use disorders.

Disclosures: A.D. Gaulden: None. **E.A. Tepe:** None. **E. Sia:** None. **S.S. Rollins:** None. **J.R. McReynolds:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.16

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH GM139807
NIH DA042057

Title: Identification of Fos-neuronal ensembles in the Nucleus Accumbens that participate in cocaine-primed reinstatement in female and male rats.

Authors: *A. TROMBLEY[1], S. KALLAKURI[2], S. A. PERRINE[2];
[2]Psychiatry and Behavioral Neurosciences, [1]Wayne State Univ., Detroit, MI

Abstract: Despite decades of research on cocaine use disorder (CUD), persistently high relapse rates continue to contribute to a vicious public health crisis. Elucidating the mechanisms that underlie cocaine relapse is a key step in identifying new treatment targets for CUD. In the Nucleus Accumbens (NAc) of male rats, a sparse group of highly active, Fos-expressing neurons, known as neuronal ensembles, encode learned associations involved in the reinstatement of cocaine-seeking and promote relapse. However, the role of these ensembles in this paradigm has only been tested in male rats. This gap is important to address because, as females exhibit greater cocaine-seeking following abstinence, the role of Fos-based ensembles in cocaine-reinstatement may differ between sexes. To examine this knowledge gap, female and male Wistar rats underwent ten 3-hour sessions of intravenous cocaine self-administration (0.5 mg/kg/infusion) followed by a 14-day drug-free period in their home cages. On the 14th drug-free day, animals were primed with an injection of cocaine (10 mg/kg, IP) and immediately placed into the self-administration chamber. Active lever pressing did not result in an infusion of cocaine but was recorded. After the session, animals were euthanized, and their brains were processed for Fos analysis via immunofluorescent microscopy. We hypothesized that females would exhibit greater cocaine-seeking and display greater Fos activation in the NAc than their male counterparts. Our results so far indicate that this paradigm induces cocaine-primed reinstatement in both males and females. This study remains ongoing with Fos analysis underway. This work will elucidate the role of Fos-ensembles in contributing to the known sex effects related to relapse to cocaine-seeking, and ultimately may inform treatment for men and women with CUD.

Disclosures: **A. Trombley:** None. **S. Kallakuri:** None. **S.A. Perrine:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.17

Topic: G.09. Drugs of Abuse and Addiction

Support: UPenn Undergraduate Neuroscience Research Fellowship

Title: The role of amygdalar GLP-1 signaling in cocaine withdrawal behaviors and reinstatement

Authors: *R. MERKEL, R. HERMAN, Y. ZHANG, H. D. SCHMIDT;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Activation of central glucagon-like peptide-1 receptors (GLP-1Rs) attenuates voluntary cocaine taking and cocaine-seeking behavior during abstinence. However, the neural circuits mediating the suppressive effects of GLP-1R agonists on cocaine-mediated behaviors are not fully described. GLP-1Rs are abundantly expressed in the central amygdala (CeA), a nucleus necessary for drug-related learning and cocaine seeking. We hypothesized that activation of GLP-1Rs in the CeA would attenuate the reinstatement of cocaine-seeking behavior. Here, we show that intra-CeA administration of the GLP-1R agonist exendin-4 (Ex-4) dose-dependently attenuated the ability of an acute priming injection of cocaine and drug-paired cues to reinstate cocaine seeking without affecting ad libitum food intake or kaolin intake. Neural tracing and fluorescent in situ hybridization techniques were used to determine the targets of GLP-1R-expressing neurons in the CeA. We hypothesized that the BNST is a primary downstream target of CeA GLP-1R-expressing neurons due to its role in withdrawal-mediated phenotypes. Our data suggest that GLP-1Rs are expressed on a subset of CeA GABA neurons that project from the central medial region of the amygdala to the BNST. Additionally, we identified a novel group of GLP-1R expressing GABA interneurons that reside in the central lateral region of the amygdala. Given the role of the CeA in both drug and anxiety circuitry, CeA GLP-1 signaling may regulate drug reinforcement indirectly by attenuating anxiety-like phenotypes that promote drug seeking during cocaine withdrawal . Preliminary data suggest that systemic administration of Ex-4 reverses the anxiogenic properties of cocaine withdrawal following 14 days of abstinence. These findings establish a functional role for CeA GLP-1R signaling in cocaine reinstatement and further support re-purposing GLP-1R agonists for treating CUD, while highlighting a novel avenue of exploration for the intersection of anxiety and drug-mediated behaviors.

Disclosures: **R. Merkel:** None. **R. Herman:** None. **Y. Zhang:** None. **H.D. Schmidt:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.18

Topic: G.09. Drugs of Abuse and Addiction

Support: Commonwealth of Pennsylvania CURE Addiction Center of Excellence: Brain Mechanisms of Relapse and Recovery (Childress)
NIDA U54 DA039002 (Kampman and Childress)

NIDA R01 DA039215 (Childress)
NIDA UG1 DA050209 (Kampman and Childress)

Title: Dangerous liaisons? In cocaine cue-reactivity paradigms, non-drug cues may acquire the ability to trigger relapse-predictive limbic activation

Authors: A. R. CHILDRESS[1], K. JAGANNATHAN[2], P. REGIER[1], T. FRANKLIN[1], R. WETHERILL[1], D. LANGLEBEN[1], K. KAMPMAN[1], C. P. O'BRIEN[1];
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Abstract: Aims: Seeing a street corner where we once experienced the smell of warm cinnamon rolls may itself trigger salivation, desire and food-seeking, even though the street corner itself was never *directly* linked to eating the cinnamon roll, only to its smell. The sight of the street corner is termed a 'second-order' signal for the desired food. In the human addiction domain, 'second order' signals for drug (e.g., ***non***-drug cues that signal drug-related cues, rather than the drug itself) likely play a role in relapse to drug-seeking, but this has not been studied. *We hypothesized that drug cue-reactivity paradigms where **non**-drug cues often precede cocaine cues would offer an opportunity to model a 'dangerous liaison': the development of 'second order' activation of brain motivational (limbic) circuitry by **non**-drug cues - and further, that these 'second order' responses would be linked to future relapse.* **Methods:** Treatment-seeking cocaine inpatients (n=12 pilot) were studied in a 'fast' event-related BOLD fMRI paradigm (3T; TR 2s), featuring 24 non-drug and 24 cocaine-related visual cues of 1000 ms duration presented in quasi-random order, repeated once (96 trials total). Image pre-processing (SPM 8) was followed by linear regression (Time Modulation) to model (first level) the change in limbic response to repeated ***non***-drug cues, first and second halves of the time series. Brain response (r maps) for cocaine patients with "GOOD" (avg. 20% urines cocaine-positive) vs. "POOR" (avg. 88% urines cocaine-positive) drug use outcomes during outpatient treatment were compared with a two-sample T-test. **Results:** Consistent with our hypothesis, cocaine patients who went on to POOR clinical outcome showed progressive *increases* in multiple limbic regions to ***non***-drug cues in the second half of the task, and these were significantly greater than the GOOD outcome group in amygdala, v. striatum, v. pallidum, hippocampus/parahippocampus, and insula (t range, 2-7). In contrast, the GOOD outcome group differentially activated a cortical ('regulatory') region in the second task half. **Conclusions:** These preliminary results suggest that 'second order' effects (limbic brain activation, similar to first-order responses) can develop to ***non***-drug cues. Importantly, cocaine patients who readily develop these 'second order' effects in the lab paradigm proceed to POOR clinical outcome, suggesting the relevance of these phenomena for screening anti-relapse interventions, and for identifying patients at relapse risk. Formal paradigms that include explicitly unpaired signals are needed to confirm the associative nature of the observed effects; these designs are upcoming in our laboratory.

Disclosures: A.R. Childress: None. **K. Jagannathan:** None. **P. Regier:** None. **T. Franklin:** None. **R. Wetherill:** None. **D. Langleben:** None. **K. Kampman:** None. **C.P. O'Brien:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.19

Title: WITHDRAWN

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.20

Topic: G.09. Drugs of Abuse and Addiction

Support: R01DA052953
5R01DA037216
VA-Merit Award IO1BX004440
Roy J. Carver Charitable Trust
DA049139
DA048055

Title: Carbonic anhydrase 4 deletion prevents cocaine withdrawal induced synaptic and behavior adaptations

Authors: *S. C. GUPTA[1], R. J. TAUGHER-HEBL[2], A. GHOBBEH[1], R. FAN[1], R. T. LALUMIERE[3], J. A. WEMMIE[1];
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Abstract: Chronic cocaine use followed by withdrawal induces changes in synapse structure and function in the nucleus accumbens (NAc), which are thought to underlie subsequent drug-seeking behaviors and relapse. Previous studies suggested that these cocaine-induced synaptic changes depended on acid-sensing ion channels (ASICs) in the NAc and suggested a role for synaptic pH buffering. Here we investigated the potential involvement of carbonic anhydrase 4 (CA4), an extracellular enzyme in brain thought to catalyze pH buffering at synapses. We examined effects of CA4 on ASIC activation during synaptic transmission in medium spiny neurons (MSNs) in the NAc core, as well as on cocaine-induced synaptic changes and behavior. We found that CA4 protein is expressed in the NAc in mice and is present in synaptosomes. Disrupting CA4 either globally, or locally in NAc MSNs, increased ASIC-mediated synaptic currents and protected against cocaine withdrawal-induced changes, including changes in: AMPAR/NMDAR ratio, AMPAR subunit composition, miniature EPSCs, synaptic plasticity, dendritic spine morphology, and locomotor responses to an acute cocaine challenge. Finally, we found that disrupting CA4 reduced cocaine-seeking behavior and AMPAR/NMDAR ratio after

withdrawal from cocaine self-administration. Together, our results suggest that CA4 acts post-synaptically in MSNs to regulate ASICs, and that CA4 disruption prevents synaptic and behavioral changes caused by cocaine exposure and withdrawal. These findings raise the possibility that CA4 might be a novel therapeutic target for reducing synaptic and behavioral changes thought to underlie addiction and relapse.

Disclosures: S.C. Gupta: None. **R.J. Taugher-Hebl:** None. **A. Ghobbeh:** None. **R. Fan:** None. **R.T. LaLumiere:** None. **J.A. Wemmie:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.21

Topic: G.09. Drugs of Abuse and Addiction

Title: Alterations in dendritic spines of differentially reared rats following cue-induced reinstatement of cocaine-seeking

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Abstract: Early environmental experience produces structural and neurochemical changes that impact drug abuse susceptibility later in life. Altering the early environment by rearing rats in enriched (EC) or impoverished (IC) conditions post-weaning, produces a protective effect in EC rats; demonstrated as EC rats self-administer less psychostimulant than IC rats at low doses. Previous work in our laboratory has implicated the infralimbic cortex (IL) to nucleus accumbens shell (NAshell) and the prelimbic cortex (PrL) to nucleus accumbens core (NAcore) projections in this protective effect following cocaine reinstatement. The current study sought to investigate alterations to dendritic spine morphology in the IL and PrL of differentially reared rats following cue-induced reinstatement of cocaine seeking. Male Sprague Dawley rats arrived in the lab at 21 days of age and were reared in EC or IC contexts for 30 days. Following the rearing period rats were infused with FLAG and retrograde Cre dependent AAVs into the NAshell and IL or the NAcore and PrL, and implanted with jugular catheters. Rats underwent a standard 2-hr cocaine or saline self-administration paradigm, including acquisition, extinction and cue-induced reinstatement. Following cue-induced reinstatement, rats were perfused, and brains were extracted for immunohistochemistry, confocal imaging, and spine quantification. Proximal apical and basal spine segments were quantified in the nucleus accumbens projecting PrL and IL neurons. Results show greater spine density and spine head diameter in proximal apical and basal segments in the IL of cocaine compared to saline animals, independent of rearing condition. Proximal apical and basal spine head diameter was also greater in the PrL of cocaine compared

to saline rats. In the IL we observed that EC cocaine rats had greater proximal apical spine density, but less basal spine density compared to IC rats. IC rats also had a greater proximal apical spine head diameter in the IL than EC rats independent of treatment. In the PrL, IC rats displayed a greater basal spine density than EC rats. These findings confirm previous studies demonstrating greater spine head diameter in cocaine compared to saline rats in the PrL. Results suggest that enrichment rearing alters spine morphology in the IL and PrL, which may contribute to the protective effect observed in EC rats.

Disclosures: A. Zimbelman: None. **B.M. Siemsen:** None. **M.D. Scofield:** None. **M.J. Gill:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.22

Topic: G.09. Drugs of Abuse and Addiction

Support: CONACYT-FOSISS project No. 0201493
CONACYT-Cátedras project No. 2358948

Title: Functional pathology in cocaine use disorder with polysubstance use: a functional connectivity analysis.

Authors: *S. DUVVADA[1], J. R. TOLEDO[2], V. ALLURI[1], E. A. GARZA-VILLARREAL[2]; [1]Intl. Inst. of Information Technol., Hyderabad, India; [2]Inst. of Neurobio., Univ. Nacional Autónoma de México (UNAM), Querétaro, Mexico

Abstract: Abstract Long-term cocaine abuse has been associated with alterations across different brain networks (Ma et al. 2015). In a previous study, we found white and gray matter pathology among interconnections between frontal hemispheres, frontal to parieto-temporal lobes and subcortical regions (Rasgado-Toledo et al. 2020). In this study, we expanded our results by investigating variability in functional connectivity (FC) between regions identified with gray and white matter pathology in cocaine use disorder patients (CUD). We included 63 CUD patients along with 42 matched non-dependent healthy controls (HC), paired by age, sex, handedness and education, recruited as part of the SUDMEX_CONN database (Angeles-Valdez et al., 2022). FC was computed using time-series data based on the Desikan Killiany Atlas. We performed the Mann-Whitney test for the identification of significant differences between groups. These were further checked using a non-parametric permutation test (10,000 permutations). Results revealed significantly greater FC between the right posterior cingulate (PCC) and postcentral gyrus for CUD than HC. Although this region is outside the common studied mesolimbic-cortical system, this is consistent with previous cocaine cue-craving related task fMRI activations in PCC (Duncan et al. 2007), and higher activations to inhibition tasks

within the postcentral gyrus for patients with positive cocaine use (Prisciandaro et al. 2013). We also found significantly decreased FC for CUD among several right hemispheric regions of the prefrontal, subcortical and cerebellum suggesting a pathological network state. Interestingly, the higher connectivity between the PCC, a node of the default mode network, and the postcentral gyrus, the primary somatosensory cortex, may imply an increase in interoception possibly related to compulsive behaviour.

Disclosures: S. Duvvada: None. **J.R. Toledo:** None. **V. Alluri:** None. **E.A. Garza-Villarreal:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.23

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA052967
NIH Grant DA046227
NIH Grant DA052101

Title: Cell Subtype Specific Role of Nab2 in Cocaine Seeking Behavior

Authors: *E. Y. CHOI[1,2], R. CHANDRA[1,3], K. K. COVER[4], M. MCGLINCY[1], A. CHOW[1], M. LOBO[1];
[1]Dept. of Anat. & Neurobio., [2]Grad. Program in Life Sciences, Biochem. & Mol. Biol., [3]Virus Vector Core, Univ. of Maryland Sch. of Med., Baltimore, MD; [4]Natl. Eye Inst., Bethesda, MD

Abstract: Substance use disorder is a debilitating chronic disease which is a leading cause of disability around the world. Drug seeking after repeated drug exposure is prevalent despite the devastating personal consequences. The nucleus accumbens (NAc, a.k.a. ventral striatum) is a major brain hub that mediates reward behavior. The NAc plays a role in drug seeking and addiction related behaviors in response to drug exposure. Studies have shown that exposure to psychostimulants, such as cocaine, is associated with molecular and functional imbalance in the two medium spiny neuron subtypes (MSNs) in the NAc, the dopamine receptor 1 and 2 enriched MSNs (D1-MSNs and D2-MSNs). While the study of D1-MSNs in the NAc with exposure to cocaine has been and is being extensively done, molecular changes and functional imbalance in the D2-MSNs remain largely elusive. We have previously reported the down regulated expression of a transcription factor, early growth response 3 (Egr3), in D2-MSNs in the NAc with exposure to cocaine. Furthermore, mice with Egr3 overexpression in D2-MSNs in the NAc showed altered extinction of cocaine seeking behavior after forced abstinence from cocaine self-administration. In this study, we show that the NGFI-A binding protein 2 (Nab2), a corepressor of Egr3, is altered in bidirectional manner to Egr3 expression in D2-MSNs of mice repeatedly

exposed to cocaine. Furthermore, we show that Nab2 overexpression leads to decreased levels of Egr3, and Nab2 inhibition leads to increased levels of Egr3. A2A-Cre mice with D2-MSN specific knock-down of Nab2 in the NAc showed decreased cocaine-induced locomotion. We then tested if Nab2 perturbation in D2-MSNs has a behavioral impact in cocaine self-administration. A2A-Cre mice with D2-MSN specific knockdown of Nab2 in the NAc showed reduced cocaine intake during the 10 days of 2hr cocaine self-administration sessions compared to the control mice. These mice also made significantly reduced cocaine-paired active nose pokes during cocaine seeking test after 10 days of cocaine self-administration. Interestingly, we observed a sex specific difference in which we saw a greater degree of reduction in cocaine intake in female mice compared to male mice during cocaine self-administration. Our future plan is to study the brain tissues collected from these animals to elucidate transcriptomic changes occurring in selective cell types in the NAc via single nuclei RNA-seq. Collectively, our studies identify distinct cell type specific molecular mechanisms of Nab2 in behavioral responses to cocaine including drug seeking behavior.

Disclosures: **E.Y. Choi:** None. **R. Chandra:** None. **K.K. Cover:** None. **M. McGlincy:** None. **A. Chow:** None. **M. Lobo:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.24

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH-R01DA041455

Title: Inhibition of Microglial Phagocytosis Reduces Cocaine-seeking in Male Rats Following a Protracted 30-day Abstinence Period

Authors: *T. BELLINGER[1], A. TESTEN[1], J. VANRYZIN[1], K. J. REISSNER[2];
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Abstract: The activated microglial response to drugs of abuse has been implicated in the development and maintenance of substance use disorders. Phagocytosis is a prominent function of activated microglia, which is associated with behavioral consequences in both development and pathology. Given this, we sought to determine whether microglial phagocytosis contributes to cocaine-seeking behaviors during abstinence. To investigate this question, we utilized long-access (6h/day) cocaine self-administration in adult male Sprague Dawley rats for ten days, followed by a 30-day home cage abstinence. Starting on abstinence day 1, rats received intra-NAc microinjections of neutrophil inhibitory factor peptide (NIF, 0.5 uL per hemisphere) or vehicle every 7 days (4 microinjections total). The NIF peptide binds to the CD11b subunit of the microglial C3 receptor, inhibiting the initiation of microglial phagocytosis (Moyle et al.,

1994, Kopec et al., 2018). On abstinence day 30, all rats underwent cue-primed behavioral testing to measure drug-seeking behavior. Rats that received intra-NAc NIF peptide demonstrated a statistically significant reduction in lever-pressing (Vehicle = 254.0 +/- 26.25, NIF = 183.8 +/- 19.95, p-value = 0.0380). Ongoing experiments will analyze microglia morphology as well as lysosomal activity and evidence of phagocytosis in these samples.

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

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.25

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA- F32DA056191
NIDA-R01DA047843

Title: Mechanisms within VTA-projecting ventral pallidum neurons critical to cocaine-seeking

Authors: *R. R. CAMPBELL, V. RHODES, S. KEY, R. CHANDRA, M. LOBO;
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Abstract: Cocaine induces long-lasting changes within the reward circuitry that promote cocaine-seeking. The ventral pallidum (VP) is one node within the reward pathway known to receive input from and projects to several regions that mediate cocaine-seeking. This includes VP afferents to the ventral tegmental area (VTA-projecting VP) which are required for cocaine relapse. However, the cellular and molecular adaptations that occur within VTA-projecting VP neurons to promote cocaine-seeking are unknown. Here, we demonstrate that inhibition of VTA-projecting VP neurons is sufficient to reduce cue-induced reinstatement of cocaine-seeking in male and female mice following intravenous cocaine-self administration (IVSA). Furthermore, we found that *cFos* mRNA expression within the ventral pallidum is enhanced within male and female mice following cue-induced reinstatement of cocaine-seeking. Currently, we are examining the effects of cocaine IVSA on dendritic remodeling within VTA-projecting VP neurons. Altogether, these investigations aim to reveal the neural adaptations that occur within the VP circuitry to drive cocaine relapse.

Disclosures: R.R. Campbell: None. **V. Rhodes:** None. **S. Key:** None. **R. Chandra:** None. **M. Lobo:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.26

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA048280

Title: Presentation of an aversive white noise causes cocaine intake while inhibiting nucleus accumbens core dopamine signaling

Authors: *E. GRAFELMAN[1], D. WHEELER[1], L. VLACH[1], B. COTE[1], M. GELIN[1], E. GEISE[1], P. LAMBERTON[1], M. HEARING[1], J. R. MANTSCH[2], R. WHEELER[1]; [1]Marquette Univ., Milwaukee, WI; [2]Pharmacol. and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Stressful stimuli have complex effects on the neurophysiological systems that mediate the pursuit of rewards. Dopamine in the nucleus accumbens (NAc) is reduced during exposure to an aversive stimulus. Correspondingly, aversive stimuli can punish reward-seeking behaviors. However, in other situations, the same stimulus can promote drug-seeking. Here we investigated the relationship between aversive stimuli, NAc dopamine, and drug-seeking behaviors using *in vivo* fiber photometry. Female and male rats underwent surgery in which they received an infusion of AAV5-hSyn-dLight into the NAc core and implantation of an optic fiber to the same location. Additionally, rats were implanted with intrajugular catheters. Following recovery, rats were trained to press a lever for an intravenous infusion of cocaine. The opposing lever produced no consequence. After stable responding for the drug reward was achieved, rats were exposed to periods of aversive (90 dB) white noise during the self-administration session. Rats received alternating days of white noise sessions and quiet sessions. Dopamine levels were examined throughout both types of test sessions. The aversive white noise caused a reduction of dopamine in both male and female rats. At the same time, rats self-administered more cocaine during white noise periods than during quiet periods. These data show that an aversive stimulus can increase the motivation to seek a drug reward, while simultaneously inhibiting NAc DA signaling. Ongoing studies are investigating the effect of an innocuous stimulus in this design.

Disclosures: E. Grafelman: None. **D. Wheeler:** None. **L. Vlach:** None. **B. Cote:** None. **M. Gelin:** None. **E. Geise:** None. **P. Lamberton:** None. **M. Hearing:** None. **J.R. Mantsch:** None. **R. Wheeler:** None.

Poster

733. Behavioral and Neural Mechanisms of Cocaine Reinforcement, Seeking, and Reinstatement

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 733.27

Topic: G.09. Drugs of Abuse and Addiction

Support: NIAAA R01AA026281

Title: Investigating the Role of Glyoxalase 1 in Cocaine Induced Locomotor Activation Through Genetic Over Expression

Authors: *E. ALCANTARA[1], C. A. ORTEZ[1], A. ILUSTRISIMO[1], A. A. PALMER[2];
[1]Psychiatry, UC San Diego Hlth., La Jolla, CA; [2]Psychiatry, UCSD, La Jolla, CA

Abstract: Millions of people suffer from cocaine use disorder (CUD) and cocaine related overdoses cause nearly 20,000 deaths in the U.S. Even though CUD has a detrimental impact on society, there are no effective pharmacological treatment options. Previous studies by Silverman et.al (2018) showed the GABA-A agonist Gaboxadol (GBX) potentiates the locomotor activation of cocaine. Other studies by Distler & Palmer (2012) have shown that the methylglyoxal (MG) acts as a partial GABA-A agonist. Glyoxalase 1 (Glo1) is the greatest catabolic pathway for MG, and we chose it as the target to manipulate MG and GABA-A signaling. We investigated the role of Glo1, through pharmacological inhibition of mice on a C57BL/6J background, on it's effect on cocaine induced locomotor activation. We used 120 male/female C57BL/6J animals where Glo1 was pharmaceutically manipulated through the Glo1 inhibitor,S-bromobenzylglutathione cyclopentyl diester (pBBG) at four doses 0, 12.5, 25, and 50 mg/kg while co-administered with 10 mg/kg cocaine. A three-day open field test was done, where mice received saline i.p. on the first two days and a cocaine injection on the final day following pre-treatment with pBBG. Next we tested if Glo1 inhibition with pBBG could block reward seeking behavior to cocaine measured by the conditioned place preference test. 120 male and female C57BL/6J mice were used, and were administered the dose of cocaine previously mentioned. We used a two-compartment unbiased conditioned design. Mice received four days of alternating conditioning trials. After conditioning, mice received a 30-minute drug-free preference test following a 1.5 hours pre-treatment with pBBG. In ongoing studies, we are investigating the role of GLO1, through genetic manipulation, using transgenic overexpressing GLO1 mice on a C57BL/6J background. Similarly, 120 male/female GLO1 overexpressing mice were administered 10 mg/kg cocaine and tested for locomotor activation. We found that inhibiting Glo1 and increasing MG levels, animals who received co-administration of pBBG and cocaine, showed increasing pBBG dose potentiated the locomotor activation caused by cocaine. Lastly, animals showed robust CPP however, administration of pBBG was not able to block reward seeking behavior in the cpp paradigm and animals continued to exhibit drug seeking behavior at every dose of pBBG. Although Glo1 manipulation through inhibition via pBBG doesnt affect drug seeking behavior as measured by CPP, co-administration with cocaine does alter locomotor activation. These findings suggest that Glo1 plays a role in CUD as locomotor activation has long been studied in relation to the addictive properties of cocaine.

Disclosures: E. Alcantara: None. **C.A. Ortez:** None. **A. Ilustrisimo:** None. **A.A. Palmer:** None.

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.01

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA P01DA047233
NIMH R01MH051399

Title: Assessing the effects of ΔFOSB induction on the in vivo activity of nucleus accumbens medium spiny neurons

Authors: *T. MARKOVIC, A. GODINO, E. M. PARISE, T. M. GYLES, E. J. NESTLER; Icahn Sch. of Med. at Mount Sinai, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: ΔFOSB has been shown to be a key transcription factor that mediates gene expression changes in the nucleus accumbens (NAc), a brain area that integrates rewarding and aversive stimuli, in response to chronic exposure to stress or drugs of abuse. The NAc is composed of GABAergic medium spiny neurons (MSNs) that express either dopamine receptor 1 (D1) or dopamine receptor 2 (D2), which differ in their outputs to subcortical structures. Previous work in rodents demonstrated that chronic exposure to several types of stimuli induce ΔFOSB in the NAc in a cell-type-specific manner: drugs of abuse such as cocaine predominantly induce ΔFOSB in D1 MSNs, chronic stress induces the protein in D2 MSNs in stress-susceptible animals but in D1 MSNs in stress-resilient animals, natural rewards induce ΔFOSB in both D1 and D2 MSNs, and antipsychotic drugs predominantly induce it in D2 MSNs. This cell-type-specific regulation of ΔFOSB expression in the NAc correlates with differential effects of the protein on synaptic properties of NAc MSNs: ΔFOSB decreases excitatory synaptic strength and increases silent synapses onto D1 MSNs analyzed ex vivo, with opposite effects seen for D2 MSNs. However, no studies have investigated how changes in ΔFOSB expression levels in the NAc alter the in vivo activity of NAc MSNs upon exposure to rewarding or aversive stimuli. To address this gap in knowledge, we injected D1-Cre and D2-Cre mice with Cre-dependent adeno-associated viral vectors that express a calcium sensor and epigenome-editing tools that either induce or repress endogenous ΔFOSB. We then recorded in vivo neuronal activity of D1 and D2 MSNs using fiber photometry in response to social reward, saccharin reward, foot shock, and drug rewards (cocaine or morphine). Our preliminary findings demonstrate that repression of ΔFOSB increases calcium transients in D1 MSNs upon social interaction (a form of natural reward), whereas induction of ΔFOSB increases calcium transients in D2 MSNs in the same assay. We found similar results in response to saccharin reward in a self-administration paradigm. This finding of opposite in vivo modulation of D1 vs. D2 MSN activity by ΔFOSB directly relates the downstream consequences of transcriptional regulation to altered circuit activity and will help delineate how such cell-autonomous mechanisms control complex behavioral responses.

Disclosures: T. Markovic: None. **A. Godino:** None. **E.M. Parise:** None. **T.M. Gyles:** None. **E.J. Nestler:** None.

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.02

Topic: G.09. Drugs of Abuse and Addiction

Support: P01DA047233
R01DA007359

Title: Circuit-wide gene network analysis reveals a role for phosphodiesterase enzymes in cocaine addiction

Authors: *C. D. TEAGUE[1], X. ZHOU[1], F. J. MARTINEZ[3], A. M. MINIER-TORIBIO[4], K. E. LUCERNE[1], A. GODINO[4], R. FUTAMURA[2], C. J. BROWNE[5], Y. VAN DER ZEE[6], A. RAMAKRISHNAN[3], D. M. WALKER[7], L. SHEN[1], B. ZHANG[1], E. J. NESTLER[2]; [2]Neurosci., [1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [4]Nash Family Dept. of Neurosci., [5]Neurosci., [3]Icahn Sch. of Med. at Mount Sinai, New York, NY; [6]Dept. of Psychiatry and Neuropsychology, Maastricht Univ., Maastricht, Netherlands; [7]Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Cocaine use disorder is a serious public health issue without an effective pharmacological treatment. Successful treatments are hindered in part by an incomplete understanding of the molecular mechanisms in the brain that drive long-lasting maladaptive plasticity and addiction-like behaviors. In this study, we conducted unbiased gene co-expression network analysis on a published RNA sequencing (RNA-seq) dataset comprising 6 interconnected regions of the brain's reward circuitry from mice that underwent saline or cocaine self-administration, followed by a 24-hour or 30-day withdrawal period and a saline or cocaine challenge. We identify phosphodiesterase 1b (*Pde1b*), a Ca^{2+}/calmodulin-dependent enzyme that catalyzes the hydrolysis of cAMP and cGMP, as a key regulator of a gene network in the nucleus accumbens (NAc) that was bioinformatically associated with addiction-like behavior. Within the NAc, the genes in this network are primarily enriched in *Drd1*- and *Drd2*-expressing medium spiny neurons (D1 and D2 MSNs). Cell-type-specific measurements reveal increased levels of *Pde1b* within D2 MSNs in the NAc following chronic cocaine treatment. To further investigate the effect of cocaine on gene transcription within D2 MSNs, we performed RNA-seq on isolated D2 MSNs from mice treated with chronic cocaine and identified differential regulation of numerous other genes within this network. At the behavioral level, viral-mediated overexpression of *Pde1b* in NAc D1 or D2 MSNs oppositely regulates the acute locomotor response and locomotor sensitization to cocaine, without affecting conditioned place preference for cocaine. Importantly, *Pde1b* overexpression in the NAc elevates active lever presses, infusions, and drug intake during cocaine self-administration. These data suggest that small molecule inhibitors directed towards *Pde1b* may be effective at reducing addiction-like behavior in a rodent model of cocaine use disorder. Given successful drug discovery efforts focused on phosphodiesterase enzymes, this work may guide novel therapeutic development for cocaine use disorder.

Disclosures: C.D. Teague: None. **X. Zhou:** None. **F.J. Martinez:** None. **A.M. Minier-Toribio:** None. **K.E. Lucerne:** None. **A. Godino:** None. **R. Futamura:** None. **C.J. Browne:**

None. **Y. Van Der Zee:** None. **A. Ramakrishnan:** None. **D.M. Walker:** None. **L. Shen:** None. **B. Zhang:** None. **E.J. Nestler:** None.

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.03

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA Grant P01DA047233

Title: Transcriptomic analysis of the nucleus accumbens after volitional heroin intake implicates Mbd3 as a key regulator of relapse susceptibility

Authors: *R. FUTAMURA[1], C. J. BROWNE[1], X. ZHOU[1], A. RAMAKRISHNAN[1], A. M. MINIER-TORIBIO[1], M. SALERY[1], A. GODINO[1], B. ZHANG[2], Y. L. HURD[1], L. SHEN[1], E. J. NESTLER[1];
[1]Nash Family Dept. of Neurosci. and Friedman Brain Inst., [2]Genet. and Genomic Sci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Repeated opioid use causes molecular changes in the nucleus accumbens (NAc), a brain region critical for coordinating motivated behavior and reward processing. Dysfunction of the NAc can perpetuate compulsive drug-seeking and drug-taking behaviors to the extent of which voluntary control over these behaviors is lost. Further, molecular changes within the NAc may support long-term susceptibility to relapse despite cessation of opioid use, induced by drug-related cues or re-exposure to the drug itself triggering intense drug craving. However, transcriptome-wide regulation within the NAc induced by opioid-seeking behavior has not been previously examined. Ongoing studies in our laboratory have identified broad patterns of transcriptional regulation throughout the brain reward circuitry induced by volitional opioid exposure and drug-seeking behavior using heroin intravenous self-administration in mice. In these studies, mice self-administered saline or heroin for 15 days and underwent a 30-day homecage forced abstinence period, after which mice were challenged with either saline or heroin, placed back in the self-administration context, and euthanized 2 hours later. NAc tissue was then analyzed by RNA-sequencing. Here, we focus on how transcriptional regulation within the NAc contributes to drug-seeking behavior. Using multiscale embedded gene co-expression network analysis (MEGENA), we identified a highly significant gene network in this brain region that is enriched with upregulated genes induced by heroin-primed drug-seeking. Within this network, methyl-CpG binding domain protein 3 (*Mbd3*), one of the most significantly upregulated genes within the NAc in this condition, was also found to be a key hub gene. In addition, exploratory factor analysis linking behavioral outcomes from self-administration with gene expression uncovered a positive association between *Mbd3* and a composite measure of addiction-like behavior. Taken together, these data suggest that *Mbd3* is an important driver in controlling this gene network that associates with relapse-like behavior. Ongoing efforts include

determining the cell-type-specificity of *Mbd3* regulation in NAc D1 or D2 medium spiny neurons, manipulating *Mbd3* using knockdown and overexpression approaches, and examining changes to behavior that promote drug craving, and ultimately, relapse.

Disclosures: **R. Futamura:** None. **C.J. Browne:** None. **X. Zhou:** None. **A. Ramakrishnan:** None. **A.M. Minier-Toribio:** None. **M. Salery:** None. **A. Godino:** None. **B. Zhang:** None. **Y.L. Hurd:** None. **L. Shen:** None. **E.J. Nestler:** None.

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.04

Topic: G.09. Drugs of Abuse and Addiction

Support: K01DA054306
P01DA047233
R01DA07359

Title: Transcriptional correlates of drug-associated memories in the nucleus accumbens

Authors: F. J. MARTINEZ-RIVERA[1], S. TOFANI[1], L. HOLT[2], S.-Y. YEH[1], R. DURAND-DE CUTTOLI[1], M. ESTILL[3], A. M. MINIER-TORIBIO[4], R. FUTAMURA[5], D. MASON[1], G. ROJAS[1], H. ALEYASIN[1], S. J. RUSSO[1], L. SHEN[6], E. J. NESTLER[5];
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Abstract: Substance use disorders exemplify a maladaptive imbalance wherein drug seeking persists despite negative consequences or drug unavailability. This maladaptation correlates with neurobiological alterations that hijack reward seeking and consequently withdrawal, extinction, and relapse processes. Extinction, a form of learning in which drug-seeking responses are attenuated by repeated cue exposure in the absence of the drug, represents a valuable tool to suppress drug-associated memories at the behavioral and molecular level. While there is increasing evidence linking addiction phases to faulty epigenetic and transcriptional modifications in brain reward regions such as the nucleus accumbens (NAc), there is a pressing need to characterize these molecular events in a phase, subregion, and cell-specific manner. Here, we used cocaine self-administration (SA) in rats combined with RNA-sequencing (RNAseq) of NAc subregions (core/shell) to transcriptionally profile the impact of extinction learning on counteracting drug memories. As expected, we first observed that rats receiving extinction training in the original SA context (cues/no drug) significantly reduced active lever pressing when compared with rats receiving force abstinence in either their home-cages or the SA context (no cues/no drug). Further analysis revealed that rats undergoing withdrawal in the original drug context increased drug seeking and incubation. Consistent with these behavioral

features, RNAseq and subsequent bioinformatic analyses correlate transcriptional profiles with distinct behavioral phenotypes, and the influence of extinction training on attenuating the transcriptional burden upon withdrawal. Additional studies extend these finding to identify the transcriptional basis of transferring extinction memories across contexts. Such contextual SA experiments (renewal) involve rats acquiring and extinguishing SA in different contexts. Ongoing transcriptomic analyses highlight particular gene expression patterns and hub genes that encode these phenotypes. Complementary to these datasets, with the goal of subsequent cell-specific characterizations, we are using RNAscope, electrophysiology, pharmacology, and optogenetic/chemogenetic approaches to validate the use of transgenic rats expressing Cre-recombinase selectively in D1 or D2 NAc medium spiny neurons. Together, these approaches will provide unprecedented evidence of how extinction, withdrawal, and renewal reprogram the transcriptome of the NAc to identify novel avenues to prevent drug relapse.

Disclosures: F.J. Martinez-Rivera: None. **S. Tofani:** None. **L. Holt:** None. **S. Yeh:** None. **R. Durand-De Cuttoli:** None. **M. Estill:** None. **A.M. Minier-Toribio:** None. **R. Futamura:** None. **D. Mason:** None. **G. Rojas:** None. **H. Aleyasin:** None. **S.J. Russo:** None. **L. Shen:** None. **E.J. Nestler:** None.

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.05

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA 5P01DA047233

Title: Elucidation of the astrocyte-specific transcriptome following cocaine self-administration

Authors: *L. HOLT[1], A. M. MINIER-TORIBIO[1], C. J. BROWNE[1], R. FUTAMURA[1], E. M. PARISE[1], S.-Y. YEH[1], M. ESTILL[1], F. MARTINEZ-RIVERA[1], Y. DONG[2], E. J. NESTLER[1]; [1]Nash Family Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Univ. of Pittsburgh, Univ. of Pittsburgh, Pittsburgh, PA

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. Indeed, candidate genes in astrocytes have been identified and, furthermore, manipulation of astrocyte function has been demonstrated to influence rodent behavioral responses to cocaine administration. However, the astrocyte-specific transcriptome following exposure to drugs of abuse has not yet been investigated. Therefore, 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". We determined that astrocytes exhibit a robust transcriptional response, including regionally- and contextually-specific transcriptional signatures. Subsequent gene ontology analysis revealed several key pathways, including synaptic regulation, calcium signaling, and GPCR signaling, in both brain regions as being prominently regulated by cocaine exposure. Interestingly, additional analysis revealed CREB as a predicted upstream regulator of this abnormal transcription. We confirmed that cocaine exposure alters CREB phosphorylation in nucleus accumbens astrocytes and that viral-mediated manipulation of CREB activity selectively within astrocytes in this brain region modulates addiction-related behaviors in a conditioned place preference paradigm. Current studies are extending our findings utilizing cocaine self-administration to establish the role of astrocytic CREB's contribution to the pathophysiology of cocaine addiction and to identify CREB target genes that mediate this action.

Disclosures: L. Holt: None. **A.M. Minier-Toribio:** None. **C.J. Browne:** None. **R. Futamura:** None. **E.M. Parise:** None. **S. Yeh:** None. **M. Estill:** None. **F. Martinez-Rivera:** None. **Y. Dong:** None. **E.J. Nestler:** None.

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.06

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA R01DA014133
NIDA P01DA047233
NIDA P30DA018343
NIDA DA018343

Title: Proteomic Profiling of Nucleus Accumbens Synaptosomes Following Withdrawal From Cocaine or Heroin Self-Administration.

Authors: *Y. YIM[1], C. J. BROWNE[1], A. GODINO[1], A. M. MINIER-TORIBIO[1], F. MARTINEZ-RIVERA[1], A. LY[2], J. CALLENS[1], R. FUTAMURA[1], J. A. LANDRY[1], R. S. WILSON[3], A. C. NAIRN[4], Y. L. HURD[1], E. J. NESTLER[1];
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Abstract: Addiction is a devastating disorder that is exceptionally difficult to treat due to the high propensity for relapse even long after prolonged abstinence. The persistence of addiction is mediated at least partly by drug-induced changes in the physiology of reward-processing brain regions, such as the nucleus accumbens (NAc). Dysregulated signaling within the NAc is thought to play a critical role in promoting drug-seeking and relapse. However, the molecular

details underlying these signaling changes and adaptations remain incompletely understood. Determining these changes may reveal more effective targets to treat substance use disorders. Here, we extend previous work focused mainly on candidate proteins of interest by contrasting whole-proteome changes in NAc that are induced by cocaine or heroin self-administration (SA) that persist through extended abstinence. Rats underwent 10 days of extended-access (6 hr/day) of intravenous cocaine, heroin, or saline SA followed by 24 hrs or 30 days of forced abstinence, after which the NAc was extracted. Synaptosomes from NAc tissues were purified and analyzed by lipid chromatography-tandem (LC-MS/MS) mass spectrometry followed by label-free quantification. Using this approach, we identified induction or repression of numerous synapse-enriched proteins following prolonged withdrawal from cocaine or heroin SA. While most of these drug-regulated proteins are expressed by neurons, a significant subset is enriched in astrocytes or microglia, consistent with the intimate association of processes from these cell types with synapses. Interestingly, long-term withdrawal is associated with a greater degree of repression rather than induction of protein expression overall. We are now validating these findings and characterizing particular synaptic proteins that directly contribute to drug-seeking behavior. These studies will enhance our understanding of the molecular restructuring of synapses in the reward circuitry that underlie susceptibility to relapse.

Disclosures: **Y. Yim:** None. **C.J. Browne:** None. **A. Godino:** None. **A.M. Minier-Toribio:** None. **F. Martinez-Rivera:** None. **A. Ly:** None. **J. Callens:** None. **R. Futamura:** None. **J.A. Landry:** None. **R.S. Wilson:** None. **A.C. Nairn:** None. **Y.L. Hurd:** None. **E.J. Nestler:** None.

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.07

Topic: G.09. Drugs of Abuse and Addiction

Support: National Centre of Science 2020/37/N/NZ4/02888

Title: Whole-brain study of neuronal activity after addictive (cocaine) and natural (sucrose) reward exposure

Authors: ***L. D. BIJOCH**[1], M. PAWLOWSKA[3], D. LEGUTKO[2], J. WISNIEWSKA[1], L. KACZMAREK[2], A. BEROUN[1];
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Abstract: Natural rewards, such as food, and sex are appetitive stimuli available for animals in their natural environment. On the other hand, addictive rewards e.g. various drugs of abuse also have positive valence, but their action rely on their pharmacological properties. Nevertheless, it is believed that both of these rewards activate similar brain circuitry. The present study aimed to

discover in which parts of the brain natural and addictive rewards are being processed in rodent's brain. To holistically address this question, we used a single-cell whole-brain imaging approach to find patterns of activation for acute and prolonged sucrose and cocaine exposure.As a model of addictive reward, we chose cocaine injections, while sucrose self-administration mimicked the natural one. After the behavioral training, brains from three- to six-months old mice of both sexes were extracted and processed with iDisco protocol to optically clear the tissue. During this procedure, we immunohistochemically labelled activity-dependent c-Fos protein to mark cells, which were processing these rewards. Then, cleared samples were imaged with a light-sheet microscope. Finally, we fitted our images into virtual map of the mouse brain to automatically calculate number of all c-Fos-positive neurons. We analyzed almost 400 brain structures and created a brain map of specific c-Fos-positive neurons corresponding to these rewards. We found the dispersed network of activated structures, supporting the brain-wide task-related activity hypothesis. This universal mapping allowed us to create a general pattern of brain activation after natural and addictive treatment. We found assemblies processing both these rewards (e.g. nucleus accumbens, fundus of striatum). However, we found also structures selectively activated by addictive rewards (e.g. visual and auditory cortexes) or natural ones (e.g. olfactory system or lateral septum). Moreover, the functional connectivity analysis unraveled the affected modularity of the brain after exposure to these rewards. We found out that while initially the effect of both types of rewards is similar, after prolonged exposure cocaine, but not sucrose, caused sustained reorganization of the brain modularity. Together, these results may support the concept that cocaine with its pharmacological effect is a reward causing prolonged alternations on the brain-wide scale. Moreover, these findings may act as a guide for further studies describing how addictive and natural rewards shape the brain.

Disclosures: L.D. Bijoch: None. **M. Pawlowska:** None. **D. Legutko:** None. **J. Wisniewska:** None. **L. Kaczmarek:** None. **A. Beroun:** None.

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.08

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA R01 DA047265

Title: Effect of PICK1 Knockout in The Nucleus Accumbens on CocaineSelf-administration and Reinstatement in Mice

Authors: *M. Y. ROBERTS, E. A. BIRMINGHAM, M. C. KNOUSE, L. A. BRIAND; Psychology and Neurosci., Temple Univ., Philadelphia, PA

Abstract: Following chronic cocaine use, AMPA receptor (AMPAR) trafficking and signaling are altered, affecting rodent cocaine-seeking behavior. AMPAR trafficking is mediated by two

scaffolding proteins, glutamate receptor-interacting protein (GRIP) and protein interacting with C kinase 1 (PICK1). While GRIP facilitates the insertion of AMPARs into the cell membrane, PICK1 promotes the internalization of the receptors. Previous studies have shown that knocking out GRIP in the nucleus accumbens (NAc) potentiates cocaine-seeking in mice and global knockout (KO) of PICK1 in male mice attenuates cocaine seeking. However, it is unknown whether these effects of global PICK1 KOare due to its actions within the NAc. The current study examined the role of PICK1 in the NAc using a site-specific injection of Cre recombinase in PICK1 floxed mice. Firstly, male and female mice either injected with a GFP control virus or Cre virus to knockout PICK1, were trained to perform an operant response for food. Although all mice acquired the operant behavior, PICK1 KO in the NAc increased the rate of acquisition in male mice but not female mice. Following the acquisition of the operant response, mice then underwent cocaine self-administration. Although there was no significant effect of viral infusion on cocaine taking, male PICK1 KO mice exhibit a trend towards an increase in both intake and responding. NAc PICK1 KO did not alter extinction responding or the rate of extinction. Ongoing studies are examining the impact of NAc PICK1 KO on cue-induced reinstatement of cocaine seeking. Overall, our data suggest that the role of PICK1 in the NAc may be sex specific and that the effects of global knockout may be due to actions of PICK1 in other brain regions or actions during development.

Disclosures: M.Y. Roberts: None. **E.A. Birmingham:** None. **M.C. Knouse:** None. **L.A. Briand:** None.

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.09

Title: WITHDRAWN

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.10

Topic: G.09. Drugs of Abuse and Addiction

Support: NRF Grant 2021R1A4A2001803
NRF Grant 2018R1A3B1052079
NRF Grant 2018M3C7A1024152
Health fellowship foundation

Title: Rewiring of prelimbic inputs to nucleus accumbens core underlies cocaine-induced behavioral sensitization

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Abstract: Unbalanced activity of medium spiny neurons of the direct and indirect pathways (dMSNs and iMSNs, respectively) mediates reward-related behaviors induced by addictive drugs. Prelimbic (PL) input to MSNs in nucleus accumbens core (NAcC) plays a key role in cocaine-induced acute locomotor sensitization (LS). However, the adaptive plastic changes at the PL-to-NAcC synapses underlying acute LS remain unclear. Using transgenic mice and retrograde tracing, we identified NAcC-projecting pyramidal neurons (PNs) in the PL cortex based on expression of dopamine receptor types. NAcC-projecting PNs were segregated into D1R- and D2R-expressing PNs (D1 and D2-PNs, respectively), and their intrinsic excitability was opposingly regulated by respective dopamine agonists. Next, to study cocaine-induced changes in PL-to-NAcC synapses, we measured EPSC amplitudes evoked by opto-stimulation of PL afferents to MSNs. Both D1/D2-PNs exhibited balanced innervation of dMSNs and iMSNs in naïve animals, but, repeated cocaine injections resulted in biased connectivity toward dMSNs through presynaptic mechanisms. This rewiring was more pronounced in D2-PN-to-NAcC synapses, although D2R activation reduced the D2-PN excitability. However, under group 1 metabotropic glutamate receptors co-activation, D2R activation enhanced the D2-PN excitability. The cocaine-induced rewiring accompanied LS, and both rewiring and LS were precluded by PL infusion of riluzole, which reduced the intrinsic excitability of PL neurons. These findings indicate that cocaine-induced rewiring of PL-to-NAcC synapses correlates well with early behavioral sensitization, and that rewiring and LS can be prevented by reducing the excitability of PL neurons.

Disclosures: **J. Kwon:** None. **H. Kim:** None. **H. Lee:** None. **W. Ho:** None. **J. Kim:** None. **S. Lee:** None.

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.11

Topic: G.09. Drugs of Abuse and Addiction

Support: NARSAD24847
R01MH116901
1F31MH125510
T32NS099042

Title: Cocaine induces cell-type specific plasticity in ventral subiculum to nucleus accumbens circuit

Authors: *J. KIM, E. E. BOXER, J. AOTO;
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Abstract: Ventral subiculum (vSUB) is the major output region of ventral hippocampus (vHIPP) and sends major projections to nucleus accumbens medial shell (NAcMS). Hyperactivity of vSUB-NAcMS pathway is thought to be a major cause of dopamine dysregulation and is associated with substance use disorders and schizophrenia. Emphasizing the relevance of vSUB to substance use disorders, previous work revealed that pharmacological, electrical or optogenetic modulation of vSUB activity altered drug seeking and drug reinstatement behavior in rodents. However, to the best of our knowledge, despite the importance of vSUB, the cell-type-specific connectivity and synaptic transmission properties of the vSUB-NAcMS circuit have never been directly examined. Instead, previous functional studies have focused on ventral hippocampal output to NAcMS without distinguishing vSUB from other subregions of vHIPP. Using transgenic mice, imaging, optogenetics and *ex vivo* electrophysiology, we systematically characterized the vSUB-NAcMS circuit with cell-type- and synapse-specific resolution and found that vSUB output to dopamine receptor type-1 (D1R) and type-2 (D2R) expressing medium spiny neurons (MSNs) display a unique cell-type specific bias and exhibit distinct synaptic transmission properties in NAcMS that have not been previously observed in drug naïve mice. Furthermore, we found that cocaine exposure induces plasticity at vSUB-D1R and vSUB-D2R synapses that is distinct from other previously studied glutamatergic inputs. These results indicate that vSUB projections represent a distinct population of excitatory synapses on D1R and D2R MSNs, which exhibit unique basal synaptic transmission properties and undergo unique cocaine-induced plasticity. Our work represents an important first step toward understanding how the vSUB-NAcMS circuit contributes to the etiologies that underlie substance use disorders.

Disclosures: **J. Kim:** None. **E.E. Boxer:** None. **J. Aoto:** None.

Poster

734. Cocaine: Circuit Effects

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 734.12

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH RO1 MH096093 (ELB)
NIH RO1 DA018184 (REJ)
Harvey Family Endowment (ELB)

Title: Brain-wide mapping of prefrontal cortical projections

Authors: *E. L. BEARER[1,2], T. W. USELMAN[1], C. S. MEDINA[1], R. E. JACOBS[3];
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Abstract: Medial prefrontal cortex (mPFC) plays major roles in behavioral flexibility, and is implicated in cocaine misuse. Loss of volume in mPFC of cocaine users theoretically leads to decreased executive function and compulsive drug use. Using manganese-enhanced magnetic resonance (MEMRI) for projection mapping in parallel with histologic tract-tracing, we reported that mPFC projects into striatum, thalamus, hypothalamus, and reaches ventral tegmental area, dorsal raphe (midbrain) and even locus coeruleus (pons) - nuclei for monoaminergic systems: dopamine, serotonin and noradrenaline, target of cocaine. Genetic disruptions of each monaminergic transporter redirect mPFC projections. We now test whether mPFC plasticity can be induced by experience in adulthood, such as acute threat. Mice were exposed for 30 min to predator odor (2,3,5-Trimethyl-3-thiazoline, TMT), an ethological stressor. Three weeks later $MnCl_2$ (3-5nL of 0.6M in sterile saline) was injected into mPFC (ML=0.59±0.1; AP=+0.7±0.5; DV=-1.6±0.4 (n= 24). Videos of activity before and during odor presentations, and before intracerebral injection recorded expected responses to TMT. Longitudinal images were captured before, immediately and at successive time points after injection. After imaging animals were sacrificed, and perfusion-fixed brains processed for microscopy. Voxel-wise SPM comparisons between time points revealed progression of Mn(II) distally. Application of our new *In Vivo* digital mouse brain atlas allowed automated digital measurements of Mn(II) signal, revealing dramatic anatomical differences in projections between animals experiencing acute threat and those without. Acute threat further impacted mPFC projections in mice lacking serotonin transporter (SERT), a target of cocaine and of anti-depressants. Regional segmentation of projection maps of threat-exposed mice compared with our previous data of non-threat exposed mice showed decreased projection after threat to anterior and basolateral amygdala, preoptic hypothalamus and superior central raphe, and increased to posterior and cortical amygdala, periaqueductal gray and dorsal raphe. These changes may best correlate with those after NET disruption, which increases the amount of noradrenaline in the synaptic cleft similar to an effect of cocaine and may also mimic stress. No mPFC volume loss was detected in non-threat exposed, NET-deleted mice by SPM of DTI ($p<0.005$ FDR). Thus a single experience of acute threat redirects mPFC distal connections independent of volume loss, which may explain one aspect for how life-threatening experiences pose long lasting risks for anxiety and substance use disorders.

Disclosures: E.L. Bearer: None. **T.W. Uselman:** None. **C.S. Medina:** None. **R.E. Jacobs:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.01

Topic: G.09. Drugs of Abuse and Addiction

Support: Supported by the statutory activity of Maj Institute of Pharmacology PAS

Title: Proteomics profile of cocaine self-administration and extinction training in prefrontal cortex in rats

Authors: *M. FRANKOWSKA[1], K. GAWLINSKA[2], P. MIELCZAREK[3], R. PIENIAZEK[2], I. SMAGA[2], M. FILIP[2];
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Abstract: Growing evidences suggest that chronic cocaine, an addictive psychostimulant, exposure revealed metabolic and structural differences in the function of the prefrontal cortex (PFCx), which is involved in behavioral and cognitive functions and leads to the loss of inhibitory control over drug-seeking and drug-taking behavior. Proteomic analysis is one of the modern biomedical techniques that is increasingly used to reveal the substances' mechanisms of action, and ultimately can be used to program pharmacotherapy. In the present study, we were focus on a combination of proteomic analysis related to the PFCx with complex maintenance of cocaine self-administration and extinction training, and control animals receive saline in yoked procedure to characterize the molecular mechanisms with the potential to regulate reward properties of the drug in rats. Between 201 to 437 proteins and 700 to 1389 unique peptides in the PFCx were detected wherein in order to understand the biological relevance the 918 identified proteins (PANTHER classification system; www.pantherdb.org), classified to 11 categories of functional classification and 19 categories of biological processes. A functional classification demonstrated that 42.4% of all expression differentiating proteins were classified as binging proteins and 34.4% as catalytic activity. Detected protein in a variety of biological processes including 3 dominated groups: cellular process (33.8%), metabolic process (18.1%), and biological regulation (14.2%). Similar distribution for identified proteins was observed for each of four experimental groups i.e., cocaine (0.5 mg/kg/infusion) self-administered rats and their controls (yoked saline) during maintenance self-administration and extinction training in the experimental cage through proteomics into their molecular functions and biological processes in the PFCx. Employed animal models of cocaine self-administration with their control groups and proteomics assay in this study give a possibility to identify and separated protein expression changes related to the motivational aspects of drug-taking behavior and also to identify those important during abstinence. Besides the information that has been obtained provides useful mechanistic insights into the effects of cocaine on PFCx proteins that can be closely tracked with a drug addiction model that more accurately reflects human experiences. A detailed understanding of the observed changes in proteins expressed in response to addictive drugs may also allow the identification of future therapeutic targets.

Disclosures: M. Frankowska: None. **K. Gawlinska:** None. **P. Mielczarek:** None. **R. Pieniazek:** None. **I. Smaga:** None. **M. Filip:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.02

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA Grant DA000069

Title: Zinc induces sex-specific changes in dopamine transmission in response to cocaine in mice

Authors: *O. SOLÍS CASTREJÓN, E. VENTRIGLIA, F. CURRY, J. GOMEZ, M. MICHAELIDES;
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Abstract: Glutamatergic signaling in the striatum is implicated in cocaine use disorder. Within a subset of glutamatergic neurons, vesicular zinc (Zn^{2+}) is co-released with glutamate and modulates dopamine transmission. In line with these findings, we demonstrated that the absence of vesicular Zn^{2+} induces a decrease in conditioned place preference, locomotor sensitization and self-administration to cocaine. Previous studies showed that estrogen reduces Zn^{2+} in the brain and that Zn^{2+} exerts sexually dimorphic effects on locomotion and at skilled motor learning tasks. However, the interaction between synaptic zinc and sex on dopamine transmission has not been characterized. Thus, we investigated the role of Zn^{2+} in the dorsal striatum (DS) in the development and expression of behavioral sensitization by cocaine. Female and male mice were microinjected into the DS with saline or TPEN (Zn^{2+} chelator) followed by cocaine challenge for 5 days. After 2 weeks of withdrawal, mice were challenged with cocaine to study the expression of the locomotor sensitization. Our preliminary results showed that Zn^{2+} chelation differently affects cocaine-induced locomotor sensitization in female and male mice. In addition, we performed dopamine transporter (DAT) and dopamine D1 receptor (D1R) autoradiography using the cocaine analog [^{3}H]WIN-35,428 and [^{3}H]SCH23390 respectively, in the presence of physiological concentrations of Zn^{2+}, in female and male mice. We found that Zn^{2+} induces sex specific differences in [^{3}H]WIN-35,428 binding to DAT, but no differences in [^{3}H]SCH23390 binding to the D1R. Our results suggest that Zn^{2+} affects dopamine transmission in a sex-specific manner.

Disclosures: O. Solís Castrejón: None. **E. Ventriglia:** None. **F. Curry:** None. **J. Gomez:** None. **M. Michaelides:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.03

Topic: G.09. Drugs of Abuse and Addiction

Support: Center on Compulsive Behaviors Fellowship

Title: Serotonergic actions of cocaine at corticostriatal synapses onto cholinergic interneurons

Authors: *M. E. AUTHEMENT[1], J. SHIN[3], C. TERESI[2], V. A. ALVAREZ[4];
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Abstract: Cholinergic interneurons (CINs) of the striatum are necessary for behavioral flexibility and their dysfunction may underlie the pathology of compulsive behaviors seen in substance use disorders. Although CINs account for approximately 1% of striatal neurons, they serve as the major source of striatal acetylcholine and their activity can evoke local striatal dopamine signals. CINs receive excitatory input from cortical regions such as the prefrontal cortex (PFC), a brain region necessary for inhibitory control which is compromised in compulsive behaviors. Recent work from our lab demonstrated that cocaine, a potent drug of abuse, acutely depresses excitatory transmission from cortical synapses onto CINs. However, the mechanism underlying this depression is unknown. Here we used whole-cell electrophysiology in mice injected with Channelrhodopsin-2 in the PFC and found that cocaine's action on excitatory corticostriatal transmission onto CINs is mediated by presynaptic 5HT-1B receptors. Furthermore, acute application of both cocaine and serotonin induces a long-term depression at these synapses through 5HT-1B receptors. We next tested whether repeated *in vivo* administration of cocaine induced a long-term depression at excitatory corticostriatal synapses onto CINs. Mice were injected with either cocaine (15 mg/kg) or saline over a 5-day period and whole-cell recordings in were performed 14 days later in striatal brain slices. Indeed, repeated administration of cocaine induced a long-term depression at corticostriatal synapses onto CINs as evidenced by a decrease in the AMPA:NMDA ratio compared to saline controls. This work highlights the importance of cocaine's serotonergic actions in the striatum and may hint at a synaptic mechanism by which cocaine can compromise the PFC's ability to influence striatal activity.

Disclosures: M.E. Authement: None. **J. Shin:** None. **C. Teresi:** None. **V.A. Alvarez:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.04

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA023206
NIH Grant DA040620

Title: Astrocyte proximity to glutamate synapses in the rat accumbens core: impact of cocaine self-administration

Authors: *S. R. SESACK[1], T. PLUTE[1], J. J. BALCITA-PEDICINO[1], J. WANG[2], Y. DONG[1]; [1]Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; [2]Neurosci., Mount Sinai Sch. of Med., New York, NY

Abstract: Many regulatory mechanisms control extracellular glutamate levels and contribute to plasticity at the excitatory synapses that govern learning and memory. Astrocytes represent a key factor in regulating glutamate levels by determining transmitter diffusion channels and by expressing essential proteins for glutamate uptake and exchange. Maintenance of normal extracellular glutamate within the nucleus accumbens contributes to adaptive goal-directed behavior, and this function can be altered by exposure to psychostimulants like cocaine that disrupt astrocytic glutamate homeostasis. We sought to investigate potential ultrastructural changes in the proximity of astrocytes to glutamate synapses within the accumbens core that might underlie the physiological and behavioral alterations identified in cocaine seeking. We also compared astrocytic associations with glutamate synapses in naïve rats versus the saline animals used as controls for cocaine self-administration. Adult male rats were trained to self-administer cocaine or saline 2 hours a day for 5 days and then sacrificed by fixative perfusion 24 hours after the last session. Serial brain sections through the accumbens core were imaged by electron microscopy from cocaine self-administering, saline-treated, and naïve rats. *Reconstruct*^{TM} was used to generate 3-dimensional reconstructions of excitatory axospinous synapses and adjacent astrocytes. Within each group, extensive variation was observed in the degree to which astrocytes contacted glutamate synapses on spines. No significant differences were observed between cocaine (n = 77 synapses in 2 rats) and saline-treated animals (n = 72 synapses in 2 rats) in: 1) the size of axons, spines or synapses, 2) the proportion of astrocytic contact on glutamate synapses, or 3) the shortest extracellular distance between the active zone and the nearest astrocyte. Mean spine and synapse volumes appeared to be reduced, with overall lower variance, in saline-treated versus naïve animals (n = 292 synapses in 6 rats). Similar reductions were seen in cocaine self-administering rats, and these outcomes matched qualitative observations of an increased number of small spines in both treated groups. These results suggest the potential induction of spinogenesis by exposure to the self-administration protocol (as opposed to drug), in which case both groups of treated rats may have perceived the 5-day procedures as enriching compared to naïve rats with no handling. Additional animals and longer treatment times are needed to better test potential differences in astrocytic coverage of glutamate synapses between cocaine and saline self-administering animals.

Disclosures: S.R. Sesack: None. **T. Plute:** None. **J.J. Balcita-Pedicino:** None. **J. Wang:** None. **Y. Dong:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.05

Topic: G.09. Drugs of Abuse and Addiction

Title: The effects of chronic cocaine exposure and withdrawal on dopamine functioning

Authors: *M. LOVE[1], P. NALAN[2], R. L. PACE[1], S. BERRETTA[3], D. B. LESTER[3]; [1]Univ. of Memphis, Memphis, TN; [2]Univ. of Memphis, Bartlett, TN; [3]Univ. of Memphis, Univ. of Memphis, Memphis, TN

Abstract: The mesolimbic dopamine pathway plays a role in mediating reward processing and consists of dopamine cell bodies in the ventral tegmental area that project to limbic regions, particularly the nucleus accumbens (NAc). Cocaine increases extracellular dopamine concentrations by blocking dopamine transporters (DATs). The present study examined the effects of chronic cocaine exposure and withdrawal on mesolimbic dopamine functioning. Mice were exposed to chronic cocaine or saline (daily i.p. injections for 7 days). In half of the mice, dopamine recordings took place the day after drug exposure (on day 8). The remaining mice were given a weeklong withdrawal period, with no injections, prior to dopamine recordings (on day 15). In vivo fixed potential amperometry was used on anesthetized mice to quantify stimulation-evoked dopamine release in the NAc before and after a cocaine challenge (20 mg/kg i.p.). Baseline dopamine release (prior to the in-test cocaine challenge) was not affected by previous cocaine exposure or withdrawal; however, there was a significant interaction between previous drug exposure and withdrawal on the baseline synaptic half-life of dopamine, indicating that cocaine exposure led to faster synaptic clearance of dopamine but that this effect was negated by the withdrawal period. The percent change in dopamine release following the in-test cocaine injection was not different between groups, but there was a main effect of previous cocaine exposure on percent change in dopamine half-life following the in-test cocaine injection. The time dopamine remained in the synapse was increased by cocaine to a greater degree in mice chronically exposed to cocaine compared to saline-exposed mice, regardless of withdrawal. Overall, these results indicate that cocaine exposure and withdrawal had the greatest effects on measurements related to DAT functioning rather than release properties. These findings highlight cocaine-induced changes in dopamine functioning that persist beyond the acute drug effects.

Disclosures: M. Love: None. **P. Nalan:** None. **R.L. Pace:** None. **S. Berretta:** None. **D.B. Lester:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.06

Topic: G.09. Drugs of Abuse and Addiction

Support: RO1 DA038042
NIH Grant 410898 5U54MD007579-37

Title: Astrocytic gap junction communication in the prefrontal cortex mediates cocaine-associated memory retrieval

Authors: *M. R. SLUPEK[1], M. FITZGERALD[2], Z. T. KNAUSS[1], J. L. BURKARD[2], D. S. DAMRON[1], D. MUELLER[1];
[1]Biol. Sci., Kent State Univ., Kent, OH; [2]Univ. of Wisconsin - Milwaukee, Milwaukee, WI

Abstract: The estimated cost of drug abuse in the United States is more than $740 billion a year and continues to grow (NIDA, 2021). Preventing drug-associated memory retrieval could reduce relapse rates in addicts. Activity levels in the prefrontal cortex (PFC) have been correlated in rats and humans with the formation and intensity of drug craving in response to drug-associated cues and contexts. Data suggests the prelimbic medial PFC (PL-mPFC) is necessary for retrieval of cocaine-associated memory (Otis et al., 2013). Although little is known about gap junction involvement in the PL-mPFC, neuronal and astrocytic gap junction inhibition (GJI) can alter neuronal activity and plasticity (Palacios-Prado et al., 2014; Pannasch et al., 2011). We investigated the role of GJI during retrieval of cocaine-associated memory using a model of conditioned place preference (CPP). Before the first retrieval test, adult male rats received a single bilateral microinfusion of neuronal (quinine hydrochloride 100μM, n = 10), astrocytic (IRL-1620 0.1μM, n = 9), general (carbenoxolone disodium 100μM, n = 10) GJI, or vehicle (n = 11) into the PL-mPFC followed by daily testing. General and astrocytic GJI disrupted retrieval of a cocaine-CPP on days 2-4 of retrieval testing ($p > 0.05$), while the control group maintained a CPP through day 3 ($p < 0.05$), and neuronal GJI maintained a CPP through the end of testing ($p < 0.05$), indicating a level of drug seeking higher than controls. Thus, astrocytic GJI in the PL-mPFC persistently disrupts, while neuronal GJI enhances, cocaine-associated memory retrieval. To assess the effects of GJI on intrinsic, unstimulated, intracellular Ca^{2+} dynamics, frequency of fluorescently labeled cells in day 12-14 primary cell cultures from the PFC of P0 rat pups (N = 12; 3 cultures, male = 6, females = 6) were perfused for 5 minutes with Tyrode's solution followed by 5 minutes under each GJI condition. Compared to a preceding 5 minutes of control, neuronal GJI persistently decreased Ca^{2+} transients by at least 25% in 96.5% of active neurons ($n_n = 113$) and 94.6% of active astrocytes ($n_a = 56$). Astrocytic GJI decreased Ca^{2+} transients in 80.0% of active neurons ($n_n = 245$) and 86.5% of astrocytes ($n_a = 281$). General GJI reduced Ca^{2+} transients in 84.7% of active neurons ($n_n = 314$) and 79.6% of astrocytes ($n_a = 304$). Our findings suggest that desynchronizing specifically astrocytic communication disrupts synaptic maintenance and efficacy, leading to the long-term synaptic depotentiation that underlies persistent retrieval deficits. Thus, gap junction communication in PL-mPFC may play a critical role in the maintenance of drug-associated memories that provoke relapse.

Disclosures: M.R. Slupek: None. **M. Fitzgerald:** None. **Z.T. Knauss:** None. **J.L. Burkard:** None. **D.S. Damron:** None. **D. Mueller:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.07

Topic: G.09. Drugs of Abuse and Addiction

Support: DA04041513

Title: Astrocytic KCNQ channels in rat nucleus accumbens contribute to different cellular and behavioral effects of short and extended cocaine access

Authors: *M.-F. XIA, P. ORTINSKI;
Univ. of Kentucky, Lexington, KY

Abstract: Nucleus accumbens is involved in motivational and affective behavioral processing, and plays a significant role in development and maintenance of substance use. The release of dopamine from the ventral tegmental area into the nucleus accumbens regulates incentive salience and facilitates reinforcement and reward-related motor function learning. Recent studies reveal that, in the context of cocaine exposure, dopamine transmission in the ventromedial striatum is pivotal in the control of initial drug use. In addition, astrocyte morphology has been shown to be affected by cocaine, but the functional role of astrocytic signaling in cocaine use remains unknown. The goal of this study is to address astrocytic adaptions within nucleus accumbens under two different cocaine exposure regimes. To characterize astrocytes' response to cocaine-induced dopamine elevation we used a rat self-administration model. Two groups of animals went through short- (1h/day) and extended- (6h/day) access cocaine self-administration for 14 days. To identify functional effects of cocaine on astrocytes, we imaged astrocytes expressing calcium indicator, GCamp6f and performed whole-cell patch-clamp recordings. Extended-access, but not short-access, to cocaine led to elevation of drug taking behavior as previously described. Calcium signaling within NAc astrocytes was differentially affected by short- or extended- access cocaine self-administration. Extended exposure significantly decreased the amplitude of spontaneous Ca2+ transients. Dopamine treated astrocytes generated larger amplitude potassium currents compared to naïve ones. This could be attributed to up-regulation of KCNQ type-potassium channels. On-going experiments examine whether the astrocytic Kcnq channels are responsible for different behavioral outcomes under short- and extended-access to self-administered cocaine. Our results indicate a potential regulatory role of astrocytic signaling in the NAc on neural mechanisms underlying substance use, via cell-specific upregulation of the KCNQ potassium channels.

Disclosures: M. Xia: None. **P. Ortinski:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.08

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH R01 DA025224 to H.E.M

Title: Nociceptin Signaling in the Ventral Striatum: Actions on Dopamine Transporter Trafficking and Cocaine Reward

Authors: *N. C. BOLDEN, H. E. MELIKIAN;
UMASS Med. Sch., UMASS Med. Sch., Worcester, MA

Abstract: Dopamine (DA) transmission is required for reward, motivation, and habit formation. The nucleus accumbens (NAcc) receives dense DAergic innervation via the mesolimbic circuit, and DA transmission in the NAcc is required for reward acquisition. Once released, extracellular DA levels are constrained by presynaptic reuptake, mediated by the DA transporter (DAT). DAT is the primary target for addictive psychostimulants, including cocaine, which potently inhibit DAT and increase extracellular DA, which drives salience and reward in response to these drugs. DAT surface expression is not static. Striatal DAT surface levels are dynamically modulated via mGluR5 (G_q-coupled) and DRD2 ($G_{i/o}$-coupled) autoreceptors which accelerate DAT internalization and surface delivery rates, respectively. However, it remains unknown whether, or how, regulated DAT trafficking impacts DA signaling and DA-dependent behaviors, such as cocaine reward. The nociceptin opioid peptide receptor (NOPR) is a $G_{i/o}$-coupled receptor expressed pan-neuronally, including in mesolimbic projecting DA neurons. Nociceptin infusion into the NAcc significantly dampens cocaine-mediated increases in extracellular DA, as well as the characteristic resultant hyperlocomotion. However, the mechanism(s) by which NOPR activation attenuates acute cocaine responses is unknown. We hypothesize that presynaptic NOPRs increase DAT surface levels, and thereby increase DA reuptake and limit cocaine's ability to increase extracellular DA. We found that NOPR activation with either nociceptin or the NOPR agonist, MCOPPB, rapidly increased DAT surface levels in mouse *ex vivo* NAcc slices, which was blocked by pre-treatment with the NOPR-selective antagonist, J-113397. NOPR and DRD2 co-activation additively increased DAT surface levels, suggesting that nociceptin signaling further boosts DAT surface levels over DRD2 autoreceptor-mediated surface delivery resulting from tonically released DA. Ongoing studies will leverage conditional gene silencing and *in vivo* expression of DAT trafficking dysregulated mutants, to directly test whether: 1) nociceptin-stimulated DAT trafficking in NAcc is mediated by presynaptic NOPRs in DAergic terminals, 2) NAcc nociceptin infusion suppresses cocaine-mediated reward, and 3) NOPR-stimulated DAT surface delivery is required for nociceptin to dampen reward. The results are expected to shed light on the role of regulated DAT trafficking in addictive behaviors.

Disclosures: N.C. Bolden: None. **H.E. Melikian:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.09

Topic: G.09. Drugs of Abuse and Addiction

Support: NIMH R01 MH111604
MSU Lyman Briggs College Undergraduate Summer Research Award
NINDS R25 NS090989

Title: Lateral entorhinal cortex neurons that project to nucleus accumbens are necessary for the expression of cocaine reward

Authors: H. M. KUHN[1], B. R. MURRAY[1], D. I. BERMUDEZ[2], L. COLON-SERRANO[3], B. D. SANDY[1], A. J. ROBISON[1], ***A. L. EAGLE**[1];
[1]Michigan State Univ., East Lansing, MI; [2]Univ. of Arizona, Tucson, AZ; [3]Univ. of Puerto Rico - Cayey, Cayey, PR

Abstract: Neuronal circuits that synapse onto nucleus accumbens (NAc) medium spiny neurons are critical for regulating motivated behaviors, including those underlying drug reward. The lateral entorhinal cortex (LEC) sends axonal projections to the NAc (LEC-NAc neurons) suggesting this circuit may be important for drug reward. Supporting this, LEC is activated by cocaine-associated cues in cocaine-dependent subjects and cocaine self-administering rats. Moreover, we show here that mouse LEC-NAc neurons have increased cFos expression after chronic cocaine, suggesting that this circuit is activated by cocaine exposure. However, whether LEC-NAc neurons regulate cocaine reward is currently unknown. To address this question, we sought to determine whether LEC-NAc neurons mediate the expression of a place preference for cocaine, which measures cocaine reward and cocaine-context associative memory. We used blinded behavioral experiments in both sexes of mice (8-12 weeks at time of experiment) and replicated our findings across multiple cohorts to ensure scientific rigor. Our approach used intersecting viral-mediated, circuit-specific DREADDs (Designer Receptors Activated by Designer Drugs) to inhibit and activate LEC-NAc neurons during a cocaine conditioned place preference task. We found that LEC-NAc neurons are necessary for the expression of place preference for cocaine. However, we also discovered that LEC-NAc neuron activity is neither inherently rewarding nor is it sufficient to enhance the place preference for cocaine. Current studies will determine whether LEC-NAc neurons are specifically necessary for either encoding and/or retrieval of a place preference for cocaine. The findings of this study suggest that the understudied LEC-NAc circuit is necessary for cocaine reward and implicate an entirely novel key pathway in the regulation of motivated behavior.

Disclosures: H.M. Kuhn: None. **B.R. Murray:** None. **D.I. Bermudez:** None. **L. Colon-Serrano:** None. **B.D. Sandy:** None. **A.J. Robison:** None. **A.L. Eagle:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.10

Topic: G.09. Drugs of Abuse and Addiction

Support: National Institute on Drug Use, USA, DP1DA042232

Title: Reelin deficiency exacerbates cocaine-induced hyperlocomotion by enhancing neuronal activity in the dorsalmedium striatum

Authors: *R. AHAMMAD[1], A. IEMOLO[1], A. NUR[1], A. MARTINEZ[2], C. CROOK[2], A. TURNER[1], P. MONTILLA-PEREZ[1], G. GUGLIELMO[2], F. TELESE[1];
[1]Dept. of Med., [2]Dept. of Psychiatry, Univ. of California San Diego, La Jolla, CA

Abstract: Reelin is an extracellular matrix glycoprotein expressed in Cajal Retzius (CR) cells during early brain development when it is required for neuronal migration, spine formation, synaptogenesis. In the postnatal brain, Reelin is expressed mainly in γ-aminobutyric acid-(GABA)ergic interneurons and regulates synaptic plasticity and adult neurogenesis. Alterations in the Reelin signaling pathway are associated with several neurodevelopmental and psychiatric disorders such as autism, and schizophrenia (SCZ). Heterozygous Reeler (HR) mice expressing a reduced level of *Reln* gene exhibit learning and memory impairment, decreased behavioral inhibition, and increased impulsivity. These behavioral traits are linked to the vulnerability and development of substance use disorders (SUD). However, the role of Reelin in regulating cellular and behavioral effects of addictive drugs remains largely unknown. Here, we compared HR mice to wild-type (WT) littermate controls to investigate the contribution of Reelin signaling to the hyper-locomotor and rewarding effects of cocaine. After a single dose of cocaine injection, HR mice showed enhanced cocaine-induced locomotor activity compared to WT controls, however sex does not play a role in the increased stimulatory effects of cocaine in HR mice. After repeated injections of cocaine, Reelin deficiency also led to increased cocaine-induced locomotor sensitization, which persisted after a week of withdrawal. In contrast, Reelin deficiency did not affect the rewarding effects of cocaine measured in the conditioned place preference assay. The elevated cocaine-induced hyper-locomotion in HR mice resulted in increased Fos expression in the dorsal medial striatum (DMS) compared to WT. Finally, we found that *Reln* was highly co-expressed with the Drd1 gene, which encodes for the dopamine receptor D1, compared to Drd2 gene in the DMS. Our findings demonstrated that Reelin signaling has a role in modulating the hyperlocomotor effects of cocaine and gave insight into the neurobiological mechanisms of the Reelin mediated dopaminergic system in the DMS.

Disclosures: R. Ahammad: None. **A. Iemolo:** None. **A. Nur:** None. **A. Martinez:** None. **C. Crook:** None. **A. Turner:** None. **P. Montilla-Perez:** None. **G. Guglielmo:** None. **F. Telese:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.11

Topic: G.09. Drugs of Abuse and Addiction

Support: T32AA007456
R01AA023183
R01DA037294

Title: Brain-wide neurocircuit profiling using NeuroInfo-Rat: neuronal ensembles reactive to relapse-promoting vs. relapse-suppressing cues

Authors: *H. NEDELESCU[1], N. J. O'CONNOR[2], B. EASTWOOD[2], B. WANG[1], J. D. SITARAS[1], A. H. THAN[1], H. C. CHANG[1], E. WHITNEY[1], N. EMERSON[1], Z. MIKULSKI[3], F. WEISS[1], J. R. GLASER[2], N. SUTO[1];
[1]The Scripps Res. Inst., Scripps Res. Inst., La Jolla, CA; [2]MBF Biosci., MBF Biosci., Williston, VT; [3]La Jolla Inst. of Immunol., San Diego, CA

Abstract: Environmental stimuli signaling drug availability (S+) are well-known to promote relapse. However, we have also demonstrated that stimuli signaling drug omission (S-) can suppress relapse in rats. This bidirectional modulation of drug relapse is regulated by two functionally distinct coactive groups of infralimbic cortex (IL) neurons - neuronal ensembles or engram cells - with each group selectively reactive to S+ or S-. To date, the neuroanatomical source of afferents that activate these engrams remains unknown. We have thus conducted brain-wide analysis to identify engrams that send axonal projections (AAV2retro-GFP) to the IL and that are evoked by S+ or S- (Fos) in different groups of rats trained to self-administer cocaine or alcohol. Automated brain-wide neuronal profiling is available for mice but similar methods are not yet available for rats, even though rats are the preferred animal model for studying more complex behaviors to model drug addiction. We, therefore, developed an automated 3D brain-wide profiling method for rats where image data and cell counts were registered using NeuroInfo-Rat to the Waxholm rat atlas. Briefly, imaged serial brain sections are aligned and registered to the Waxholm rat atlas coordinate system. Then, Fos- and GFP-positive IL-projecting neurons are detected with single cell resolution in NeuroInfo-Rat using a deep learning algorithm with anatomic specificity conferred by matching image data to the atlas coordinate space. In summary, this study provides a new tool for automated 3D brain-wide profiling of rat brain tissue expanding our knowledge of brain circuitry mediating environmental modulation of drug relapse.

Disclosures: H. Nedelescu: None. **N.J. O'Connor:** None. **B. Eastwood:** None. **B. Wang:** None. **J.D. Sitaras:** None. **A.H. Than:** None. **H.C. Chang:** None. **E. Whitney:** None. **N. Emerson:** None. **Z. Mikulski:** None. **F. Weiss:** None. **J.R. Glaser:** None. **N. Suto:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.12

Title: WITHDRAWN

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.13

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH NIDA R01DA052465 Epigenetic mechanisms of sustained transcription across cocaine abstinence

Title: Epigenetic regulation of drug addiction susceptibility by Nr4a1 enhancer variant

Authors: *J. WINTER, M. T. WOOLF, K. S. KRICK, D. K. FISCHER, S. ZHANG, E. A. HELLER;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Despite the high numbers of cocaine dependent individuals in the US, effective and targeted therapies are still missing. Our research focuses on persistent cocaine-induced transcriptional changes in the brain during abstinence. We were able to identify the nuclear orphan receptor Nr4a1 as a critical player during abstinence. Nr4a1 is a transcription factor acting as an immediate early gene upon various stimuli. We could show that cocaine regulates Nr4a1 and target gene expression via histone post-translational modifications (HPTMs). In addition, we could show that CRISPR-mediated regulation of Nr4a1 bidirectionally modulates cocaine behavior. We aim to further characterize this potential master regulator of cocaine-induced transcription during abstinence to enable the development of new therapeutics for cocaine dependence. Recent evidence shows that HPTMs regulate gene expression via chromatin accessibility and transcription factor recruitment. To investigate the functional relevance of certain HPTMs, we make use of a novel method called ICuRuS currently established by our group to perform transcriptional and epigenetic profiling of specific neuronal cell types in the mouse brain. We also apply epigenetic editing using a modified dCas9 protein to further functionally characterize HPTMs identified by ICuRuS. In a second approach we use chromatin conformation capture and a CRISPR-dCas9-based approach to identify and characterize potential enhancer regions of Nr4a1 affected by cocaine abuse. Since genetic variation plays a major role in addiction neurobiology, we are screening these cis-regulatory elements for potential genetic variants to validate addiction-associated risk loci previously identified in genome-wide association studies.

Disclosures: J. Winter: None. **M.T. Woolf:** None. **K.S. Krick:** None. **D.K. Fischer:** None. **S. Zhang:** None. **E.A. Heller:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.14

Topic: G.09. Drugs of Abuse and Addiction

Support: R00DA045795
P30DA033934
R25GM090084

Title: Zfp189 function in the nucleus accumbens regulates cocaine-induced transcription and behaviors in a cell type specific manner

Authors: *G. SILVA[1], J. PICONE[2], A. KAPLAN[4], R. L. NEVE[5], X. CUI[3], P. J. HAMILTON[6]; [1]Pharmacol. and Toxicology, [2]Neurosci. Grad. Program, [3]Dept. of Anat. and Neurobio., Virginia Commonwealth Univ., Richmond, VA; [4]Virginia Tech. Univ., Blacksburg, VA; [5]Gene Delivery Technol. Core, Massachusetts Gen. Hosp., Boston, MA; [6]Virginia Commonwealth Univ. Hlth. Syst., Virginia Commonwealth Univ. Hlth. Syst., Richmond, VA

Abstract: Previous work has demonstrated that *Zfp189* is a gene target through which the cAMP-response element binding (CREB) transcription factor (TF) regulates the reinforcing effects of cocaine within the nucleus accumbens (NAc). However, the exact NAc cell-type specific mechanisms through which *Zfp189* expression is able to regulate cocaine behavior remains unclear. The *Zfp189* gene product is a Krüppel associated box (KRAB) zinc finger TF of unknown function. To directly interrogate the transcriptional function and gene targets of ZFP189, we reprogrammed the endogenous ZFP189^{WT} by replacing the repressive KRAB domain with an enhanced transcriptional activation domain (VP64-p65-Rta (ZFP189^{VPR}) or by removing the functional moiety entirely (ZFP189^{DN}). We demonstrate that these synthetic ZFP189 TFs exert divergent transcriptional regulation at a *luciferase* target gene, *in vitro*. Upon packaging these ZFP189 TF constructs in herpes viral vectors (HSVs) and surgically delivering to mouse NAc, we identify that the synthetic ZFP189^{VPR} specifically affects cocaine, but not morphine or saline, behaviors. Further, in analyzing these tissues with bulk RNA sequencing (RNAseq) approaches, we see only mice with ZFP189^{VPR} intra-NAc and treated with cocaine experience significant NAc transcriptional regulation. To understand the NAc cell-type specific correlates of this drug-specific result, we are in the process of performing single nuclei RNA sequencing (snRNAseq) on infected NAc tissues. We next investigated the NAc cell type specific contribution of our ZFP189 variants to cocaine-induced locomotor behavior. We utilized transgenic mice that express Cre recombinase under the *Drd1*- or *Drd2*-promoter in combination with Cre-dependent expression vectors to express our synthetic ZFP189 TFs selectively in *Drd1*+ or *Drd2*+ NAc medium spiny neurons (MSNs). By delivering ZFP189^{VPR} to *Drd1*+ MSNs, we observed an increase in cocaine-induced locomotor behavior. Interestingly, by delivering ZFP189^{WT} to *Drd2*+ MSNs, we observed a similar cocaine-induced increase in locomotive behavior. Given the noted opposing roles of the two MSN subtypes in reward-related behaviors, and the observed opposite transcriptional control of our synthetic ZFP189 TFs, it is possible that we are dysregulating a ZFP189-governed opponent process between the MSN subtypes. Lastly, we investigated the consequences of altered ZFP189-mediated transcriptional function on dendritic spine density and morphology in *Drd1*+ or *Drd2*+ MSNs. Collectively, this work links the MSN-specific function of a drug-induced TF in governing lasting drug-related transcriptional neuroadaptations and behaviors.

Disclosures: G. Silva: None. **J. Picone:** None. **A. Kaplan:** None. **R.L. Neve:** None. **X. Cui:** None. **P.J. Hamilton:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.15

Topic: G.09. Drugs of Abuse and Addiction

Support: NRF-2021R1I1A1A01044359
NRF-2020R1A6A3A01099508
2018M3C7A1024152

Title: Silent synapse contribution to behavioral alterations after chronic cocaine exposure by D1-MSN specific GluN2B modulation

Authors: *H.-J. KIM, K.-B. SUNG, H.-Y. LEE, T. YOO, J. SHIN, J.-H. KIM;
POSTECH, POSTECH, Pohang, Korea, Republic of

Abstract: Silent synapse expresses only NMDAR subtype 2B (GluN2B)-containing NMDARs without AMPARs in the postsynaptic membrane. They are predominant during the developing stage of neurons and will be un-silencing by AMPARs recruiting (synaptic maturation) or disappear by synaptic elimination. However, silent synapses remerged significantly after repeated cocaine exposure. Cocaine induced silent synapse generation is prominent subsequential plasticity of striatal medium spiny neurons (MSNs), and *De-novo* synthesis of GluN2B is necessary for cocaine induced silent synapse formation. Its formation and maturation are highly correlated with addiction-like behavior expression and maintenance. However, GluN2B is hard to modulate since GluN2B encoded gene *GRIN2B* is lethal, critical for neuronal development, and expressed in various cell types. Thus, we adapted *cre* inducible GluN2B modulation by *CRISPR-Cas9* or *shRNA* system to overcome limitations that enable cell type (D1R-MSNs) and area-specific (NAc shell area) modulation without unwanted effects, such as developmental or global KO impacts of target gene deletion. By conditional GluN2B modulation during cocaine exposure, the silent synapse formation was disabled, but the cocaine induced behavioral changes were not all disrupted. From the electrophysiological and anatomical evidence, we will discuss and suggest how silence synapses contribute to behavioral changes during drug addiction progress.

Disclosures: H. Kim: None. **K. Sung:** None. **H. Lee:** None. **T. Yoo:** None. **J. Shin:** None. **J. Kim:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.16

Topic: G.09. Drugs of Abuse and Addiction

Support: T32 NS007433-23

Title: Investigating sucrose- and cocaine-associated ensembles in the nucleus accumbens of mice

Authors: *T. SCHALL[1], Y. DONG[2], K.-L. LI[1];
[2]Univ. of Pittsburgh, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Drug craving and relapse are prominent in substance use disorders (SUD) and are often instigated by re-exposure to the cues previously associated with drug taking, even after prolonged drug abstinence. Rodent studies reveal that drug-induced changes in principal medium spiny neurons (MSNs) within the nucleus accumbens (NAc) play a critical role in cue-induced drug seeking. One such critical change is cocaine-induced generation of AMPA receptor (AMPAR)-silent excitatory synapses, which rewire the NAc circuit and are proposed as key synaptic substrates in forming NAc ensembles that support cocaine-associated memories at the circuit level. However, it is unclear if silent synapses form in response to natural rewards or if silent synapses are a unique synaptic substrate generated in response to cocaine exposure. Our current study is designed to examine the roles of silent synapses and NAc ensembles in sucrose vs. cocaine seeking. Our results show that silent synapses are generated at different magnitudes in the NAc following cocaine vs. sucrose self-administration. Furthermore, we detected cocaine-cue and sucrose-cue ensembles in the NAc, each of them comprising of a small population of NAc neurons displaying temporally contingent activities with cue-induced operant responding. Collectively, these preliminary findings provide evidence for sucrose-cue vs. cocaine-cue ensembles in the NAc and set up the study to determine the role of silent synapses in forming these reward-specific ensembles.

Disclosures: T. Schall: None. **Y. Dong:** None. **K. Li:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.17

Topic: G.09. Drugs of Abuse and Addiction

Title: Sex differences in cocaine-induced activation of the posterior paraventricular thalamic nucleus

Authors: *A. VASQUEZ, J. R. MARTZ, J. M. DOMINGUEZ;
Univ. of Texas At Austin, Austin, TX

Abstract: The paraventricular thalamic nucleus (PVT) is a subregion of the thalamus that has connections to the mesolimbic system via monosynaptic projections to the nucleus accumbens,

which makes it a potential neural target for reward modulation. While evidence supports a modulatory role for the PVT in cocaine-induced neural and behavioral activity in males, whether this is true for females and whether sex differences in this modulation exist is still unknown. To this end, we examined cocaine-induced Fos-immunoreactivity (Fos-ir), as a marker of neural activation, in the PVT of male and female rats. Cocaine-induced changes in locomotion, as a marker of behavioral changes, were also obtained. Results showed increases in locomotion after cocaine administration, but no differences between males and females were found. However, cocaine increased neural activity in the PVT of males, but not females. Further analyses revealed that the posterior PVT of males, but not the anterior, had greater cocaine-induced Fos-ir. The present study provides evidence for sex differences in cocaine activity within the PVT. Specifically, our results suggest sexual dimorphism in how the PVT responds to cocaine and also suggests anatomical specificity within the PVT in the processing of this drug stimulation.

Disclosures: A. Vasquez: None. **J.R. Martz:** None. **J.M. Dominguez:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.18

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH-DA044204
NIH-R21-DA045277

Title: Effect of rate of intravenous cocaine infusion on locomotor sensitization in female rats using DeepAnimalToolkit, a new automated approach to behavioral analysis

Authors: *A. D. MAITLAND[1], G. KAUL[1], A. EBAN-ROTHSCHILD[1], T. E. ROBINSON[1], C. R. FERRARIO[1,2];
[1]Psychology, [2]Pharmacol., Univ. of Michigan, Ann Arbor, MI

Abstract: The speed at which addictive drugs reach the brain influences the magnitude of their neurobehavioral effects and increases abuse liability. For example, in rats fast rates of i.v. cocaine infusion (5 s) induce greater cocaine self-administration, and enhance psychomotor sensitization compared to the same dose of drug delivered slowly (90 s). In addition, fast cocaine infusion produces stronger c-fos activation within nucleus accumbens (NAc) than slow infusion. However, most rate of infusion (ROI) studies examined effects of just one or two infusions, and none had examined ROI effects on c-fos in females. Therefore, we examined locomotor sensitization and c-fos induction in female Long-Evans rats given repeated fast (5 s) or slow (90 s) cocaine (50 µl, 2.0 mg/kg i.v.) or saline infusions (50 µl, i.v.). Rats were given one infusion per session, three sessions per week, for 8 total infusions. Videos were recorded throughout each session. To examine long-lasting effects, some rats were then re-exposed to cocaine (fast or slow) after 14 days of withdrawal, and cocaine-induced c-fos induction in the NAc and

dorsolateral striatum (DLS) was examined. Saline controls given a single saline or cocaine infusion (fast or slow) were also included. We applied a novel approach to measure locomotion using DeepAnimalToolkit (DpA), a computer vision toolbox to track animals in low lighting conditions recently developed (Kaul and Eban-Rothschild, in preparation). Results from this automated approach were directly compared to traditional hand scoring measures. DpA measures of locomotor activity strongly correlated with hand-scored locomotor measures, providing an unbiased and reliable method to quantify this behavior. Initial results show that fast repeated cocaine infusions induced locomotor sensitization, whereas slow repeated infusions did not. To our knowledge, this is the first demonstration that repeated slow infusions of cocaine do not produce sensitization in either sex, and suggests that although total drug exposure is identical, the speed of drug delivery strongly influences cocaine-induced behavioral plasticity in females. Ongoing studies are examining cocaine-induced c-fos induction. Based on previous studies, we expect more robust induction in the 5 s group, but that this effect may be more pronounced in DLS than NAc of females. Together these data reveal how varying pharmacokinetics influence cocaine-induced neurobehavioral plasticity in females, and apply a new method for automated quantification of locomotor sensitization behavior.

Disclosures: **A.D. Maitland:** None. **G. Kaul:** None. **A. Eban-Rothschild:** None. **T.E. Robinson:** None. **C.R. Ferrario:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.19

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH-NIDA R01DA044204
NIH-NIDA T32 DA7281

Title: Sex-differences in cocaine-induced glutamatergic plasticityin the nucleus accumbens

Authors: *A. M. CATALFIO[1], T. L. FETTERLY[1], A. M. NIETO[1], T. E. ROBINSON[2], C. R. FERRARIO[1,2];
[1]Pharmacol., [2]Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: The development and persistence of addiction is in part mediated by drug-induced alterations in nucleus accumbens (NAc) function. Activity of this region mediates drug-craving and drug-seeking behaviors. AMPA-type glutamate receptors (AMPARs) provide the main source of excitatory drive to the NAc and enhancements in transmission of calcium-permeable AMPARs (CP-AMPARs) mediate increased cue-triggered drug-seeking following prolonged withdrawal. Cocaine treatment regimens that result in psychomotor sensitization enhance subsequent drug-seeking and drug-taking behaviors. Furthermore, cocaine-induced locomotor sensitization followed by 14 days of withdrawal (WD) results in an increase in NAc GluA1 and

GluA2 subunit surface expression, consistent with an increase in GluA2-containing, non-CP-AMPARs, and increases in NAc AMPA/NMDA ratio, consistent with enhanced glutamatergic synaptic transmission. However, very few studies have examined cocaine-induced alterations in synaptic transmission of females or potential effects of experimenter administered cocaine on NAc CP-AMPAR mediated transmission in either sex. Therefore, here male and female rats were given repeated systemic cocaine (coc) injections to induce locomotor sensitization (15mg/kg, i.p. 1 injection/day, 8 days). Controls received repeated saline (sal; 1 mL/kg, i.p). After 14-16 days of WD brain slices were prepared and whole-cell patch clamp approaches were used to measure spontaneous excitatory postsynaptic currents (sEPSC), paired pulse ratio, and CP-AMPAR transmission using the selective CP-AMPAR antagonist naspm (200uM) in the NAc core. Additional rats from this same cohort were instead given a challenge injection of coc at WD14 to assess the expression of locomotor sensitization. Repeated coc produced locomotor sensitization in both sexes that was apparent during initial induction and at WD14. When recordings were made, we found an increase in sEPSC frequency, but not amplitude, in coc vs sal pretreated males. However, there were no differences in paired pulse ratio between these groups. Sensitivity to naspm was also similar in coc and sal pretreated males. In contrast, in females there were no significant differences between coc and sal groups on any measure, despite females showing robust locomotor sensitization. Overall, data in males suggest that experimenter administered coc does not produce enhancements in NAc postsynaptic AMPAR transmission. They also reveal striking sex differences in cocaine-induced NAc glutamate plasticity. Ongoing studies are examining potential sex differences following intermittent access cocaine self-administration.

Disclosures: A.M. Catalfio: None. **T.L. Fetterly:** None. **A.M. Nieto:** None. **T.E. Robinson:** None. **C.R. Ferrario:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.20

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant RO1 DA053743-01A1

Title: Reelin protein marks cocaine-sensitive Drd1+ medium spiny neurons and modulates the behavioral response to cocaine

Authors: *K. BRIDA[1], R. A. PHILLIPS[1], N. DAVIS[1], K. R. MAYNARD[2], K. MARTINOWICH[3], J. J. DAY[1];
[1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]Mol. Neuroanatomy, Lieber Inst., Baltimore, MD; [3]Lieber Inst. for Brain Develop., Pasadena, MD

Abstract: Reelin is a large, secreted glycoprotein with a well-characterized role in brain development and links to numerous neuropsychiatric disorders. While *Reln* mRNA transcripts, which encode Reelin protein, are abundantly expressed in the adult striatum, hippocampus, and cerebellum, Reelin's cellular distribution and functional role in the adult brain remains poorly characterized. Using a recently generated cellular atlas of the rat nucleus accumbens (NAc) following cocaine experience, we identified *Reln* mRNA as a marker of cocaine-responsive *Drd1*+ medium spiny neurons (MSNs). Here, we sought to further delineate the cellular distribution of *Reln* mRNA in the NAc, to define Reelin's role in dopamine-dependent striatal functions, and to determine whether *Reln* contributes to behavioral responses to cocaine. Using multiplexed fluorescence in situ hybridization for *Reln* and markers of striatal neuron subtypes, we observed broad expression of *Reln* mRNA throughout the rat striatum, with enrichment in *Drd1*+ MSNs. These results were mirrored in postmortem human NAc tissue, where *RELN* mRNA was significantly more abundant in NAc *DRD1*+ MSNs as compared to other cell types (N=2 donors, 2 sections/donor, 1,156 cells). Next, we designed a CRISPR sgRNA targeting the *Reln* promoter to enable bidirectional manipulation of *Reln* mRNA and protein levels with CRISPR activation (CRISPRa) or CRISPR interference (CRISPRi). Notably, CRISPRa overexpression of *Reln* in rat primary striatal neuron cultures enhanced stimulus-dependent transcription of immediate early genes following dopamine stimulation. Likewise, CRISPRi-mediated *Reln* knockdown blunted dopamine-induced increases in MSN firing rate, without altering baseline electrophysiological properties. Further, targeted striatal knockdown of *Reln* via stereotactic delivery of *Reln* CRISPRi lentiviral expression vectors prevented formation of conditioned place preference for cocaine in Sprague-Dawley rats. Taken together, these results reveal a key role for Reelin in the transcriptional and physiological response to dopamine and demonstrate that Reelin is required for cocaine-related behavioral adaptations. Ongoing studies are combining pharmacological, genetic, and slice electrophysiological approaches to identify molecular mechanisms of Reelin signaling and further explore Reelin's contribution to striatal function.

Disclosures: K. Brida: None. **R.A. Phillips:** None. **N. Davis:** None. **K.R. Maynard:** None. **K. Martinowich:** None. **J.J. Day:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.21

Topic: G.09. Drugs of Abuse and Addiction

Support: BBRF/NARSAD YI Award
McKnight NBD Award
R01MH114990
R01DA053743

Title: Multiomic profiling of the rat nucleus accumbens reveals cell-type specific chromatin remodeling and transcriptional alterations after cocaine experience

Authors: *J. J. TUSCHER[1], R. A. PHILLIPS, III[1], L. IANOV[1], S. L. FULTON[2], A. E. LEPACK[2], I. S. MAZE[2], J. J. DAY[1];
[1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Cocaine use elevates dopamine levels in the nucleus accumbens (NAc) to initiate cell signaling cascades that engage transcriptional machinery and promote long-lasting synaptic and behavioral adaptations. At the molecular level, enduring drug-induced changes in gene expression in the NAc are thought to be mediated in part by chromatin reorganization within cocaine-affected cell populations. Prior studies using epigenomic profiling of bulk NAc tissues have identified widespread changes in chromatin-associated proteins, histone modifications, and DNA methylation following cocaine experience. However, little is known regarding how cocaine intake alters chromatin dynamics in a cell-specific manner within the NAc, or whether these changes persist long after cessation of drug use. Here, we used an extended access cocaine intravenous self-administration (IVSA) model to profile long-lasting chromatin and transcriptional alterations induced by volitional cocaine use with single-cell resolution in a rat model system. We observed previously described features that model aspects of human substance use disorders, including escalation of intake across acquisition and increased cocaine seeking following 30 days of withdrawal from cocaine IVSA. Multiomic profiling with single-nucleus RNA sequencing (snRNA-seq) and single-nucleus Assay for Transposase Accessible Chromatin (snATAC-seq) on 39,325 nuclei from the rat NAc after 30 days of withdrawal confirmed previously identified neuronal and non-neuronal cell types in the NAc. Comparison of accessible chromatin regions between annotated cell types revealed thousands of cell-selective regulatory elements, many of which are linked to genes previously implicated in substance use disorders and motivated behavior. Moreover, this dataset revealed enduring and cell-specific chromatin alterations present 30 days after cocaine withdrawal. These results provide key insights into how cellular diversity contributes to chromatin remodeling and transcriptional alterations following cocaine experience, and suggest the importance of cell-type specific genomic regulation in the progression of substance use disorders.

Disclosures: **J.J. Tuscher:** None. **R.A. Phillips:** None. **L. Ianov:** None. **S.L. Fulton:** None. **A.E. Lepack:** None. **I.S. Maze:** None. **J.J. Day:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.22

Topic: G.09. Drugs of Abuse and Addiction

Support: Swedish Research Council, VR project number 2018-02320

Title: The role of the central amygdala transporter GAT-3 in cocaine addiction in male and female Wistar rats

Authors: *A. LGUENSAT, G. AUGIER, E. AUGIER;
Ctr. for Social and Affective Neuroscience, BKV, Linköping Univ., Linköping, Sweden

Abstract: Substance use disorder is a major public health problem. Cocaine is one of the most abused substances and cocaine use disorder (CUD) is characterized by high and escalating levels of drug intake. Despite the availability of many animal models of CUD, little is known about the neurobiological substrates underlying the transition from controlled to pathological use. The central amygdala (CeA) is amongst the substrates playing a role in the transition to compulsive drug use. In particular, decreased expression of the GABA transporter GAT-3 within the CeA was shown to be causal for addiction-like state to alcohol but no data is currently available about the role of GAT-3 in CUD. The main aims of this study were to investigate whether GAT-3 function is impaired in the CeA of a rat model of CUD and whether experimentally inhibiting the function of GAT-3 in the CeA would promote the loss of control over cocaine consumption and the emergence of addiction-like behaviors in rats of both sexes. Using intravenous operant self-administration, we first gave rats an extended access to cocaine (LgA), which promoted escalation of their intake and found that, GAT-3 expression in the CeA was down-regulated. We then investigated the functional role of GAT-3 in both male and female Wistar rats by injecting a viral vector (AAV) containing either a shRNA targeting *Slc6a11* (the gene coding for GAT-3) or a scrambled vector control into the CeA. We demonstrated that GAT-3 knockdown animals under short access (ShA) escalated their cocaine intake, produced enormous efforts to get cocaine injections during a progressive ratio schedule of reinforcement session and showed higher cocaine craving levels. These findings may help advance the current knowledge about the neural substrates of cocaine addiction. They also indicate that GAT-3 and GABAergic transmission in the CeA may be relevant targets for developing new pharmacotherapies to treat CUD.

Disclosures: **A. Lguensat:** None. **G. Augier:** None. **E. Augier:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.23

Topic: G.09. Drugs of Abuse and Addiction

Title: Projections from the ventral tegmental area to the medial prefrontal cortex are intact in trpc4 knockout rats that display a reduction in cocaine self-administration.

Authors: *K. R. ILLIG[1], W. D. KLIPEC[2];
[1]Univ. of St. Thomas, Saint Paul, MN; [2]Drake Univ., Des Moines, IA

Abstract: Rats lacking the canonical transient receptor potential channel (TRPC) *trpc4* gene display a reduction in cocaine self-administration, without displaying a reduction in learning or performance for natural rewards (Klipec et al. 2016, Behavioural Brain Research). We have hypothesized that this results from the relative lack of dopaminergic cells in the VTA that exhibit high spontaneous activity in in *trpc4* knockout (KO) animals. However, the reduction in neurons exhibiting high spontaneous activity in KO animals also may cause changes in axon pathfinding during development, such that the observed behavioral traits may result from a compromised VTA-to-prefrontal pathway, rather than a lack of activity in the VTA. This pathway is part of a circuit that has been proposed to incorporate novelty and memories into motivated action (e.g., Lisman and Grace, 2005). To investigate the nature of the VTA-mPFC pathway in WT and KO rats, we injected a retrograde tracer (Fluoro-Gold) into the medial prefrontal cortex (mPFC) in WT and *trpc4* KO littermate rats and compared the proportion of mPFC-projecting neurons in the VTA. Rats were Long Evans strain KO and WT littermates that originated from a Fisher 344 lineage as previously described (Klipec et al. 2016). Genotyping was carried out using quantitative polymerase chain reaction. Rats (350-450 g) were anesthetized and stereotaxically injected in mPFC with the retrograde tracer Fluoro-Gold (Fluorochrome LLC, Denver, CO). After a 10-14 day survival, rats were euthanized and perfused with 4% paraformaldehyde, the brains extracted and post-fixed, cryoprotected with 30% sucrose, and sectioned with a cryostat. Flouro-Gold was visualized using immunocytochemical methods using fluorescence, and cells were evaluated using confocal laser scanning microscopy. Results show that nearly half of VTA cells in both WT and KO animals displayed a projection to mPFC (mean WT = 44.7% SD = 11.2%; mean KO = 49.6% SD = 8.6%; ns). These results demonstrate that although the VTA in *trpc4* KO animals lacks cells with high spontaneous activity, the VTA projection to the mPFC remains intact. This suggests that the lack of cocaine self-administration and impulsivity in *trpc4* KO animals (see adjacent poster) may result from the decreased excitability of dompaminergic neurons in the VTA rather than from the lack of a VTA-mPFC pathway.

Disclosures: K.R. Illig: None. **W.D. Klipec:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.24

Topic: G.09. Drugs of Abuse and Addiction

Title: The effects of acute cocaine and amphetamine on complex reversal learning in trpc4 knockout and wild type rats

Authors: *W. KLIPEC, L. GUCK, S. CHAUDHARY, S. SEETHAMRAJU, A. CLARK, H. MILLER, B. GATEWOOD;
Psychology & Neurosci., Drake Univ., Des Moines, IA

Abstract: Our previous research showed deletion of the *trpc4* gene produced a brain-wide elimination of TRPC4 channels, including a subpopulation of TRPC4-bearing dopamine neurons in the ventral tegmental area (VTA). That research reported that compared to wild-type (WT) rats, *trpc4* knockout (KO), rats exhibited reduced cocaine self-administration and reduced cell-firing rates in VTA dopamine neurons, with no differences between genotypes in simple or complex reversal learning. Subsequently, using a DRL reinforcement schedule, we have found that cocaine administration produces a greater dose-dependent increase in early responding (impulsivity) in WT than KO rats. Here we examined the effects of acute cocaine on the performance in a Y-Maze learning and reversal tasks. All three experiments used separate groups of naive KO (n=6) and WT (n=6) rats, counterbalanced across mazes, and trained to a criterion of 95% correct responses before testing and reversals. In Experiment 1, rats were trained to run to the lighted arm of the Y-Maze, reversed to running to the unlighted arm, and reversed again to running to the lighted arm. We found no significant differences in rate of acquisition or terminal performance between the genotypes. In Experiment 2, rats were trained to run to the lighted arm of the Y-Maze. Subsequent testing with cocaine (0, 5, 10 and 15 mg/kg) revealed no significant reduction in correct responding for either genotype. In Experiment 3, we trained rats to run to the lighted arm and then reversed to run to the unlighted arm. Acute cocaine (0, 5, 10 and 15 mg/kg) revealed no significant disruption of performance for either genotype. Following a week of retraining on the same reversal, and testing with 0, 1, 2, and 3 mg/kg of d-amphetamine, we found that d-amphetamine produced a significant dose dependent increase in errors for both KO and WT rats. These results replicate previous findings that KO and WT rats do not differ in learning discrimination tasks. Importantly, these results also show that the reduction in cocaine self-administration and decreased cocaine induced impulsivity on the DRL task in KO compared to WT rats are specific to those tasks and do not represent a more general disruption of learning or performance. The finding that amphetamine but not cocaine disrupts performance in both KO and WT rats suggests a possible selective role for TRPC4 channels in impulse-dependent dopamine pathways. We have also identified dopaminergic the pathways for both phenotypes between PFC and the VTA and nAcc (see adjacent poster). Taken collectively, our research suggests a potentially important role for the TRPC4 channels in cocaine addiction and dopamine disorders.

Disclosures: **W. Klipec:** None. **L. Guck:** None. **S. Chaudhary:** None. **S. seethamraju:** None. **A. Clark:** None. **H. Miller:** None. **B. Gatewood:** None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.25

Topic: G.09. Drugs of Abuse and Addiction

Support: Davidson college Faculty Study and Research Grant

Title: Unable to Attend-Elucidating the molecular mechanisms of action of cocaine by leveraging transcriptomics performed in specific populations of neurons in C. elegans

Authors: *R. EL BEJJANI;
Davidson Col., Davidson, NC

Abstract: Cocaine is one of the most widely abused drugs around the world and is also one of the better studied addictive drugs. Pharmacological, biochemical, and behavioral studies have shed significant light on some of the main molecular mechanisms of cocaine associated with drug seeking behavior. However, inhibition of these pathways alone is not sufficient to treat cocaine addiction, suggesting that additional mechanisms that remain unknown are involved. The fast generation time, paired with the huge number of genetic resources available, and with imaging and behavior tractability make *C. elegans* a very attractive model system to accelerate the process of discovery in the elucidation of the cellular and molecular mechanisms involved in the complex process of addiction. In our recent paper, we showed that Acetylcholine release is required for cocaine dependent egg laying in *C. elegans*. The impact of this work is two pronged, first, it highlights the power of simple behavioral analysis in *C. elegans* for the rapid interrogation of the molecular mechanisms of actions of drugs of abuse, second, it uncovered the role Ach signaling plays in cocaine-mediated behavior using a very well described model circuit, the *C. elegans* egg laying circuit. To follow up on our findings, we asked how acute exposure to cocaine affects gene expression in Acetylcholine neurons. We treated animals with cocaine twice and performed cellular dissociations and FACS sorting for all Acetylcholine neurons followed by RNA Seq analysis of the sorted neurons in cocaine treated and control animals. We identified 286 significantly differentially expressed genes, the majority of differentially expressed genes are upregulated in cocaine treated animals (230 upregulated genes) with the rest downregulated (56 genes). Clusters of differentially expressed genes include signaling enzymes, ion channels, neuropeptides and their receptors, transcription factors, as well as genes know to affect neuronal differentiation, axon guidance, synaptogenesis, and other neurodevelopmental mechanisms. We are currently following up on these results using genetic analysis and behavioral methods in *C. elegans*.

Disclosures: R. El Bejjani: None.

Poster

735. Cocaine: Pharmacology

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 735.26

Topic: G.09. Drugs of Abuse and Addiction

Support: R01DA07359
P01DA047233
K99AA027839
BBRF

Title: Epigenetic priming underlies cell-type-specific gene expression after cocaine withdrawal

Authors: *P. MEWS[1], Y. VAN DER ZEE[1], H. KRONMAN[1], A. GURUNG[1], A. RAMAKRISHNAN[1], C. J. BROWNE[1], R. FUTURAMA[1], M. ESTILL[1], M. RYAN[1], A. REYES[1], S. SIDOLI[2], L. SHEN[1], E. J. NESTLER[1];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Albert Einstein Col. of Med., New York, NY

Abstract: Substance use disorders represent an enormous public health crisis and are among the most intractable illnesses in our society. An ongoing focus of research into the molecular pathology of addiction are mechanisms by which neuronal gene regulation is altered in a central brain region of reward, the nucleus accumbens (NAc). Stable changes in chromatin are proposed to underlie the maladaptive transcriptional states in this brain region, which persist despite long-term drug withdrawal. However, there is no direct link between drug-induced epigenetic marks and aberrant gene expression programs that drive relapse. A fundamental challenge is determining which neuronal subtypes are responsible: the NAc is composed primarily of two opposing types of medium spiny neurons (MSNs), D1 and D2 dopamine receptor-expressing subtypes, which exhibit dramatic differences in activity and effects on drug reward. In these distinct subtypes, we examined how chronic cocaine modifies chromatin structure and characterized immediate versus persistent changes in gene regulation. We surveyed circuit-specific chromatin accessibility genome-wide in combination with unbiased histone modification profiling by mass spectrometry and ChIP-sequencing. We discovered that chronic cocaine persistently ‘scars’ chromatin structure in D1 MSNs, involving dramatic depletion of the histone variant H2A.Z at key neuronal genes related to synaptic plasticity. Genome accessibility is prominently increased at these genes even after prolonged withdrawal, linked to aberrant gene expression upon drug relapse. The histone chaperone ANP32E promotes the removal of H2A.Z. We demonstrate that cocaine withdrawal induces ANP32E selectively in D1 MSNs and that D1 MSN-selective ANP32E knockdown prevents cocaine-induced H2A.Z depletion and effectively blocks cocaine-conditioned place preference and self-administration. In contrast, the D2 MSN-specific knockdown of ANP32E enhances cocaine-related reward learning. These findings provide new insight into circuit-specific epigenetic priming as a critical mechanism and promising clinical target employed by drugs of abuse to modify brain function and behavior in lasting ways.

Disclosures: P. Mews: None. **Y. Van Der Zee:** None. **H. Kronman:** None. **A. Gurung:** None. **A. Ramakrishnan:** None. **C.J. Browne:** None. **R. Futurama:** None. **M. Estill:** None. **M. Ryan:** None. **A. Reyes:** None. **S. Sidoli:** None. **L. Shen:** None. **E.J. Nestler:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.01

Topic: H.04. Executive Functions

Support: BBSRC (Buckley PI)
MRC (Buckley PI)

Title: Low-dimensional neural population dynamics in macaque prefrontal areas during rule guided decision-making in a Wisconsin Card Sort Task (WCST) analogue.

Authors: *J. M. GALEAZZI, I. SALARIS, M. AINSWORTH, M. J. BUCKLEY;
Dept. of Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: Lesion studies in macaques have found dissociable impairments to rule-guided decision-making in a WCST analogue following damage to different prefrontal areas (Buckley et al., 2009). However, in order to elucidate the underlying computations and functional interactions operating within and between these regions it is necessary to record neuronal activity in multiple prefrontal areas simultaneously. In this study, we chronically implanted multi-electrode micro-arrays ('Utah arrays') in dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), orbitofrontal frontal cortex (OFC) and frontopolar cortex (FPC) of two rhesus macaques, allowing us to simultaneously record single and multiunit activity and local field potential (LFP) from all four regions together while the animals performed a WCST analogue; a task that requires flexible and uncued abstract rule shifts. Here we present preliminary results from these recordings showing the changes in the neural activity of each region across different task epochs and conditions. We document the extent to which different aspects of the task can be accurately decoded from the neural activity recorded on each of the arrays employing a variety of commonly used machine learning classification algorithms, and we present the decoding performance of individual cells, as well as the decoding accuracy from the population activity of each region. Even when information about the relevant abstract rule can be found in all recorded areas, we show the dynamic differences of time evolving neural trajectories of population activity in a low dimensional state space. Variations in the neural distance between the rule conditions show that changes in distance/dynamics occur at different times in different areas. Lastly, we show preliminary results across the four areas on detecting different latent states and neural states transitions using a Hidden Markov model (HMM).

Disclosures: J.M. Galeazzi: None. **I. Salaris:** None. **M. Ainsworth:** None. **M.J. Buckley:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.02

Topic: H.04. Executive Functions

Support: Clinician Investigator Program

Title: Neuronal ensembles in the primate prefrontal cortex during an associative memory task in virtual reality

Authors: *M. ABBASS[1], B. W. CORRIGAN[2], R. JOHNSTON[3], R. A. GULLI[4], A. J. SACHS[5], J. C. LAU[1], J. C. MARTINEZ-TRUJILLO[6];
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Abstract: The prefrontal cortex (PFC) is considerably expanded in anthropoid primates, and likely contributes to cognitive control and goal-directed behaviour. Single neurons in the primate PFC are reportedly tuned to task-related features in associative memory tasks; however, previous work has relied on tasks with limited ethological value. We therefore sought to utilize virtual reality to simulate an associative memory task while recording from ensembles of primate PFC neurons. Our goal was to characterize the spatiotemporal characteristics of PFC neurons during a naturalistic task. Two male rhesus macaques (*macaca mulatta*) were trained to navigate a virtual reality environment using a joystick and learn a context-colour association rule. We implanted each monkey with two 96-channel Utah arrays (Blackrock Microsystems) in the lateral PFC (dorsal and ventral areas 9/46) and simultaneously recorded from many single neurons. Neuron selectivity was evaluated using a linear regression (alpha = 0.05), and population decoding was performed using a linear support-vector machine with five-fold cross-validation. Mean decoding accuracy with standard error across sessions is presented. We recorded from 813 single neurons, with 299 (36.8%), 271 (33.3%) and 496 (57.7%) of neurons demonstrating significant selectivity to context, colour location and chosen side respectively. These features were decoded with a maximum of 73.0 ± 2.3% (context), 82.0 ± 2.0% (colour location) and 94.5 ± 0.7% (chosen side) accuracy. Context and colour location could be better decoded from neurons in the ventral PFC compared to the dorsal PFC. This information was decoded in a sequential manner as the primates made their decision, with context information appearing first, followed by colour location, and chosen side. In summary, PFC neuronal ensembles encode the elements needed for implementing a cognitive task, and these ensembles are activated sequentially when required. Context and colour order are more robustly decoded in the ventral PFC prior to decoding chosen side. This suggests the ventral PFC receives task-relevant visual information, in keeping with previous findings that the dorsal and ventral PFC receive information from the dorsal and ventral visual streams respectively. Regional specificity for different task features needs to be further studied and validated in human subjects, and this can have implications regarding neurosurgical planning and patient counselling. Additionally, brain-machine-interface systems may benefit by integrating neural data from the PFC, providing salient goal-related information including the content of a goal and its spatial location.

Disclosures: M. Abbass: None. **B.W. Corrigan:** None. **R. Johnston:** None. **R.A. Gulli:** None. **A.J. Sachs:** None. **J.C. Lau:** None. **J.C. Martinez-Trujillo:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.03

Topic: H.04. Executive Functions

Support: R01MH110831
P50MH094258
BCS-1554105
U01NS117839

Title: Single-neuron correlates of domain-general performance monitoring in the human medial frontal cortex and medial temporal lobe

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Abstract: Monitoring our own behavior without explicit feedback is a prominent human ability, enabling us to evaluate the accuracy and quality of action performance. In real life situations, we often need to rapidly learn to perform novel tasks with minimal instruction and time for practice, which requires domain-general monitoring that functions "out-of-the-box". At the same time, we need to improve our performance of each task by resolving performance disturbances with task-specific measures, which would require monitoring processes that specialize within certain domains or tasks. How does the medial frontal cortex (MFC) and medial temporal lobe (MTL) support both domain-specific and domain-general performance monitoring? We recorded single neurons in the MFC and MTL in 34 patients evaluated for epilepsy surgery. Subjects performed two tasks that involved three types of cognitive conflict: the Stroop task and Multi-source Interference Task (MSIT). Subjects estimated the frequency of conflict trials ("conflict probability" or "CP"), which was reflected in their reaction times and modelled using a hierarchical Bayesian framework. There are single neurons encoding conflict, error, and CP in either or both tasks, precluding a simplistic interpretation of domain generality. By contrast, population activity factorizes into a task dimension and a task-invariant dimension that decodes performance monitoring variables invariably across tasks. Interestingly, this task-invariant coding dimension still allowed readout of task-specific information. The geometry of such representation, formed by the same group of neurons, thus allowed downstream brain regions to read out both domain-general and domain-specific signals to initiate corresponding physiological and/or behavioral adaptations. The geometry and latency of performance monitoring signals depend on the brain areas. We found that the information occurred first in the pre-SMA, followed by ACC and MTL areas in both tasks. Performance monitoring signals may be conveyed to the MTL to form episodic memory of task experience, or for further evaluation of affective salience of such signals. Our analyses also revealed a putative neuronal mechanism for computing action errors. These findings reveal how representations of evaluative signals can be both abstract and task-specific, and a putative communication channels of performance monitoring information between areas.

Disclosures: Z. Fu: None. **A.N. Mamelak:** None. **R. Adolphs:** None. **U. Rutishauser:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.04

Topic: H.04. Executive Functions

Support: NIH Grant MH116526

Title: Differential Actions of Glutamatergic and GABAergic Prefrontal Corticotropin-Releasing Factor Neurons on Working Memory and Sustained Attention

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Abstract: The prefrontal cortex (PFC) supports multiple cognitive processes that guide goal-directed behavior, including working memory and sustained attention. While PFC-dependent cognitive dysfunction is associated with multiple behavioral disorders, our ability to treat this dysfunction is impeded by a limited understanding of the neurobiology of PFC-dependent cognition. Corticotropin-releasing factor (CRF) neurons and receptors have long been known to be prominent in the PFC. However, their potential role in higher cognitive function has been overlooked. In prior studies we demonstrated that chemogenetic activation of CRF neurons in the caudal, but not rostral, dorsomedial PFC (dmPFC) of rats impaired working memory. Conversely, inhibition of these neurons improved working memory. Similar cognitive actions of caudal dmPFC CRF neurons were observed in a task of sustained attention. Interestingly, while the working memory impairing actions of PFC CRF neurons were dependent on local CRF receptors, this was not the case for sustained attention. Consistent with this, direct activation and blockade of CRF receptors in the caudal dmPFC impairs and improves working memory, respectively, but have no effect on sustained attention. These observations indicate that caudal dmPFC CRF neurons regulate distinct cognitive processes via divergent projection pathways. We recently demonstrated that ~85% of caudal dmPFC CRF neurons are glutamatergic (CRF_{Glu}), while the remaining ~15% are GABAergic (CRF_{GABA}). Combined, these observations suggest the differential involvement of CRF_{GABA} vs. CRF_{Glu} subpopulations across working memory and sustained attention. To address this issue, we initiated studies to selectively chemogenetically activate caudal dmPFC CRF_{Glu} vs. CRF_{GABA} neurons in working memory and sustained attention tested animals. We observed that activation of CRF_{GABA} neurons impairs working memory but not sustained attention. In contrast, activation of CRF_{Glu} neurons impaired both working memory and sustained attention performance. The mediodorsal nucleus of the thalamus (MD_{thal}) plays a central role in PFC-dependent cognition. In additional studies, we have observed an unusually dense projection from caudal dmPFC CRF neurons to this nucleus and that CRF acts directly in the MD_{thal} to impair sustained attention. Collectively, these findings suggest that caudal dmPFC CRF_{Glu} neurons regulate PFC-dependent cognition via projections to the mediodorsal thalamus.

Disclosures: S.K. Cooke: None. **A. Martin:** None. **S. Nicol:** None. **J. Kiraly:** None. **C.W. Berridge:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.05

Topic: H.04. Executive Functions

Support: NIH Grant R01 5270633
COBRE 5-27132

Title: Representation of credit-deserving feature information and feature-specific reward prediction errors among prefrontal cortical areas during credit assignment

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Abstract: In reinforcement learning, the credit assignment problem, which is how an agent attributes the outcome of choice to a relevant event when there is a temporal gap or multiple inputs, has been a long-lasting question. The prefrontal cortex is well-suited for resolving this problem, but its neural mechanisms are still debated. To determine how the prefrontal cortex (PFC) helps to resolve this problem, we trained two monkeys on a credit assignment task and implanted large arrays of independently-positionable electrodes over the PFC, including ventral lateral PFC (vlPFC) and orbitofrontal cortex (OFC) (96 and 128 electrodes, respectively). Animals learned to attribute a choice outcome to one of several earlier cue features. Specifically, they were required to attend to both cue identity and cue location, but the location was relevant for only the immediate choice, whereas identity was relevant in future trials and so needed to be learned. Credit assignment, therefore, was required for identity but not location. Generic feedback for correct vs. incorrect outcomes was provided after the animal's choice, without conveying specific information about why that choice was correct or incorrect, thereby requiring an implicit linkage between outcome and remembered antecedent (cue identity) at that moment. We fit a hybrid reinforcement learning (RL) model to behavior and then applied those inferred RL parameters to two multi-regression models to understand the neural representation of cue identities, cue locations, choice outcomes, cue values, and reward prediction errors (RPEs). During initial cue presentation, vlPFC and OFC neuronal activity conveyed both cue identity and location. During feedback, neuronal activity conveyed feature-specific reward prediction errors (RPEs that also signaled which specific cue deserved credit) in both areas. Interestingly, in the vlPFC, location information necessary for the immediate response was evident during the delay but decreased after the choice was made. Moreover, during feedback, vlPFC activity conveyed cue identity and feature-specific RPEs earlier than OFC. This information is the key ingredient requiring credit assignment in this task. These results suggest that vlPFC may be more centrally involved than OFC during critical steps in the credit assignment process.

Disclosures: E. Lee: None. **W.F. Asaad:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.06

Topic: H.04. Executive Functions

Support: NSF Grant BCS-1827752

Title: Investigating neural dynamics of proactive control in a standard AX-CPT using high density electroencephalography

Authors: *A. MYSORE, C. BLAIS, M. SANTELLO;
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Abstract: The ability to inhibit a planned but inappropriate response, and switch to executing a goal-relevant motor response, are critically important for the regulation of motor behaviors. Movement control exhibited as execution, inhibition, or switching could be mediated by different mechanisms. Proactive control, an anticipatory form of control, uses contextual information (cues) to predict the nature of an interference event (probe) and plan a response accordingly. Previous work has speculated the contingent negative variation (CNV) identified through EEG to be an indicator of proactive control. Additionally, some fMRI studies indicate the dorsolateral prefrontal cortex and pre-supplementary motor area to be involved in proactive control. However, the brain signal dynamics and network interactions are still debated. We used an AX-version of the continuous performance task (AX-CPT) to evaluate the neural correlates of proactive inhibition and switching of motor actions. In an AX-CPT trial, a contextual cue stimulus (A or B) is presented, followed by a probe stimulus (X or Y) after an interstimulus interval. Different combinations of stimuli require the participant to either produce a target keypress response, or a non-target response by switching to a different keypress or inhibiting all responses. Our task was designed such that 40% of the time A was followed by an X requiring a target response keypress (habitually-trained movement execution condition). Hence, context A primes a habitual preparation of the target response requiring a last-minute override 10% of the time when Y appears as the probe to produce a non-target response. In contrast, context B is a definitive non-target response condition entailing a proactive preparation of non-target responses irrespective of the nature of the probe (X: 10%; Y: 40%). Twenty subjects (15 M, 5 F; age: 18-45 years) performed 2 experimental sessions: response inhibition (No-Go) and response switching (Go) AX-CPT while EEG (64-channel) was recorded. We found that participants predominantly used proactive control during both task sessions. Importantly, we found a statistically significant difference in the CNV between the A and B contexts from 600 ms to 1400 ms after the presentation of the cue at Cz in both sessions ($p < 0.01$). This finding indicates that CNV is a reliable neural correlate of proactive response modulation as a function of task context.

Disclosures: A. Mysore: None. **C. Blais:** None. **M. Santello:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.07

Topic: H.04. Executive Functions

Support: NIH R00MH116100
NIH EY017921
ONR N00014-22-1-2453
ONR N000142212453
The JPB Foundation
1R01EY027402-01
2T32EY007135-26

Title: A preserved spectro-laminar motif of local field potential power across cortical areas maps onto histologically-identified layers

Authors: *A. M. BASTOS[1], D. MENDOZA-HALLIDAY[6], A. J. MAJOR[7], N. LEE[6], M. LICHTENFELD[2], B. CARLSON[2], B. MITCHELL[2], P. D. MENG[2], Y. XIONG[3], J. A. WESTERBERG[4], J. H. KAAS[5], A. V. MAIER[4], R. DESIMONE[8], E. K. MILLER[7]; [1]Vanderbilt Univ., Nashville, TN; [2]Vanderbilt Univ., Brentwood, TN; [3]Psychology, [4]Dept. of Psychology, [5]Psychology Dept., Vanderbilt Univ., Nashville, TN; [7]The Picower Inst. for Learning and Memory, [6]MIT, Cambridge, MA; [8]mcgovern institute, Mit, cambridge, MA

Abstract: The mammalian cerebral cortex is organized into a six-layer motif with distinct cytoarchitectonic characteristics. This motif is ubiquitous across most of cortex and is thought to form the underlying architecture for a canonical cortical microcircuit that can be used to execute a wide variety of functions. Despite extensive anatomical characterization of this laminar motif, little is known about whether there is a corresponding physiological motif. Here, we report the discovery of such a motif in local field potential (LFP) power.
We analyzed electrophysiological recordings from laminar probes implanted across layers in a variety of cortical areas (V1, MT, V4, MST, LIP, 7A, right and left LPFC) in five macaque monkeys from three studies performed in different labs. We found that the relative power of the LFP across layers follows a characteristic pattern that distinguishes superficial from deep layers. Power in the gamma (40-150 Hz) frequency band was stronger in superficial electrode contacts. Power in the alpha/beta (8-30 Hz) band was stronger in deep electrode contacts. This spectro-laminar pattern generalized across cortical areas, monkeys, and studies. We then asked whether the pattern maps onto the six anatomical layers of the cortex. In several cortical areas of three monkeys, we first identified the spectro-laminar pattern and performed small electrolytic lesions at distinctive recording contacts to reference our electrode contacts to the laminar anatomy. In Nissl-stained histological sections, we mapped the spectro-laminar pattern with respect to the 6 cortical layers. The peak gamma band power was consistently localized in layers II/III whereas the peak alpha/beta band power was localized in layers V/VI. The cross-over between the

relative power of the gamma and alpha/beta bands was centered at layer IV.
Our results reveal the presence of a ubiquitous spectro-laminar motif of neuronal activity across cortex that maps onto the six-layered anatomical architecture. This motif represents a putative physiological signature of the canonical cortical microcircuit. Taking advantage of this motif, we propose a method for cortical layer identification in in vivo laminar electrophysiological recordings and demonstrate major advantages over the current source density method now used.

Disclosures: **A.M. Bastos:** None. **D. Mendoza-Halliday:** None. **A.J. Major:** None. **N. Lee:** None. **M. Lichtenfeld:** None. **B. Carlson:** None. **B. Mitchell:** None. **P.D. Meng:** None. **Y. Xiong:** None. **J.A. Westerberg:** None. **J.H. Kaas:** None. **A.V. Maier:** None. **R. Desimone:** None. **E.K. Miller:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.08

Topic: H.04. Executive Functions

Support: R01-MH55806
R01-EY019882
P30-EY08126
Canadian Institutes of Health Research Postdoctoral Fellowship

Title: Functional characterization of feedback-related negativity and associated sensory event-related potentials in medial frontal cortex

Authors: *A. SAJAD[1,2], S. P. ERRINGTON[1], J. D. SCHALL[2];
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Abstract: To evaluate our performance, we rely on external feedback. The feedback-related negativity (FRN) is an event-related potential (ERP) associated with feedback monitoring. However, the origin of the FRN and associated ERPs and the cognitive computations they reflect are not fully understood. To address this, we simultaneously recorded EEG over medial frontal cortex, and local field potentials within the dorsomedial frontal cortex (DMFC; 27 sessions) and mid-cingulate cortex (MCC; 28 sessions) in macaque monkeys performing a stop-signal task. Fluid reward was earned for generating a saccade to a target (no-stop trials) and for inhibiting it when a stop-signal appeared (canceled trials). The target location cued whether the upcoming reward value for the trial was high or low magnitude. Trials on which inhibition failed (noncanceled trials) were divided into those in which the saccade occurred after stop-signal presentation (i.e., explicit error trials; NC_{error}) and those in which the saccade occurred before the scheduled stop-signal delay ($NC_{premature}$). Following the response, two distinct auditory feedback tones indicated whether juice reward will be provided (canceled and no-stop trials) or not (noncanceled trials). Because $NC_{premature}$ trials were visually indistinguishable from no-stop trials

but were infrequent (~10%) the negative feedback on these trials was unexpected. The task design and set of conditions afforded the isolation of feedback-related ERP components and the assessment of their sensitivity to valence, expectancy, and value. In both DMFC and MCC, a prominent auditory-evoked potential (NP complex) was observed within the first 100 ms followed by the FRN peaking at ~160 ms and the associated positivity (P300) peaking at ~300 ms after the feedback. The auditory-evoked potentials in both MCC and DMFC exhibited a larger amplitude upon negative compared to positive feedback with enhanced amplitude when the negative feedback was expected. The FRN had a shorter duration in MCC compared to DMFC, exhibited no notable value sensitivity, and had no dependence on expectancy. The P300, especially in the DMFC, however, had a larger amplitude when the negative feedback was unexpected. These results illustrate ERPs in monkeys homologous to human feedback-related ERPs and demonstrate they are modulated by feedback valence and expectation, depending on epoch and brain area. Future work will link these features to neuronal spiking and EEG over the skull.

Disclosures: A. Sajad: None. **S.P. Errington:** None. **J.D. Schall:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.09

Topic: H.04. Executive Functions

Support: NIH R01 MH118929
NIH NEI R01 EY029250
NIH NIBIB R01 EB026953
NSF NCS 1954107/1734916
JASSO (Japan Student Services Organization)
Simons Foundation

Title: Inter-areal patterned microstimulation selectively drives PFC population activity across behavioral tasks

Authors: *J. SOLDADO MAGRANER[1], Y. MINAI[1], W. BISHOP[2], M. A. SMITH[1], B. M. YU[1];
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Abstract: A central problem in neuroscience is to understand how areas of the brain communicate. The intrinsic dynamics of each brain area are created both by the local neural circuitry as well as the inputs to that circuit from other brain regions, which shape ongoing computations. Hence, characterizing how inputs drive different population responses is key to understanding how brain circuits are controlled or modulated to flexibly produce different behaviors. To this end, we developed a novel inter-areal patterned microstimulation (uStim)

protocol that allowed us to finely manipulate the activity of a neural population in one brain area while simultaneously recording the activity of a second population in a different area. In macaques implanted with dual 96-channel Utah arrays, we manipulated the activity of different brain regions by electrically stimulating combinations of electrodes in one of the arrays while recording the effect on the other. We used our protocol to study how the prefrontal cortex (PFC)—a high-order area responsible for visuo-motor transformations and that displays robust memory encoding—is influenced by inter-hemispheric inputs. For this, we assessed the impact that different uStim patterns applied to the right-hemisphere PFC (PFC_R) had on the contralateral PFC (PFC_L) during both a visually guided and a memory guided saccade task. We were able to generate a rich repertoire of activity patterns in PFC_L and to identify the dimensions in PFC_L along which different uStim inputs from PFC_R drove the PFC_L neural population. Stimulation with individual neighboring electrodes in the uStim array (PFC_R) elicited similar activity patterns in the recording array (PFC_L), revealing a spatial map of stimulation influences between the two array locations. This allowed us to build a statistical model that predicted the PFC_R uStim effect on PFC_L activity, capturing a substantial fraction of the single-trial variance. Stimulation with multiple electrodes produced nonlinear combinations of the responses to individual electrodes. The different uStim inputs triggered transients in the PFC_L population responses lasting hundreds of milliseconds and with diverse relaxation dynamics. Finally, we found that the nature of the behavioral task minimally changed the stimulation-response relationship in PFC_L. Our approach provides a causal tool to link activity across neural circuits at high granularity, and paves the way toward data-driven models that explain how brain areas dynamically interact to produce computations.

Disclosures: **J. Soldado Magraner:** None. **Y. Minai:** None. **W. Bishop:** None. **M.A. Smith:** None. **B.M. Yu:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.10

Topic: H.04. Executive Functions

Support: R01-MH55806
R01-EY019882
P30-EY08126
Canadian Institutes of Health Research Postdoctoral Fellowship
FIU SEED Grant Wallace Coulter Foundation

Title: Cell-specific mechanisms of theta oscillations during error monitoring in medial frontal cortex: Empirical findings and biophysical modeling

Authors: *B. HERRERA[1], A. SAJAD[2], S. P. ERRINGTON[2], J. D. SCHALL[3], J. J. RIERA[1]; [1]Biomed. Engin., Florida Intl. Univ., Miami, FL; [2]Vanderbilt Univ., Vanderbilt Univ., Nashville, TN; [3]York Univ., York Univ., North York, ON, Canada

Abstract: Theta oscillations in dorsomedial frontal cortex (DMFC) are prominent signatures of cognitive control and error monitoring (Cavanagh and Frank, Trends Cogn. Sci., 2014; Cohen, Trends Neurosci., 2014). Yet, the neuronal mechanisms generating these signals remain uncertain. A recent computational study found subthalamic theta arises in response to cortical input but not from intrinsic network dynamics and requires NMDA but not AMPA currents (Moolchand et al., J Neurosci., 2022). Here, we study whether neocortical pyramidal neurons function as pacemakers of frontal theta during error monitoring by combining electrophysiological data and biophysical modeling. We recorded neuronal spiking and local field potentials (LFPs) across all layers of supplementary eye field from two macaque monkeys performing a saccade countermanding stop-signal task. In this task, subjects were required to generate a saccade to a peripheral target, but to inhibit this planned saccade when a stop signal appeared. Errors occurred when monkeys generated saccade despite the appearance of a stop signal. We utilized the recorded spiking activity of putative L3 and L5 pyramidal neurons to estimate the synaptic inputs of these neurons in realistic biophysical neuronal models around the period in which a saccade was generated (L3 model: Eyal et al., Front. Cell. Neurosci., 2018; L5 model: Hay et al., PLoS Comput. Biol., 2011). We focused on reproducing the spiking activity of correct and error trials and considered only excitatory synaptic inputs (AMPA and NMDA synapses). After reproducing the spiking activity of these cells, we simulated the LFPs produced by the activity of the neurons at 16 equally spaced (150 μm) vertically aligned points located at the center of the cortical column. We found that L5 pyramidal neurons alone, but not L3 pyramidal neurons, produce theta oscillations. Both basal and apical synaptic inputs onto L5 pyramidal neurons elicited theta oscillations. However, activation of apical dendritic synapses resulted in theta oscillations with a higher power. We show this increase in power is associated with dendritic Ca2+ spikes, elicited by combined activation of basal and distal apical excitatory synapses or distal apical excitatory synapses alone. When hundreds of L5 pyramidal neurons were simulated, the induced theta oscillations were not detectable on the LFPs in the pre-target period due to random phase profiles of individual neurons. Synchronous synaptic inputs around the saccade onset resulted in a phase-reset of these oscillations, which make them detectable on the LFPs.

Disclosures: B. Herrera: None. **A. Sajad:** None. **S.P. Errington:** None. **J.D. Schall:** None. **J.J. Riera:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.11

Topic: H.04. Executive Functions

Support: NIH, R01 MH110449
Brown University Office of the Vice President of Research Seed Award

Title: The neural dynamics of sequence-specific behavior in obsessive compulsive disorder

Authors: *H. DOYLE, C. BOISSEAU, S. GARNAAT, S. RASMUSSEN, T. DESROCHERS; Brown Univ., Providence, RI

Abstract: Humans naturally organize series of tasks into internally bounded structured sequences, known as abstract sequences. For example, the sequence of making a cup of coffee is not defined by external stimuli, but rather by internally imposed boundaries filled with ordered tasks such as grinding the beans, placing a filter, pouring the coffee in a cup, and stirring in the sugar. A prominent phenotype in obsessive compulsive disorder (OCD) is the repetition of thoughts and tasks, which could arise from dysfunctional abstract sequence representation. For instance, if the ability to represent the sequence of making a cup of coffee is impaired, someone with OCD might repeatedly check to make sure the coffee grounds are in the filter and ultimately cause the sequence to remain uncompleted. Although dysfunction at the level of task-switching has been largely studied in this population, the potential for impaired sequence representation to underlie documented behavioral phenotypes in OCD remains to be explored. We tested the hypothesis that OCD symptoms result from dysfunction at the level of abstract sequence representation. Participants kept track of four-item sequences while making simple judgements about image color and shape on each trial. To make accurate choices throughout a block, participants had to remember to re-initiate the sequence every four trials. Previously, in a control group, we observed higher latencies to initiate sequences compared to later sequence item responses, a feature which we now use to assess sequence processing ability (Desrochers et al., 2015; 2019). In an OCD population, we observed significantly higher latencies to initiate sequences compared to controls ($F_{3,147} = 3.6$, $p = 0.02$), suggesting the presence of sequence-specific behavioral deficits in OCD. Further, higher initiation latencies correlate significantly with increased scores on clinical measures that assess OCD symptom severity ($r = 0.69$, $p = 0.02$), suggesting this behavioral deficit correlates with symptomatology, as well. To understand the neural basis of sequence-specific deficits in OCD, we are using functional magnetic resonance imaging (fMRI) to compare neural activity between OCD participants and controls during the behavioral task. Preliminary fMRI data suggest sequence-related neural activity in the prefrontal cortex (PFC) corresponds with sequence-specific deficits in OCD. These data so far suggest that abstract sequence processing in the two groups is supported by differing neural dynamics in the PFC, and that these differences may underlie sequence-related behavioral deficits observed in OCD.

Disclosures: H. Doyle: None. **C. Boisseau:** None. **S. Garnaat:** None. **S. Rasmussen:** None. **T. Desrochers:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.12

Topic: H.04. Executive Functions

Support: JSPS KAKENHI 19H01038
AMED JP22wm0525006h

Title: Neural activity during construction of object symbols from meaningless elements in the macaque prefrontal cortex

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Abstract: Any human language system has a universal double articulation structure in which words, the smallest meaningful units representing the name of objects, are further constructed by meaningless letters. However, neural mechanisms underlying linguistic double articulation have not yet been well understood in humans. Here we examined neural activity in two Japanese monkeys (*Macaca fuscata*, one male and one female, 7-10 years old) after they learned a visual symbol system with double articulation structure—six 'objects' are represented by six different bigrams, each of which is further constructed from two meaningless elements. We initially shaped the animals to touch visually presented icons on the touch-panel device. In an object-bigram symbolization (OBS) task, the monkey was required to choose the bigram representing the object that had been presented as a visual cue. In a bigram construction (BC) task, the monkey must sequentially choose two elements constituting the bigram presented as a cue. In a symbolic bigram construction (SBC) task, the monkey was required to choose two elements constituting the correct name representing the cue object, even when the bigram itself had never been presented on the display as a hint. After the monkey learned all three tasks, we examined neural activity by recording electrocorticogram (ECoG) from the prefrontal cortex (PFC) of the monkeys. Using the power spectrum of ECoG signals, we calculated event-related spectral perturbation (ERSP), plotted activation power maps for each frequency band in time series, and analyzed similarity and contrasts of the maps across the tasks. We found that low-frequency (theta-, alpha- and beta- band) dominant powers initially increased in the anterior PFC and then propagated to the whole PFC during the cue period of all three tasks. The theta-band activity was continuously elevated in the ventral periarcuate PFC area during the delay period in the SBC task. By analyzing the phase difference of the ERSP powers across channels, we found that the phase difference between the ventral periarcuate area and dorsolateral PFC was close to π on average, but that the phase coherency was dynamically modulated during the tasks. These findings demonstrate spatiotemporal specificity of low-frequency synchronized neural activity in the PFC that may play pivotal roles in mental construction of symbols.

Disclosures: N. Liu: None. **K. Nakano:** None. **K. Kawasaki:** None. **T. Suzuki:** None. **T. Matsuo:** None. **A. Iijima:** None. **I. Hasegawa:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.13

Topic: H.04. Executive Functions

Support: CIHR Project Grant GR005660

Title: Prefrontal cortex mechanisms of the novel cognitive enhancer d-govadine

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Abstract: Cognitive impairment is a debilitating feature of many psychiatric disorders such as schizophrenia, substance use disorders (SUD) and depression, for which there are no effective treatments. Impairments in working memory, attention and behavioural flexibility strongly predict functional outcomes for patients in the long term which makes it a critical target for pharmacological development. The novel, plant-derived compound d-Govadine (d-GOV) enhances multiple prefrontal cortex (PFC)-dependent cognitive functions. We and others found that administering d-GOV to rodents facilitates working memory and behavioural flexibility, processes also impaired in schizophrenia. In addition, d-GOV enhanced extinction learning and a key measure of relapse in a rodent model of SUD. The present study investigated PFC mechanisms through which d-GOV may act to enhance cognition. Notably, d-GOV potentiates dopamine (DA) levels in the PFC and not in the nucleus accumbens, a unique property that distinguishes it from many dopaminergic drugs and which coincidentally may reduce its potential abuse liability. We have also observed that infusion of d-GOV into the PFC is sufficient to increase DA efflux in a dose-dependent manner. Following pharmacological inhibition of PFC glutamatergic projections, systemic d-GOV administration (1 mg/kg, i.p.) failed to potentiate PFC DA efflux. These data are consistent with the hypothesis that d-GOV may elevate PFC DA levels by activating the PFC-VTA dopaminergic feedback loop. In addition to potentiating PFC DA tone, d-GOV potently binds to the DA D1 receptor (D1R) and is an agonist of D1R-mediated cyclic adenosine monophosphate (cAMP) accumulation. DA activation of D1 receptors modulates N-methyl-D-aspartate receptor (NMDAR) current in the PFC, a mechanism critical for working memory and behavioural flexibility. Importantly we found that d-GOV potentiates NMDAR current in Layer 5 pyramidal neurons of rat PFC slices. This d-GOV potentiation of NMDA current likely reflects D1R-dependency as it was blocked by a D1 antagonist. Furthermore, we have observed that d-GOV does not affect GluN2A- or 2B-containing NMDAR current in recombinant HEK293 cells. Investigations into possible facilitatory effects of d-GOV on NMDA current in recombinant cells expressing both D1Rs and NMDARs are ongoing.

Disclosures: M.O. Nesbit: None. **S. Ahn:** None. **H. Zou:** None. **K. Held:** None. **Y. Wang:** None. **A.G. Phillips:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

property rights/patent holder, excluding diversified mutual funds); Patent Holder: US20150306092.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.14

Topic: H.04. Executive Functions

Support: NIH Grant F32 MH127878
NIH Grant R21 MH125010
Robert J. and Nancy D. Carney Institute for Brain Science Innovation Award
NIGMS COBRE P20 GM103645

Title: Neurons in lateral prefrontal cortex respond to sequence position and abstract pattern violations

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Abstract: The capacity to identify patterns and apply them across contexts enables a range of complex behavior and cognition. A central example of this is the detection of abstract sequences, defined by higher-order patterns that remain consistent across stimuli (e.g., AAAB, &&&*). Recent work in our lab using awake monkey fMRI identified specific subregions of LPFC with robust BOLD responses to pattern deviants during sequence viewing. This work also identified ramping in LPFC over the course of the sequence, similar to a behaviorally necessary ramping signal previously observed in human rostral LPFC. However, it is not clear how these signals translate to neuronal responses, or how ordinal position and sequence pattern combine to form a representation of the sequence as a whole.
We performed fMRI-guided neuronal recording in LPFC while monkeys performed a no-report sequence viewing task. In this task, monkeys fixated on a central point as fractals appeared in four-item sequences. Each recording session included multiple five-block runs (4-20 runs/session). Within a run, sequences were defined by a standard pattern (e.g. *AAAB*), and images for each sequence were drawn pseudorandomly from a set of fractals generated daily. Each run consisted of a habituation block (30 trials, standard sequence), followed by four blocks with deviant sequences on 20% of trials. Deviants consisted of either new images in the standard pattern or pattern deviants, and were drawn from a separate pool of fractals. Juice was delivered on a graduated schedule contingent on fixation and independent from sequence presentation.
We recorded ~500 neurons from the LPFC of one monkey and analyzed firing rates in a subset of these neurons. Approximately 30% of neurons responded differently during deviants than standard sequences, and ~15% showed different responses across sequence positions. Interestingly, the majority of position-modulated responses showed selectivity for specific ordinal positions rather than monotonic ramping, suggesting that ramping BOLD activation in

this task may reflect population-level dynamics. A subset of ordinal responses were modulated by sequence type, showing position selectivity specifically during deviant sequences. These results indicate that ordinal selectivity and deviant responses occur in overlapping LPFC networks, and provide preliminary evidence of how neuronal responses relate to fMRI data from the same monkey in the LPFC. Future analyses will test how responses to sequence position and deviant sequences vary with image identity and examine how these responses contribute to a generalizable representation of abstract sequences.

Disclosures: K.E. Conen: None. **T.M. Desrochers:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.15

Topic: H.04. Executive Functions

Support: Office of Naval Research Grant N0001421WX01144

Title: Individual differences in cognitive fatigue susceptibility and associated neural activity

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Abstract: A variety of jobs such as air traffic control or unmanned vehicle operation require managing different tasks simultaneously for extended periods. It is well known that increased time on task can lead to increased subjective fatigue as well as degradation in cognitive abilities such as attention. These combined effects are termed cognitive fatigue. Less understood is how regions that support attentional control, such as the prefrontal cortex (PFC), respond to cognitive fatigue during sustained multitasking and how these changes may vary among individuals. To assess impacts of cognitive fatigue on multitasking ability, 51 participants age 22-40 performed the computer-based Modifiable Multitasking Environment (ModME) for approximately 70 minutes. The ModME consisted of four simultaneous tasks that required participants to monitor and respond quickly to changes in the visual and auditory domains, track an object using a joystick, and maintain fill levels of two tanks that continuously drained. During the tasks, changes in PFC blood-oxygenation were measured using functional near-infrared spectroscopy. Participants also rated their subjective cognitive fatigue and workload and completed a personality assessment. Overall, self-reported cognitive fatigue increased during the experiment, while task performance and PFC activation (relative oxygenated hemoglobin concentrations) remained unchanged. To assess individual differences, participants were divided into fatigue-resistant and -vulnerable groups based on self-reported fatigue scores. However, these groups did not differ in task performance, PFC activation, or personality traits based on fatigue susceptibility. Further study will be necessary to determine whether the lack of significant

differences was due to insufficient difficulty or duration of the task or other factors. These results will inform future efforts to induce cognitive fatigue in the laboratory and may also inform selection efforts that seek to identify characteristics of individuals resistant to cognitive fatigue.

Disclosures: D.G. McHail: None. **K.A. Pettijohn:** None. **K.J. Blacker:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.16

Topic: H.04. Executive Functions

Support: NINDS Grant NS091390
NIMH Grant MH112846
NARSAD YI Award 25066
ERC-STG 101041799

Title: Single-neuronal representation of semantic space in animals and humans

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Abstract: How is semantic information represented across animal species? While most approaches to the evolutionary variability of species highlight neuroanatomical differences, similarities in neuronal encoding are starting to emerge. However, whether distinct species such as non-human primates and humans share a common semantic manifold or categorical representations of their environment remains largely unknown. Here, we focused on the primate prefrontal cortex's capacity to organize everyday experience into different categories to approach this question. We obtained single-neuronal recordings in the prefrontal cortex of Rhesus macaques and human participants. At the same time, they were given different stimuli in a visual or audio format that could be vectorially classified. Using a combination of single-neuronal and population analyses, we find that many neurons in both humans and monkeys displayed categorical selectivity and that their population activities could be used to decode distinct semantic domains in both species. We also observed differences in the precise representations of these domains across species and how they were functionally organized. Finally, to verify category-based behavior, we examined the viewing preferences of the primates to different categories in a free-viewing choice task and confirmed that the animals looked first and for longer at images of specific categories than others, e.g., abstract vs. familiar objects. Together, our findings reveal a remarkably detailed cellular representation of semantic information in the prefrontal cortex of monkeys and humans and begin to illuminate the common semantic manifold that is shared across animal species.

Disclosures: **I. Caprara:** None. **M. Jamali:** None. **M.L. Mustroph:** None. **E. Wong:** None. **B.L. Grannan:** None. **A.R. Khanna:** None. **R. Báez-Mendoza:** None. **Z. Williams:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.17

Topic: H.04. Executive Functions

Support: JSPS KAKENHI JP16H06276
JSPS KAKENHI 17K07060
JSPS KAKENHI 20K07726
MEXT KAKENHI 20H05478
MEXT KAKENHI 22H04780
AMED JP18dm0207051

Title: Increased firing variability may be an early warning signal of bifurcation in neuronal networks: Validation in action planning-related cells of monkey prefrontal cortex

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Abstract: Brain neural flexibility is required to adapt to the continuously changing environment. The lateral prefrontal cortex (lPFC) plays a crucial role in flexible action planning. In our previous study, a significant proportion of lPFC neurons showed firing rate modulation indicative of behavioral planning. During a path-planning task that required monkeys to plan a stepwise cursor movement to reach a final goal, lPFC neurons encoded the externally driven final goal during the early period of planning, whereas their firing rates reflected internally generated immediate behavioral goals in the late period of planning ("final goal-immediate goal shift neurons"). First, we developed simple spiking neuronal networks of various types (mutual excitation, mutual inhibition, and excitation-inhibition) using a single stable attractor. In these networks, saddle node, pitchfork, and Hopf bifurcations could be reproduced by controlling the bifurcation parameter. The networks showed increased firing variability with reduced attractor stability (evaluated by the Lyapunov index or newly developed generalized stiffness parameter) for all bifurcation types. Next, we analyzed the firing variability of final goal-immediate goal shift neurons. The neurons exhibited increased firing variability immediately before the final goal-immediate goal shift and decreased firing variability thereafter. Using several measures of firing variability, increased variability was confirmed in putative excitatory and inhibitory neurons, but not in other neuron types. Based on these results, we concluded that the temporal increase in firing variability may be an early warning signal of bifurcation in brain neuronal networks, and can be used to evaluate network flexibility.

Disclosures: **K. Sakamoto:** None. **H. Mushiake:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.18

Topic: H.04. Executive Functions

Support: NEI R01-EY029666

Title: The subcortical connectome of primate lateral prefrontal cortex

Authors: *R. XU, N. P. BICHOT, A. TAKAHASHI, R. DESIMONE;
McGovern Inst. for Brain Res., MIT, Cambridge, MA

Abstract: The lateral prefrontal cortex (LPFC) of primates plays an important role in executive control. Although the important functions of LPFC must arise from its interactions with the rest of the brain, these interactions were only known through coarse, connectional anatomy, based on sparse injections of tracers into different architectonic areas. To characterize the LPFC's anatomical connectivity in a finer resolution, we created a dense, parcellation-free connectome by mapping whole-brain connections of ~200 LPFC sites in two monkeys, using simultaneous electrical microstimulation and functional MRI (EM-fMRI). A part of this dataset, the LPFC-cortical connectome was published before (Xu et al., *Neuron,* 2022). Here we report new findings taking into account the LPFC-subcortical connections as well.

We predominantly observed EM-fMRI mapped connections in subcortical domains known to have monosynaptic afferents from LPFC, including striatum, thalamus, dorsal midbrain, and claustrum, with the notable exception of cerebellar cortex. These connections were also predominantly ipsilateral, except for those in cerebellar cortex, which were mainly contralateral. On the other hand, we rarely found connections in subcortical structures known to project to, but receive little inputs from LPFC, such as the amygdala. Thus, the subcortical connections mapped by EM-fMRI seem largely restricted to anterograde projection targets of the stimulation site, like the cortical ones.

In every subcortical domain, we identified layout-preserving mappings between LPFC sites and their connection zones, similar to the ones between LPFC and cortical domains. Unlike the latter, here the dimensionality is up to three per domain, matching the inherent dimensions of subcortical structures. This corroborates our previous findings that the LPFC contains overlapping, millimeter-scale maps that mirror the organization of major processing domains in both cortex and subcortex.

Finally, as one goes from one LPFC site to another, the topological structure of their connections across all cortical and subcortical domains, i.e., the *connectional manifold*, can be nonlinearly reduced to a two-dimensional representation that is highly isomorphic to the flattened cortical sheet of LPFC. This suggests that the overlap of different domains' maps in LPFC is not arbitrary but optimized, so that as one travels by unit distance anywhere and in any direction on

LPFC's surface, the amount of change in overall connectivity profile between start and end sites stays roughly the same. The orderly overlapping pattern may help maximize LPFC's overall capacity for all cognitive demands.

Disclosures: R. Xu: None. **N.P. Bichot:** None. **A. Takahashi:** None. **R. Desimone:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.19

Topic: H.04. Executive Functions

Support: PRODEP Grant TCLL-511-6/2020-8632
CONACYT EH-821866

Title: Executive Functioning in High Performance University Athletes and University Students with Regular Physical Activity.

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Abstract: Executive functions are a group of cognitive skills that helps the adaptation of the human to new and complex situations, they are fundamental for the cognitive, social, and psychological development of people. In addition to this, there is evidence that regular sports practice helps in several health factors and may be an indicator that contributes to executive functioning. The aim of this study was to compare executive functioning in high-performance university student athletes with university students who perform regular physical activity. A non-experimental design was used with a sample of 134 university students between 18 and 24 years old (M= 20.74) from the Universidad Veracruzana (Mexico), 72 high-performance university athletes and 72 university students with regular physical activity with the same number of men (n=31) and women (n=36) in each group. The Neuropsychological Battery of Executive Functioning (BANFE-II) was used with the following subtests: 1) Wisconsin Card Sorting; 2) Self-Ordered Pointing Test; 3) Alphabetical Sorting of Words; 4) Visuospatial Working Memory, and 5) Stroop Test A and B, to evaluate Executive Functions: Cognitive Flexibility, Working Memory, and Inhibitory Control. The Mann Whitney U test showed statistically significant differences in favor of high-performance university athletes ($p < .05$) for some Working Memory, Cognitive Flexibility, and Inhibitory Control tasks. Divided by gender, male high performance university athletes showed higher scores in Cognitive Flexibility tasks, and worse scores for Inhibitory Control tasks. In the case of high-performance female athletes, they had better scores in Working Memory and Inhibitory Control tasks. The results showed that

doing high-performance sports during the university period is a factor related to a better executive functioning, especially in women.

Disclosures: E. Fernandez: None. **S. Herrera-Meza:** None. **T. Cibrian-Llanderal:** None. **M.L. Marvan-Gardunio:** None. **L.F. Reynoso-Sanchez:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.20

Topic: H.04. Executive Functions

Support: ONR MURI N00014-16-1-2832
ONR N000142212453
The JPB Foundation

Title: Independent maintenance, but shared control, of working memory across prefrontal hemispheres

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Abstract: Working memory for visual stimuli in the left or right hemifield is processed largely independently in the right and left cortical hemispheres, respectively. Working memory capacity and load effects for items on one side are unaffected by memory load on the other side. However, when primates foveate stimuli, the working memory traces will be in *both* hemispheres. Does processing remain independent, or are there interactions between hemispheres suggesting cooperation or competition between them?
We recorded simultaneously from 256 sites in both prefrontal hemispheres (dorsolateral and ventrolateral PFC subdivisions) in an NHP performing a delayed match-to-sample working memory task with foveal stimuli. We examined trial-by-trial noise correlations and fine-timescale oscillatory synchrony as measures of interactions between hemispheres—positive, negative, and zero correlation would provide evidence for cooperation, competition, and independence, respectively.
We found that processing of stimuli was independent between prefrontal hemispheres. Signals thought to reflect working memory content—mean spike rates, gamma power, and the information conveyed in them about the item held in memory—exhibited similar dynamics in each hemisphere. However, there was near-zero trial-by-trial correlation and phase synchrony *between* hemispheres. These measures did show correlations between PFC subdivisions in the *same* hemisphere, confirming they do reflect long-range interactions. In contrast, alpha/beta oscillations—often associated with top-down control—exhibited robust trial-by-trial power

correlations and phase synchrony both within and between hemispheres. These results suggest that working memory storage remains independent across cortical hemispheres, even when they are holding the same memory within their shared foveal spatial representation. In contrast, inhibitory control processes may be coordinated across a broad network of brain regions, including across the cortical hemispheres.

Disclosures: S.L. Brincat: None. **M. Lundqvist:** None. **E.K. Miller:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.21

Topic: H.04. Executive Functions

Support: NIMH R01MH11559
NIGMS P01GM118269
ONR MURI N00014-16-1-2832
The JPB Foundation

Title: Propofol anesthesia destabilizes neural dynamics across cortex

Authors: *A. EISEN[1,2,3,4], L. KOZACHKOV[1,2], A. M. BASTOS[7,8,9], J. A. DONOGHUE[1,2], M. K. MAHNKE[1,2], S. L. BRINCAT[1,2], S. CHANDRA[2,5,3,4], I. R. FIETE[2,5,3,4], E. N. BROWN[1,2,10,6], E. K. MILLER[1,2];
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Abstract: Consciousness seems to depend on dynamics that are coordinated across cortex. [1,2]. Dynamical systems theory has emerged as a useful lens through which to investigate the cortical dynamics underlying cognition and behavior [3]. Are there general dynamic motifs that separate conscious states from unconscious states? One useful motif is dynamic stability. It is the ability of network activity to consistently traverse the same paths. Too much stability and networks lose flexibility and become overly fixated. Too little stability and the network activity diverges and becomes “chaotic”. Recent work has illuminated that dynamic stability is essential for cortical functioning [4].
We analyzed the spectrum of dynamic stability in local field potentials recorded from the cortex of non-human primates (NHPs) before and after induction of unconsciousness via propofol [5]. We applied and extended an approach to quantifying dynamic stability directly in neural data based on time-varying vector autoregression [6]. We implemented a rigorous approach to

selecting hyperparameters of the dynamical systems model. This approach harnesses switching linear approximations to the nonlinear dynamics inherent in the data. We found that cortex rapidly destabilizes as propofol infusion begins. After loss of consciousness, instability plateaus at levels higher than that seen in wakefulness. Our results suggest that dynamic stability is essential for conscious processing and that propofol induces loss of consciousness by derailing neural dynamics from pathways essential for communication and input integration.

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Disclosures: A. Eisen: None. **L. Kozachkov:** None. **A.M. Bastos:** None. **J.A. Donoghue:** None. **M.K. Mahnke:** None. **S.L. Brincat:** None. **S. Chandra:** None. **I.R. Fiete:** None. **E.N. Brown:** None. **E.K. Miller:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.22

Topic: H.04. Executive Functions

Support: NSF GRFP 1745302 (ICG)
NIH 5T32EB019940-05 (ICG)
MathWorks Fellowship (ICG)
Picower Institute for Learning and Memory (ENB, EKM, AJM)
Simons Center for the Social Brain Postdoctoral Fellowship (AJM)
NIH P01-GM118629 (ENB, EKM)
NIMH R37MH087027 (EKM)

Title: Using multifunctional fibers to investigate the effect of local and systemic neuropharmacology on cognitive encoding

Authors: *I. C. GARWOOD[1], A. J. MAJOR[2], M. K. MAHNKE[2], E. K. MILLER[2], E. N. BROWN[1], P. ANIKEEVA[3];

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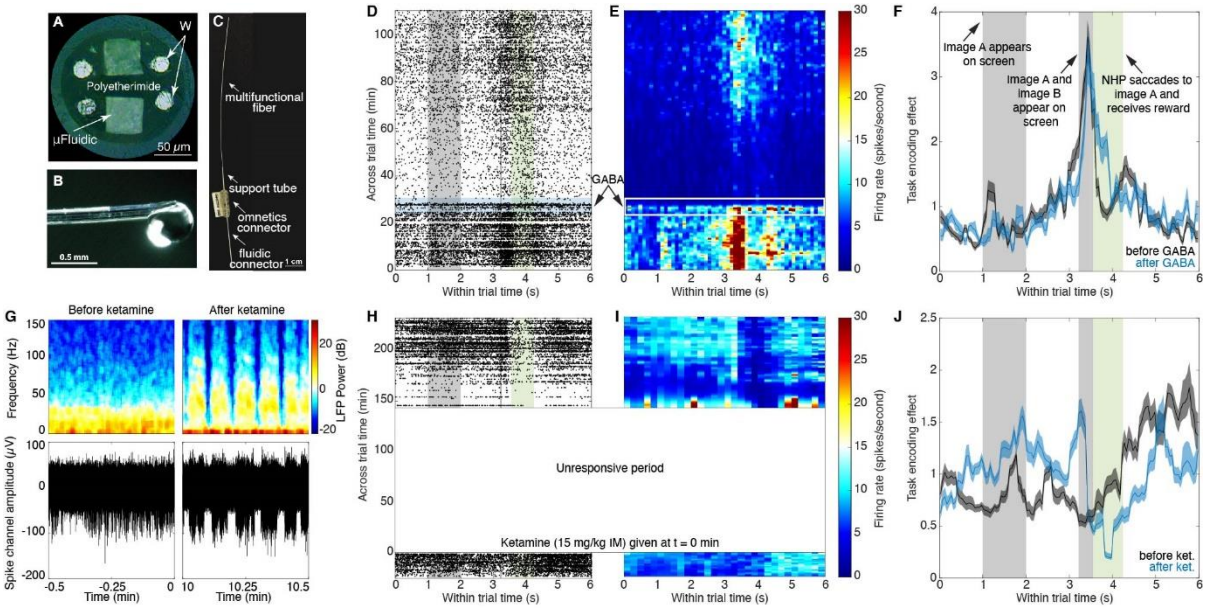
Abstract: Pharmacological manipulation of neural activity in non-human primates (NHPs) can interrogate mechanisms of cognitive encoding. Rapid adaptation of neural circuits in response to modulation has been shown to alter encoding of cognitive information, but less is known about the recovery of task-encoded activity as drugs are cleared. To study the adaptation of task-encoded neural activity following local and systemic drug delivery, we addressed two technical limitations: 1) Most devices capable of simultaneous drug delivery and neural recording are made from rigid materials which may damage neural tissue. We translated flexible multifunctional fibers from mice to NHPs to reduce tissue damage and facilitate modulation and recording of cognitive neural activity (FigA-C). 2) Standard methods of measuring task-encoded activity do not characterize time-resolved changes in neural encoding. We apply a state-space generalized linear model to characterize within and between trial dynamics following local and systemic drug delivery. We model the instantaneous firing rate of a neuron as a product of the trial-average firing rate, the task encoding effect, and the effect of spike history. When the task encoding effect is > 1, firing rate is increased from the trial-average rate; when < 1, firing rate is reduced. We tracked the effect of local GABA and systemic ketamine infusions on working memory task encoding of single units in the premotor cortex (PMC) of an NHP. We found that as GABA-mediated inhibition resolved (FigD), so did task encoding (FigE) - the 95% confidence intervals of the task encoding effect before and after GABA overlapped for 50.0% of the trial (FigF). Systemic ketamine altered neural dynamics (FigG) and resulted in unresponsiveness (FigH-I). The task encoding effect before and after ketamine varied (14.2% overlap) (FigJ). This provides evidence that, during recovery from ketamine, there is a shift in cognitive encoding in the PMC. Our results demonstrate a first-time translation of multifunctional fibers to investigate local and systemic drug effects on cognitive encoding.



Disclosures: I.C. Garwood: None. **A.J. Major:** None. **M.K. Mahnke:** None. **E.K. Miller:** None. **E.N. Brown:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ENB has licensed IP to

Masimo for the analysis of EEG under anesthesia. ENB is a cofounder of PASCALL, a company constructing control systems for anesthesia.. **P. Anikeeva:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.23

Topic: H.04. Executive Functions

Support: Simons Center for the Social Brain Postdoctoral Fellowship
NIMH R37MH087027
ONR MURI N00014-16-1-2832
The JPB Foundation

Title: Layer-specific deactivation of rhesus prefrontal cortex to test predictive coding feedback onto visual cortex

Authors: *A. MAJOR[1], A. BASTOS[2], S. BRINCAT[1], J. ROY[1], M. MAHNKE[1], E. MILLER[1]; [1]MIT, Cambridge, MA; [2]Psychology and Vanderbilt Brain Inst., Vanderbilt Univ., Nashville, TN

Abstract: Disrupted organization of neocortical layers during development can lead to altered neuronal circuits and conditions such as autism and schizophrenia. There is burgeoning interest in the physiology of superficial vs deep cortical layers and they are now recognized to perform different functions. In the laminar model of Predictive Coding, deep cortical layers of higher-order cortex send feedback signals via alpha/beta rhythms (10-30 Hz) to sensory regions (Bastos et al., *PNAS*, 2020). Conversely, superficial layers of sensory regions send feedforward projections (via gamma rhythms, > 35 Hz) to update higher-order regions. For example, it is proposed that prefrontal cortex (PFC) sends feedback alpha/beta rhythms to suppress feedforward information in visual cortex. This project will test this layer-specific model of Predictive Coding using layer-specific pharmacological deactivation of PFC. Using custom laminar probes with embedded drug-injection ports, either the superficial or deep layers of rhesus PFC were deactivated with $GABA_A$ receptor agonist muscimol.
Deactivation of deep layer PFC (the feedback layer) is hypothesized to cause a greater reduction in feedback alpha/beta to lower-order cortex. Preliminary results support this. Muscimol deactivation of PFC reduced feedback alpha/beta connectivity with visual area V4 and reduced V4 stimulus information carried by spiking. The effects were more pronounced when the stimulus was predictable (vs unpredictable). This work will perform causal tests on a prevalent model of cortical communication. It can yield insights into conditions with altered cortical communication, such as autism spectrum disorder and schizophrenia. This work was supported by Simons Center for the Social Brain Postdoctoral Fellowship, NIMH R37MH087027, ONR MURI N00014-16-1-2832, and The JPB Foundation.

Disclosures: **A. Major:** None. **A. Bastos:** None. **S. Brincat:** None. **J. Roy:** None. **M. Mahnke:** None. **E. Miller:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.24

Topic: H.04. Executive Functions

Support: NIH P40OD010996
NIH R01NS113078
DSF Charitable Foundation 1805R01

Title: Segregated Output Channels from Cerebellar Cortex to Prefrontal Cortex

Authors: *A. C. BOSTAN, R. P. DUM, P. L. STRICK;
Neurobiology, Ctr. for the Neural Basis of Cognition, Brain Inst., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: There is a growing recognition that the cerebellum is not only concerned with the control of movement, but also is involved in cognitive function. Indeed, it is now clear that a substantial portion of the output from the cerebellum is directed at non-motor areas of the cerebral cortex some of which are in the frontal lobe. These same areas of prefrontal cortex are a major source of signals back to the cerebellar cortex. We have begun to explore the mapping principles that define cerebellar circuitry with the prefrontal cortex. To do this, we injected the CVS-N2C strain of rabies virus with the mCherry marker gene (RV-MC) into area 9L of the prefrontal cortex in a Cebus monkey. In the same animal, we injected the CVS-N2C strain with the GFP marker gene (RV-GFP) into an adjacent region of the prefrontal cortex, the PrePMd. We set the survival time to allow transport of both virus strains to infect first-order neurons in regions of the thalamus, second-order neurons in the cerebellar nuclei, and then third-order neurons (Purkinje cells [P-cells]) in the cerebellar cortex. Virus transport from either injection site infected P-cells located laterally in the posterior lobe of the cerebellum. However, the densest labeling following RV-GFP transport from the PrePMd displayed limited overlap with the densest labeling following RV-MC transport from the area 9L. Three regions of the cerebellar cortex contained infected P-cells following the prefrontal injections of rabies virus: (1) the posterior bank of the cerebellar cortex in the fissure between Crus I and Crus IIa; (2) the posterior bank of cerebellar cortex in the fissure between Crus IIa and IIp; and (3) the surface of Crus IIp. Even at these sites, patches of P-cells infected by virus transport from PrePMd were interleaved with patches of P-cells infected by virus transport from area 9L. Our estimate is that the overlap in the two populations of labeled neurons is less than 6%. These results along with others confirm that a relatively large region of the cerebellar cortex in the hemisphere is interconnected with areas of the prefrontal cortex. However, our results indicate that within this region, separate channels exist that are focused on specific prefrontal areas.

Disclosures: **A.C. Bostan:** None. **R.P. Dum:** None. **P.L. Strick:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.25

Topic: H.04. Executive Functions

Support: SNSF Grant P2LAP3_199556

Title: The Prefrontal-Hippocampal pathways through the nucleus Reuniens. A synaptic tale.

Authors: *G. VANTOMME, G. DEVIENNE, J. R. HUGUENARD;
Stanford Univ., Stanford Univ., Palo Alto, CA

Abstract: The neuronal circuit interconnecting the medial prefrontal cortex (mPFC), the Reuniens nucleus of the thalamus (Re) and the hippocampus is central for memory and executive functions. A critical gap exists between known structural and behavioral aspects of this network compared to the paucity of knowledge regarding functional connectivity, especially in mouse models. We applied a combination of electrophysiological recordings and optogenetic manipulation of the Re to reveal a complex pattern of synaptic transmission. Re axons projected massively to the layer 1 of the mPFC and to a lesser extent to the deep layers. Re axons formed functional excitatory monosynaptic connections on mPFC neurons as deduced by light activation of ChR2 in Re axons. These synapses showed a high release probability and high proportion of Glun2B-containing NMDA receptors. Interestingly, activation of Re axons also generated a delayed, polysynaptic feedforward excitation. This feedforward excitation was strongly enhanced upon pharmacological blockade of GABA receptors. The feedforward excitation could induce burst discharge of action potentials in mPFC neurons, which may constitute a mechanism underlying the capacity of Re inputs to synchronize activity in the mPFC. Feedforward activation was more prominent than what has been reported in sensory thalamic regions, such as VPM and dLGN, suggesting that intracortical amplification of Re output is a specialized feature of this thalamocortical subsystem underlying memory/cognition. Using a similar approach, the Re was shown to send monosynaptic excitatory connections to pyramidal cells in the dorsal CA1 region of the hippocampus. Activation of Re afferents induced a strong polysynaptic feedforward inhibition but no feedforward excitation as in the mPFC. Initial observations in the *SCN8A* mouse model of absence seizure revealed that Re activation of mPFC neurons resulted in an increase in the excitation/inhibition ratio compared to wild-type littermates. This imbalance was accompanied by prolonged evoked postsynaptic potentials and increases in persistent depolarization upon repeated Re stimulation. These data suggest that the loss of function mutation in the sodium channel Nav1.6 in the *SCN8A* mouse model results in a hyper-excitable Re output to mPFC and a biased recruitment of principal cells over local interneurons. Altogether, these data demonstrate the fundamental synaptic properties underlying the function of the mPFC-Re-Hippocampal circuit. They also suggest that the mPFC network amplifies Re

output, which may underlie abnormal thalamocortical synchronization in the *SCN8A* mouse model of absence seizure.

Disclosures: G. Vantomme: None. **G. Devienne:** None. **J.R. Huguenard:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.26

Topic: H.03. Decision Making

Support: NIH grant R01HD093907-01A1

Title: Developmental exposure to 17-alpha-hydroxyprogesterone caproate alters decision-making in female rodents in adulthood

Authors: *P. L. GRANEY[1], M. Y. CHEN[2], R. I. WOOD[2], C. K. WAGNER[1];
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Abstract: The synthetic progestin, 17α-hydroxyprogesterone caproate (17-OHPC), is administered to women at risk for preterm birth and is likely transferred from mother to fetus. Yet, there is little information regarding the potential effects of 17-OHPC administration on behavioral and neural development in offspring. In rats, neonatal 17-OHPC exposure altered dopaminergic fiber distribution in neonates and increased dopaminergic fiber density in adolescents in the prelimbic mPFC. Additionally, in male rats, neonatal 17-OHPC exposure increased response omissions in an operant task of impulsive decision-making. In experiment 1, the present study tested the effects of developmental 17-OHPC administration on delay discounting in females, where rats chose between a small immediate reward (1 sugar pellet), and a larger delayed reward (3 pellets). We tested the hypothesis that 17-OHPC slows decision-making when choosing among multiple alternatives, thereby increasing omissions. Female rats received 17-OHPC from P1-P14. They were tested 5 days per week in 4 blocks of 12 trials. Each block contained 6 forced-choice trials (1 lever, 3x each), followed by 6 free-choice trials with both levers available. In successive blocks, the large reward was delivered after a 0, 15, 30, or 45-sec delay. Rats had 20 seconds to respond before the trial was considered an omission. As in our previous study of males, 17-OHPC administration had no effect on large reward preference in females. Likewise, 17-OHPC-treated females made more omissions than controls. However, there was no effect of 17-OHPC on response time, and omissions were comparable during free- and forced-choice trials. Experiment 2, aimed to investigate the neural mechanism regulating these omissions committed by 17-OHPC treated females. The DAT and NET inhibitor, Methylphenidate (MPH), was administered to the same female rats, and the effects on the delay discounting task were assessed. MPH treatment did not reduce omissions in 17-OHPC treated females. Interestingly, preliminary data suggest that MPH increased omissions in oil-treated

females during the longest delays in a dose-dependent manner. These results suggest that developmental 17-OHPC exposure does not increase impulsivity (measured by preference for the large reward lever) or slow decision-making (measured by response latency), regardless of the number of decision alternatives. Instead, omissions increase in both male and female rats. Furthermore, the dopaminergic and noradrenergic systems may partially mediate aspects of decision-making, such as omissions. Further investigation into the clinical use of synthetic progestins is warranted.

Disclosures: P.L. Graney: None. **M.Y. Chen:** None. **R.I. Wood:** None. **C.K. Wagner:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.27

Topic: H.04. Executive Functions

Title: Cortical and cerebellar working memory networks

Authors: L. SHAHSHAHANI, ***C. NETTEKOVEN**, J. DIEDRICHSEN;
Brain and Mind Inst., Western Univ., London, ON, Canada

Abstract: The human cerebellum shows fMRI activity during motor, cognitive and social processes, indicating that the cerebellum contributes to each of these functions. However, its precise contribution to these diverse domains is not yet clear. One core function of the human brain that involves cerebellar as well as cortical regions is working memory processing. Here, we characterised the cortico-cerebellar working memory network in terms of its distinct functional regions and task profiles as a fist step to understanding the cerebellar contribution to working memory.

We acquired high resolution (3T) fMRI data from the neocortex and cerebellum of 16 healthy participants performing a working memory task. During the task, participants were required to memorize digits on a screen (encoding phase), which they were later asked to execute with their right hand (recall phase). Digits were shown sequentially along with a colored box. The box color indicated whether participants would later have to execute the digit sequence in the same order (forward; yellow box) or in reverse order (backward; blue box). The digit sequence always consisted of 6 digits, but the number of digits to memorize varied between 2, 4 and 6 digits (memory load). Digits to memorize were highlighted and disappeared after 1s during the encoding phase and were obscured during recall.

To determine the cortical working memory regions, we calculated the mean activation map of all task conditions compared to rest. We manually parcellated the mean task network into six regions of interest in the left cortical hemisphere: These included superior parietal occipital cortex (SPOC), intraparietal sulcus (IPS), ventral premotor cortex (PMv), dorsal premotor cortex (PMd), V1 and M1. For each region, we derived a task response profile by extracting the mean activation during each of the 12 task conditions. As expected, M1 showed higher activation

overall during the recall than encoding phase, while V1 showed increasing activation with increasing load size during the encoding, but not retrieval. IPS and PMd showed higher activation during backwards than forwards conditions and higher activation during the retrieval phase compared to the encoding phase. SPOC and PMv showed increasing activation with increasing load size during the encoding phase.
To determine the cerebellar regions corresponding to the distinct cortical regions, we used a winner-take-all approach to assign every cerebellar voxel to a cortical region whose task profile showed the strongest correlation with the task profile of the cerebellar voxel.

Disclosures: L. Shahshahani: None. **C. Nettekoven:** None. **J. Diedrichsen:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.28

Topic: H.04. Executive Functions

Support: the Canadian Institutes of Health Research (PJT 159520)
the Canada First Research Excellence Fund (BrainsCAN to Western University)
discovery grant from the National Science and Engineering Research Council of Canada (RGPIN- 2022-04692 to JD)

Title: Selective recruitment of cerebellar motor areas for finger tapping of increasing speed, but not force

Authors: *L. SHAHSHAHANI[1], M. KING[2], R. IVRY[3], J. DIEDRICHSEN[4];
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Abstract: Previous fMRI studies have demonstrated that the human cerebellum is activated across a wide array of motor, cognitive, and social tasks (King et al., 2019). Nonetheless, the specific cerebellar contribution to each of the task domains remains unclear. An important problem here is that increases in the cerebellar BOLD signal cannot be taken as a sign that the cerebellum contributes to the task. Because the cerebellar BOLD signal is mainly driven by mossy-fiber inputs signaling information from the neocortex (Mathiesen et al., 2000), a specific cerebellar area may be activated whenever the corresponding cortical regions are engaged in the task, irrespective of whether the cerebellum is required for the task or not. This would make it impossible to infer specific cerebellar contributions from fMRI data alone. However, it is also possible that cortical inputs to the cerebellum are gated in a task-dependent manner, such that processes requiring cerebellar contributions are associated with higher cerebellar activity than predicted by the corresponding cortical activity. Here, we tested the selective recruitment hypothesis using the fact that we know from cerebellar patient studies that the cerebellum plays a

crucial role in the control of rapid alternating finger movements, but not for maximal finger force generation (Mai et al., 1988). We conducted a fMRI experiment, measuring the BOLD activity in both cerebellum and neocortex, while 16 human participants tapped their fingers at 1, 1.6, and 3 Hz and at 2.5, 6, and 10 N. We observed activity increases in hand motor areas of the cerebellum and neocortex for both increasing tapping speed and increasing tapping force. To determine the relevant neocortical input area for each cerebellar region, we used an optimized cortico-cerebellar connectivity model, which was trained on a comprehensive multi-domain task battery data set (King et al., 2022). Compared to the relationship between cerebellar and cortical activity for increasing force, the cerebellar activity for increasing speed significantly outstripped those in the neocortex, $t_{15} = 3.21$; $p = 0.005$. These results show that the input to the cerebellar cortex, selectively increased for rapidly alternating compared to a maximal force generation with matched levels of cortical activity. We hypothesize that information flow from the neocortex to the cerebellum maybe in general gated depending on whether cerebellar computation is required for the specific task and suggest that our analysis approach is a promising avenue to identify specific cerebellar contributions in cognitive tasks using fMRI.

Disclosures: L. shahshahani: None. **M. King:** None. **R. Ivry:** None. **J. Diedrichsen:** None.

Poster

736. Prefrontal Cortex Regulation of Brain Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 736.29

Topic: H.04. Executive Functions

Title: Interactions between large-scale cortical networks and the ascending arousal system predict individual differences in cognitive performance

Authors: *E. PODVALNY, M. W. COLE;
Ctr. for Mol. & Behavioral Neurosci., Rutgers Univ., Newark, NJ

Abstract: Regulation of arousal state by the brainstem locus coeruleus (LC) is essential for effective cognitive performance. While LC is a global hub widely projecting to cortex, select cortical regions project back to LC to potentially recruit the arousal system to serve behavioral goals. The properties of this large-scale circuit involving cortical networks and the arousal system are poorly understood in humans. Because the arousal system is impaired in multiple brain disorders, it will be crucial to delineate the properties of the large-scale circuits underlying arousal state regulation and to determine their behavioral significance. We hypothesized that cognitive control networks recruit the arousal system to induce large-scale brain network reconfiguration and improve cognitive performance. We predicted that during resting state such recruitment would result in a positive correlation between pupil size (a marker of LC activity), whereas NE release in cortex would result in delayed negative correlation between pupil size and cortical activity (because NE release results in spontaneous activity decreases in animal studies). We analyzed the Young Adult Human Connectome Project (HCP) high-field 7T functional

Magnetic Resonance (fMRI) data set of N=149 subjects, including up to 4 resting state sessions of 15 minutes with simultaneous eye tracking, and an extensive battery of tests evaluating cognitive abilities of each subject. First, we uncovered temporally distinct interactions between pupil-linked arousal and large-scale brain networks with up to 5 s delays between positive and negative correlation peaks. The cortical regions showing the strongest and earliest positive correlations between pupil size and fMRI activity were found in the cingulo-opercular network (CON), which is known to support time extended (sustained) cognition in humans. Second, we observed delayed negative interaction between pupil size and sensorimotor and visual networks, known to contain a high density of noradrenergic receptors. Third, we observed large-scale network functional connectivity changes related to arousal state. Finally, the brain-wide pattern of these large-scale circuit interactions allowed successful out-of-sample prediction of individual differences in cognition, which was assessed by principal component analysis of HCP-provided 65 behavioral metrics from cognitive tasks, including attention, impulsivity, fluid intelligence, and executive function. These results indicate the important role of cognitive control network interactions with the arousal system in human cognition.

Disclosures: E. Podvalny: None. **M.W. Cole:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.01

Topic: H.03. Decision Making

Support: NIDA RO1 DA047870
NIDA R01 DA047870-S1
NIMH R21 MH122800

Title: Single-photon calcium imaging of orbitofrontal cortex in freely-moving rat during flexible learning of delay and probability

Authors: *J. L. ROMERO-SOSA, K. EVANS, T. YE, H. T. BLAIR, IV, A. IZQUIERDO; Dept. of Psychology, UCLA, Los Angeles, CA

Abstract: The brain can associate different reward attributes to an action (action-reward associations), including the probability of reward or the delay to receive such reward; however, the relationship between the two types of learning is unclear. Here, we probed if action-delay associations are learned similarly to action-probability associations and the ventrolateral orbitofrontal cortex (vlOFC) contribution to these two different types of learning. We trained male Long-Evans rats (N=8) to respond to the left or to the right on a touchscreen. Two identical stimuli were displayed on a touchscreen under two conditions: 1) a side-probability discrimination where one side of the touchscreen was rewarded with a 90% reward probability (p=0.9) and the other with a 10% probability (p=0.1), both with a 0s reward delay; or 2) side-

delay discrimination where one side resulted in a shorter wait time (0s) than the other (8s), both rewarded at an equivalent probability as side-probability discriminations with “catch” (i.e., reward omission) trials. After two successive days with a performance of >75% correct, the rewarded sides were reversed. After two reversals, rats were switched from one of the tasks (delay or probability) to the other, in counterbalanced order. Prior to testing, rats underwent stereotaxic surgery to unilaterally infuse a fluorescent calcium indicator GCaMP6f (AAV9-CAMKII-GCaMP6f) in vlOFC. At the same time, we implanted a gradient refraction index (GRIN) lens in that region. Another week later, the rats were briefly anesthetized to cement a baseplate to the skull for mounting the miniscope over vlOFC. Data collection began >48 hours after the baseplate was mounted. As a preliminary analysis of 51 neurons from rat vlOFC (n=1), we plotted the sorted peri-event time histogram (PETH) of recorded vlOFC neurons time-locked to correct vs. incorrect responses. We used the index from the sorted PETH on correct choices to sort the same cells on incorrect choices, and vice-versa. We found that the order of maximal firing was different for correct vs. incorrect choices. This serves as preliminary, confirmatory evidence that vlOFC encodes correct vs. incorrect decisions differently. Ongoing work is focused on registering cells across days and comparing single-cell activity across probability and delay conditions.

Disclosures: **J.L. Romero-Sosa:** None. **K. Evans:** None. **T. Ye:** None. **H.T. Blair:** None. **A. Izquierdo:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.02

Topic: H.03. Decision Making

Title: Neural encoding of economic decision variables in the mouse orbitofrontal cortex differs by cortical layer

Authors: *A. LIVI[1], M. ZHANG[2], M. CARTER[1], H. SCHOKNECHT[1], T. E. HOLY[1], C. PADOA-SCHIOPPA[1];
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Abstract: Neurophysiology studies in monkeys and mice found that different groups of neurons in orbitofrontal cortex (OFC) encode individual offer values, the binary choice outcome, and the chosen value. These variables capture the input and the output of the choice process, suggesting that OFC may host a decision circuit. However, the anatomical organization of this circuit is poorly understood. Here we examined whether different cell groups identified in relation to behavior populate different cortical layers. To address this question, we developed an approach for two-photon calcium imaging of OFC in mice using GRIN lenses. We specifically examined whether the encoding of decision variables varied between layer 2/3 (L2/3) and layer 5 (L5).

Cortico-cortical input reaches primarily L2/3; conversely, output projections originate from L3 (cortico-cortical) or L5 (subcortical). Thus we hypothesized that offer value cells might populate mostly L2/3, and that most cells in L5 might encode the choice outcome. During the experiments, head-fixed mice chose between two juices offered in variable amounts. Each juice was associated with an odor, and the odor concentration indicated the juice quantity. Our data set included 2464 cells from L2/3 (5 mice, 25 field of views (FOVs)) and 584 cells from L5 (6 mice, 14 FOVs). Using established procedures (Kuwabara et al., 2020), we classified each cell as encoding the spatial configuration, the offer value, the chosen side, or the chosen value. For a population analysis, we constructed two contingency tables in which columns corresponded to cortical layers, rows corresponded to time windows or encoded variables, and entries indicated cell counts. We then computed the corresponding tables of odds ratios, which we tested using Fisher's exact test. Interestingly, all encoded variables were represented in both L2/3 and L5. At the same time, there were significant differences between layers. Specifically, L2/3 cells became tuned earlier in the trial. Furthermore, the encoding of offer values (decision input) was significantly stronger in L2/3 than in L5; conversely, the encoding of chosen side (decision output) was significantly stronger in L5 than in L2/3. These results suggest an intriguing and articulated picture. On the one hand, the prevalence of offer value signals in L2/3, and of chosen side signals in L5 is broadly consistent with our working hypothesis. On the other hand, the lack of strict variable segregation across layers suggests that aspects of the decision process take place within each layer. This account matches current notions on how winner-take-all mechanisms are implemented in cortical circuits (Douglas and Martin, 2004).

Disclosures: A. Livi: None. **M. Zhang:** None. **M. Carter:** None. **H. Schoknecht:** None. **T.E. Holy:** None. **C. Padoa-Schioppa:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.03

Topic: H.03. Decision Making

Support: Wellcome trust

Title: Retrospective choice codes for causal learning

Authors: *L. J. H. RONDOT #[1], P. P. WITKOWSKI #[1], Z. KURTH-NELSON[2], M. GARVERT[3], R. J. DOLAN[4], T. E. BEHRENS *[5], E. D. BOORMAN *[1];
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Abstract: This study assesses the human ability to appropriately assign credit of an observed outcome to the action that caused. The orbitofrontal cortex (OFC) is a key brain region involved in this function (Boorman, 2016) but the underlying neural mechanisms is not clear. A possibility is that it reactivates the representations of the chosen stimulus at feedback (Tsujimoto, 2009).
20 healthy human subjects performed a decision task in a fMRI scanner. Subjects were presented with 2 stimuli, each of which had a probability of leading to one of two gift cards that were equally preferred by each subject. The value of each card randomly changed from trial to trial. Each stimulus-outcome contingency gradually changed over time and were fully independently from each other. In a first condition, subjects selected an image on trial *t* and next saw the gift card that corresponded to that choice. In a second condition, subjects selected an image at trial *t*, but did not see the outcome of that choice until the trial (t+1) after another choice was made, allowing disambiguation of the causal choice from the most recent choice held in working memory.
Multiple linear regression analysis revealed that in condition 1 subjects appropriately credited outcomes to the *most recent* choice, ($choice_{t-1}$ X $outcome_{t-1}$: $t(19) = 9.07$, $p < .0001$) but not the previous choice ($choice_{t-2}$ X $outcome_{t-1}$: $t(19) = 1.13$, $p > .1$). In condition 2, subjects instead appropriately credited the *previous* choice ($choice_{t-2}$ X $outcome_{t-1}$: $t(19) = 3.177$, $p = .0025$) but not consistently the most recent choice ($choice_{t-1}$ X $outcome_{t-1}$: $t(19) = -1.60$, $p = .06$). This indicates subjects flexibly assigned credit to the causal choice based on the task rules.
We tested whether the pattern of voxel activity occurring at the time of feedback contained information about the choice which led to each outcome (the choice immediately preceding the feedback in condition 1 and the choice from the previous trial in condition 2). Consistent with our predictions, we found clusters in lateral OFC and extrastriate visual cortex that contained information about the previously chosen stimulus in condition 1 ($t(19) = 2.83$, $p < .005$). Similarly, in condition 2, we found information about the causal stimulus at feedback in visual cortex ((19) = 2.83, $p <.005$) and in lateral OFC ($t(19) = 1.7$, $p < .05$). Computational model-based fMRI revealed simultaneous belief update (Kullback-Liebler divergence) signals in a neural network including lOFC.
These results show a reactivation of the causal choice in these regions at feedback, coincident with learning update signals, highlighting the role of the OFC and sensory cortex during credit assignment even when feedback is not immediate.

Disclosures: L.J.H. Rondot #: None. **P.P. Witkowski #:** None. **Z. Kurth-Nelson:** None. **M. Garvert:** None. **R.J. Dolan:** None. **T.E. Behrens *:** None. **E.D. Boorman *:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.04

Topic: H.03. Decision Making

Support: ERC grant GA-340063

Title: Learning and exploration by rats in a complex environment

Authors: *M. KARAYANNI[1], Y. LOEWENSTEIN[1], I. NELKEN[1,2];
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Abstract: We wanted to study the way freely moving rats explore a complex yet controllable environment. To that purpose we implemented a complex decision task in the Rat Interactive Foraging Facility (RIFF). The RIFF is a large (1.6 meter in diameter) experimental environment that has 6 interaction areas (IAs), in which the rat can poke and receive food and water rewards. To obtain a reward, the rats are required to perform a sequence of pokes in the various IAs of the RIFF in a particular randomly-chosen unmarked order. Specifically, the task can be described as a multi-state Markov Decision Process (MDP): The states are ordered from the initial state to final state and are marked with distinct auditory and visual cues. The MDP had one more states than the length of the sequence. In the final state, poking in any of the IAs equally rewarded the rat with food pellets or water. All other states are each associated with a one "correct" IA such that poking in it advances the animal to the next state. Poking in any other IA resets the animal to the initial state. The identities of the correct IAs were kept fixed until the animal reached a satisfactory level of performance, and then changed (with no indication), forcing the rats to relearn the task. Remarkably, in a 3-state MDP, rats managed to successfully learn up to 5 different sequences within a session of less than 2 hours. Moreover, they learned the correct IA associated with the initial state before learning the correct IA associated with the second state, suggesting that the rats solve the task by learning the correct IA for each state separately and not by propagation of a reward signal. However, fewer state visits were required to learn the location of the second IA in the sequence than the first, consistent with theoretical predictions on learning with temporal discounting of reward. In each state, the probability to find the correct IA location decreased when conditioned on the number of errors, as expected from a random search pattern with repetitions, but the decrease was faster than expected suggesting an unstructured exploration strategy with a tendency to repeat unsuccessful attempts. In conclusion, rats were able to learn a complex task in the RIFF, behavior was largely consistent with hierarchical learning and random exploration with some biases in port selection.

Disclosures: M. Karayanni: None. **Y. Loewenstein:** None. **I. Nelken:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.05

Topic: H.03. Decision Making

Support: NIH Grant R21-DA042882

Title: Two-photon calcium imaging of orbitofrontal cortex in mice performing economic choices reveals high temporal stability

Authors: *M. ZHANG[1], A. LIVI[2], M. CARTER[3], H. SCHOKNECHT[4], T. E. HOLY[5], C. PADOA-SCHIOPPA[6];
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Abstract: Neurophysiology studies in monkeys and mice demonstrated that different groups of neurons in the orbitofrontal cortex (OFC) encode individual offer values, the binary choice outcome, and the chosen value. These variables capture both the input and the output of the choice process, suggesting that the cell groups identified in OFC constitute the building blocks of a decision circuit. Here we examined whether the functional role of individual neurons remains stable over time.
To address this question, we developed an approach for two-photon calcium imaging of the mouse OFC using GRIN lenses. In each session, animals chose between two juices offered in variable amounts. Offers were represented by odors and mice indicated their choice by licking one of two spouts. In each animal, we recorded from 3-5 distinct fields of view (FOVs), and recordings continued for 2-8 weeks. Thus the same FOV could be recorded from repeatedly over long periods of time. Each FOV included 50-120 distinct neurons, 50-80% of which could be matched when the same FOV was recorded from >1 week apart. We thus addressed several specific issues. (1) For each cell, we examined the activity profiles recorded in two sessions >1 week apart. We used the cosine product to quantify the similarity between the activity profiles. Typically, the activity profiles recorded for the same cell were significantly more similar than those of neurons randomly selected in the same FOV. This analysis was conducted on >1000 cells from 21 FOVs and 4 animals. (2) Using previously described procedures, we classified each cell in each session as encoding the offer value, the choice outcome or the chosen value (Kuwabara et al., 2020). We then compared the variables encoded by the same cell >1 week apart. This analysis was conducted on 1767 cells from 10 FOVs and 3 animals. For a population analysis, we constructed a contingency table in which rows and columns represented the cell group for the early and late session, respectively, and entries indicated cell counts. We then computed the corresponding table of odds ratios and found that all entries on the diagonal were significantly >1 ($p<0.01$; Fisher's exact test). Thus most cells encoded the same variable across sessions. (3) We conducted a longitudinal analysis assessing the cosine similarity and the consistency of encoded variable for each cell over 2-8 weeks. We found a high degree of stability, but some decay over time.
In conclusion, the activity profile and the variable encoded by individual neurons in OFC are largely stable over time. This result supports the notion of a decision circuit within OFC. It also lays the ground to investigate the organization and mechanisms governing this circuit.

Disclosures: M. Zhang: None. **A. Livi:** None. **M. Carter:** None. **H. Schoknecht:** None. **T.E. Holy:** None. **C. Padoa-Schioppa:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.06

Topic: H.03. Decision Making

Support: NIH Fellowship F31MH127901
NIH Grant R01 MH121480
Pew Biomedical Scholars Program
NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

Title: Decision making in the context of multi-attribute options

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Abstract: Often decisions are made between options that have multiple features, or attributes, that are relevant to one's choice. For example, when deciding between snacks to purchase, one might factor cost and taste into a selection. The orbitofrontal cortex (OFC) has an important role in decision-making and OFC neurons represent associations between stimuli and their overall values. However, it is still unknown whether OFC only evaluates options on the basis of their integrated value, as suboptimal decision-making effects such as the attraction effect indicate that within-attribute comparison may also contribute to decision-making. To investigate how multi-attribute options are represented in neural activity, we trained two rhesus macaques on a multi-attribute decision making task, in which two simultaneously-presented options were represented by stimuli reflecting the sweetness of that option's sucrose reward, and the probability of receiving that reward. These composite stimuli represented information about the attributes of the options with separate bars that either increased *or* decreased with increasing attribute value, allowing us to investigate both free-viewing gaze behavior and changes in choice behavior due to perturbations in attribute presentation. We recorded neurons in OFC and frontal eye fields (FEF) using acute electrodes and multi-contact linear probes. We found that when comparable attributes did not share a presentation mode (e.g., reward bar A increased in size with increasing sweetness, while reward bar B decreased), choice behavior became suboptimal, implying a role for within-attribute comparison. Preliminary neuronal analysis indicates a greater presence of independent information relating to attribute than integrated value of the chosen option in OFC and FEF firing rates. Our interim results support the notion that value-based decisions take place, at least partially, in the space of individual attributes, and may depend on attribute value representations in OFC.

Disclosures: A. Perkins: None. **E.L. Rich:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.07

Title: WITHDRAWN

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.08

Topic: H.03. Decision Making

Support: NIMH Grant 5T32MH019524
K99/R00 Pathway to Independence Award (5R00MH111926-05)
Alfred P. Sloan Fellowship
Klingenstein-Simons Fellowship
NIH Director's New Innovator Award (DP2MH126376)
R01 (1R01MH125571-01)

Title: Lateral OFC is required for hidden state inference

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New York Univ., New York Univ., New York, NY

Abstract: Orbitofrontal cortex (OFC) has long been considered critical for value-based decision making. Recent work suggests that OFC represents a cognitive map of task space and is important for value-based decision-making when value information is necessary to determine the current task state. However, the precise role of OFC in value-based decision making remains a point of contention. We trained rats on a novel temporal wagering task with partially hidden states (blocks of trials with low or high rewards). Rats must determine how long to wait for a reward. The amount of time rats are willing to wait for each reward provides an explicit behavioral readout of rats' subjective value for the offered reward volume. Rats' wait times are modulated by both the offered reward volume and the hidden reward state. Bilateral muscimol inactivation of lateral OFC reduces modulation of wait time by reward state, but does not impair modulation of wait time by reward volume. This suggests that lOFC is necessary to infer the current reward state based on knowledge of the task structure, but is not required to compute subjective value, per se. We also fit a behavioral model that uses Bayes' Rule to predict the identity of the current reward state. The model includes parameters representing the opportunity cost in each block (which dictates the wait time in different blocks), and a parameter capturing the extent to which rats use an optimal prior, which contains knowledge about block length and

transition probabilities. Results suggest that rats use a less informative prior when lOFC is inactivated, but other parameters are not affected. Electrophysiological recordings from lOFC reveal encoding of hidden states in single units. Furthermore, the identity of the current reward state can be decoded from population activity. It is not known whether state representations are generated through local activity within OFC or from long-range inputs. Lateral OFC receives dense projections from the submedial nucleus of the thalamus. Preliminary evidence suggests that inactivation of OFC-projecting submedial nucleus neurons qualitatively recapitulates the reduction in modulation of wait time by reward state seen when lOFC is inactivated. Together, these data suggest that lOFC promotes the use of a prior that incorporates knowledge of the task structure for inferring partially observable states of the environment and thalamic inputs to lOFC may support these computations.

Disclosures: S. Schiereck: None. **A. Mah:** None. **C. Constantinople:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.09

Topic: H.03. Decision Making

Title: Long-range projections from the lateral orbitofrontal cortex to the dorsal striatum involved in distinct reinforcement learning strategies.

Authors: *M. L. DEMAEGD, M. ADLER-WATCHER, C. M. CONSTANTINOPLE;
New York Univ., New York, NY

Abstract: Reinforcement learning (RL) methods are divided into two classes: “model-free” algorithms repeat previously rewarded actions, whereas “model-based” algorithms learn a world model and use it to select actions. Distinct neural circuits implement these algorithms: lateral orbitofrontal cortex (lOFC) and the dorsomedial striatum are critical for model-based RL, whereas the dorsal lateral striatum is thought to support model-free RL. We sought to characterize the anatomical connectivity between the lOFC and these different subregions of the dorsal striatum. We injected distinct retrograde fluorescent tracers in the dorsomedial (DMS) and dorsolateral (DLS) striatum and characterized the distribution of singly- or dually-labelled somata in the lOFC. We found that lOFC projects exclusively to the DLS, which is notable because the lOFC and DLS are thought to participate in distinct RL systems that may compete. We hypothesize that long-range lOFC-DLS projection neurons promote model-based RL by suppressing the DLS. We are currently performing projection-specific perturbations and computational modeling of behavior to test this hypothesis.

Disclosures: M.L. DeMaegd: None. **M. Adler-Watcher:** None. **C.M. Constantinople:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.10

Topic: H.03. Decision Making

Support: NSF 1937971
NIH OD011132

Title: Evidence for altered cortico-striatal interactions in mice experimentally bred to exhibit habit- and compulsive-like behavior

Authors: *S. YOUNT[1], S. L. GOURLEY[2], S. WANG[1];
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Abstract: Habitual behavior is reflexively triggered by cues and not outcome predictability. It is adaptive under many circumstances, but it could be antecedent to compulsions – intrusive thoughts that drive persistent and potentially maladaptive behavior. We first hypothesized that mice with a natural propensity for habitual behavior would exhibit compulsive-like behavior. We experimentally bred mice that failed to update instrumental behaviors when expected rewards were not delivered and instead deferred to familiar behavioral sequences. Their offspring developed the same habit-like response biases, as well as compulsive-like and risk-taking behavior. Compulsive-like behavior was corrected by fluoxetine or ketamine, pharmacotherapies that ameliorate compulsive behavior in humans. Hyperactivation of the orbitofrontal cortex (OFC) is considered a causal factor in obsessive-compulsive disorder. We thus chemogenetically inhibited excitatory OFC neurons, reducing compulsive-like grooming in experimentally bred mice. Notably, silencing OFC neurons increased levels of the excitatory synaptic marker PSD95 in the dorsal striatum, with high levels predicting less compulsive-like grooming. These patterns suggest that dampening hyperactive OFC neuron populations can normalize cortico-striatal connectivity in models for studying compulsive behavior. A prominent theory of compulsions is that they involve a loss of control over habits. Understanding how cortico-striatal connectivity contributes to compulsive-like behavior may advance future efforts to mitigate harmful compulsive and habitual behavior alike.

Disclosures: S. Yount: None. **S.L. Gourley:** None. **S. Wang:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.11

Topic: H.03. Decision Making

Title: Shape shifting: Cocaine experience warps the geometry and context of neural representations in rat prefrontal cortex during decision making

Authors: *L. E. MUELLER[1], C. KONYA[2], M. SHARPE[1], A. M. WIKENHEISER[1], G. SCHOENBAUM[2];
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Abstract: Flexible decision makers adapt to change quickly, sometimes adjusting their behavior on their first encounter with a new situation. This ability is thought to depend on specialized neural representations of events and stimuli. An ideal representation would afford high separability, allowing downstream structures to easily distinguish activity patterns evoked by different stimuli, while also maintaining generalizability, ensuring that similarities between stimuli are preserved in the representation. These goals—separability and generalization—seem at odds with one another; high-dimensional representations are ideal for separability, but generalization is usually thought to depend on similarity in a low-dimensional space. Recent theoretical work, however, has shown that carefully-structured high-dimensional representations can afford both high separability and good generalization. Here, we tested whether a decision making task that required behavioral flexibility elicited separable and generalizable task representations in rat prefrontal cortex. We further examined how prior drug experience—which is known to reduce behavioral flexibility—affected the geometry of neural representations during decision making. We recorded single-unit activity in the prefrontal cortex of rats that had previously self-administered either sucrose or cocaine as they performed an odor-guided choice task comprised of trial types defined by unique direction x size x flavor mappings. Orbitofrontal cortex (OFC) representations of trial type were highly-separable in control rats, enabling statistically-reliable classification of arbitrary groupings of trial types. However, only trial-type groupings that corresponded to identifiable task features (such as cued action) were represented in a generalizable format. Cocaine experience reduced the overall dimensionality of OFC trial-type representations, and specifically reduced the generalizability of task-relevant trial-type groupings. Further, analysis of such specific task-related representations revealed that prior cocaine weakened choice type representations, the integrity of which were related to task performance. These results are consistent with a role for the OFC in the regulation of flexible cognitive behavior and suggest that alterations in both the geometry and specific content of neural representations contribute to the maladaptive behavior that is observed in SUDs.

Disclosures: L.E. Mueller: None. **C. Konya:** None. **M. Sharpe:** None. **A.M. Wikenheiser:** None. **G. Schoenbaum:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.12

Title: WITHDRAWN

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.13

Topic: H.03. Decision Making

Support: NIH Grant K01-DA-036659-01
Busch Biomedical Foundation
Whitehall Foundation
Behavioral and Neural Sciences Graduate Program

Title: Neural mechanisms of economic decisions are reflected in orbitofrontal high-gamma

Authors: *D. SHARMA, S. LUPKIN, V. B. MCGINTY;
Rutgers Univ., Newark, NJ

Abstract: The orbitofrontal cortex (OFC) has an important role in value-based decisions, and much of what we know about its function comes from studying the spiking activity of single neurons. However, another informative measure of neurophysiological activity is local field potentials, which reflect a combination of local spikes, synaptic inputs, and dendritic activity. It has recently been observed that a high-frequency band of local field potentials, known as 'high-gamma', encodes the value of an expected reward in OFC (Rich & Wallis, 2017, *Nature Communications*). However, it is not known whether OFC high-gamma reflects more complex decision-specific computations, such as the absolute or relative value of decision offers, or if high-gamma is related to choice behavior. We recorded OFC spiking and high-gamma activity using multi-channel linear probes in monkeys performing a two-option value-based decision task, and then compared spikes and high-gamma signals recorded concurrently from the same electrodes. We report four key results. First, both spikes and high-gamma represent the values of the decision offers, with each signal explaining a unique portion of variance in value, when measured on a channel-by-channel basis. Second, on average high-gamma signals increased monotonically as a function of value, whereas spikes showed neutral value encoding on average. Third, high-gamma signals, but not spikes, reflected a comparison between the offer values. Fourth, at a single-channel level high-gamma was generally a better predictor of decision outcomes; however, when using a multi-channel, population-based decoder, spikes furnished more accurate predictions than high-gamma. Overall, our findings suggest that OFC high-gamma reflects critical decision-related computations that are not always detectable from OFC spikes. High-gamma may therefore provide novel insights into the neural mechanisms of economic decision-making. Furthermore, because high-gamma is known to be tightly related to non-invasive imaging signals, our findings have potential implications for cross-species translational work.

Disclosures: D. Sharma: None. **S. Lupkin:** None. **V.B. McGinty:** None.

Poster

737. Neural Correlates of Decision Making in the Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 737.14

Topic: H.03. Decision Making

Support: NIH Grant K01-DA-036659-01
Busch Biomedical Foundation
Whitehall Foundation
Behavioral & Neural Sciences Graduate Program

Title: Functional specialization for goods- and action-based coding in the primate orbitofrontal cortex

Authors: *S. M. LUPKIN[1,2], V. B. MCGINTY[1];
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Abstract: The primate orbitofrontal cortex (OFC) is known to play a role in value-based choices, but the underlying computations performed by OFC neurons remains unclear. At a high level, there are two general theories of OFC function, paralleling a larger debate about whether decisions are made at the level of economic goods or, if decisions are made between the actions necessary to obtain those goods. In the goods-based framework, decisions are made in the OFC itself. In the action-based framework, the OFC conveys information about available options to downstream structures where a decision is rendered between competing actions.
A potential explanation for these diverse views lies in the OFC's anatomy. Though often treated as a single functional unit, the OFC is comprised of several distinct cytoarchitectonic regions. Two of the most studied are granular area 11 in the anterior portion of OFC (aOFC), and dysgranular area 13 located more posteriorly (pOFC). Beyond cytoarchitectonic differences, these two regions also have markedly different connectivity profiles. Given these differences, we hypothesized that they may be functionally distinct as well. To explore the functional properties of these regions, we conducted simultaneous recordings in both subregions using multi-channel linear arrays while macaques were engaged in a two-alternative value-based decision making task (see Lupkin & McGinty, 2022 for details). Our results indicate a clear functional dichotomy between these two subregions: the variables encoded within the pOFC were largely related to the features of the choice options (i.e. their associated reward values), while encoding in aOFC reflected variables related to aspects of the upcoming action necessary to obtain the reward (i.e. left vs. right reach movement). These results are consistent with the two regions' respective connectivity profiles. Specifically, the convergent sensory and limbic input to pOFC makes it well suited for representing items in a goods-based framework, while the aOFC's second-degree connections with pre-motor cortex make it well suited to representing action-based variables. Together, these findings may help clarify longstanding debates over the OFC's role in economic decision making.

Disclosures: **S.M. Lupkin:** None. **V.B. McGinty:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.01

Topic: H.06. Social Cognition

Support: NIH Grant F30 MH130104

Title: Theory of mind network connectivity differences in schizophrenia during naturalistic video stimuli

Authors: *E. PRZYSINDA[1], B. SHOVESTUL[1], A. SAXENA[1], S. REDA[1], E. DUDEK[2], J. LAMBERTI[1], E. C. LALOR[1], D. DODELL-FEDER[1];
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Abstract: Schizophrenia (SCZ) is a debilitating and complex disorder, and one often overlooked symptom is marked and persistent difficulties with social information processing. Increasing work has shown that these deficits can be attributed to abnormalities in the network of brain regions supporting mental state attribution, known as the theory of mind (ToM) network; namely, medial prefrontal cortex (mPFC), temporo-parietal junction, right superior temporal sulcus, precuneus, and right posterior cerebellum. Much of the current literature generally utilizes explicit task-based paradigms that only examine isolated aspects of social processing. However, social interactions are nuanced and context-dependent, so utilizing naturalistic stimuli more representative of daily social interactions with an implicit viewing task could help us to better understand social difficulties in SCZ. Here, we used an episode of the comedy TV show, *The Office*, as our stimulus because it contains a rich variety of social interactions, including some that require complex ToM processes (i.e., awkward moments, violations of social norms). We aim to compare functional connectivity in the ToM network between neurotypical controls (NTC,n=18) to patients with schizophrenia spectrum disorders (SCZ,n=18) while participants underwent fMRI while watching an episode of *The Office* TV show. Preliminary results suggest that there is a broad decrease in functional connectivity between ToM regions in SCZ compared to NTC during this task. Specifically, graph theory results showed that in the ToM Network, the dorsal and middle mPFC have a higher global efficiency in controls than SCZ patients (network edges threshold < 0.15, analysis threshold p-FDR-cor < 0.05). These results suggest that these key ToM regions involved assessment of others' evolving mental states are less connected to the rest of the ToM network, and that these decreased connections of the mPFC may be underlying impaired ToM abilities in SCZ. Our findings converge with previous literature showing decreased functional connectivity during explicit ToM tasks in SCZ, and here we show here that these findings can be replicated in a more naturalistic paradigm. Future analyses will look at the neural dynamics in the ToM network during specific moments requiring ToM processing, such

as awkward moments. Recently collected EEG data may shed further light on the nature of the neural connectivity differences in these ToM networks.

Disclosures: E. Przysinda: None. **B. Shovestul:** None. **A. Saxena:** None. **S. Reda:** None. **E. Dudek:** None. **J. Lamberti:** None. **E.C. Lalor:** None. **D. Dodell-Feder:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.02

Topic: H.06. Social Cognition

Support: JSPS 18K13221

Title: Neural signals predict implicit attitude toward people with autism spectrum disorder

Authors: *S. YOKOTA[1], T. HASHIMOTO[2], R. KAWASHIMA[2];
[1]Fac. of Arts and Sci., Kyushu Univ., Fukuoka-Shi, Japan; [2]IDAC, Tohoku Univ., Tohoku Univ., Sendai, Japan

Abstract: Introduction: People with autism spectrum disorder (ASD) experience stigmatization rooted in negative attitudes or prejudice toward them due to social awkwardness. This study focused on implicit attitudes manifested as actions or judgments under the control of automatically activated evaluation. The purpose of this study was to investigate whether the implicit attitude towards ASD was predicted and dissociated from that toward physical disabilities using fMRI with multivoxel pattern analysis (MVPA) in a prejudice network.
Methods: Participants were 36 right-handed healthy Japanese university students (mean age = 22.6, 23 males, 13 females). The participants performed two implicit association tests (IAT) to assess implicit attitudes toward ASD (A-IAT) and physical disabilities (Phy-IAT) outside of the MRI scanner. They performed one-back task using the same picture sets of IATs in the scanner. There were six blocks in each condition (ASD, Phy, and healthy). We calculated D scores (based on the mean latency difference between incongruent and congruent conditions) reflecting participants' implicit attitudes. Using SPM12, we got contrast images of each condition and extracted brain activation from each voxel within the following ROIs of the prejudice network; bilateral amygdala, caudate, insula, medial prefrontal, and orbitofrontal cortex. In MVPA, we computed decoding performance using LIBSVM with 6-fold cross-validation and calculated Pearson's correlation coefficients between predicted and observed D scores. Decoding performance was evaluated using a permutation test (iteration = 5,000).
Results: Implicit attitude toward people with ASD was significantly negative than that toward physical disabilities ($F(1,35) = 97.9$, $p < 0.001$, $\eta^2 = 0.74$). As for MVPA, activation pattern of right amygdala in 'ASD - healthy' predicted D score of A-IAT ($r = 0.46$, $p_{perm} = 0.01$) and activation pattern of right caudate in 'Phy - rest' predicted D score of Phy-IAT ($r = 0.38$, $p_{perm} = 0.03$).

Discussion: This study indicated that neural activation patterns in the right amygdala and caudate could predict the implicit attitude toward people with disorders. The activation in the amygdala might reflect a negative emotional reaction to an outgroup, while that in the caudate might be related to the learning, representation of reward, and goal-directed behavior. These results suggested that implicit attitudes toward ASD and physical disabilities could be predicted and dissociated by neural signals of
the different regions within the prejudice network.

Disclosures: S. Yokota: None. **T. Hashimoto:** None. **R. Kawashima:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.03

Topic: H.06. Social Cognition

Support: NIMH K23MH108711
NIMH R01MH123639
NIMH R01MH121790
DANA Foundation

Title: Changes in movie-driven transient brain states in schizophrenia correlate with naturalistic social perception

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Abstract: Introduction: Perception of naturalistic social scenes requires the dynamic interplay of many cortical systems, observed as transient activation patterns in whole-brain imaging. Here we examine whether these states differ in schizophrenia participants (SzP) who have previously been reported to have social perception deficits.
Methods: 27 SzP and 21 healthy controls (HC) watched a visual-only 15-minute video clip while whole-brain BOLD-fMRI data was collected. After removal of movement-related artifacts and time-series concatenation, k-means clustering was used to cluster the brain states into co-activation pattern states based on the activity in 98 functionally localized ROIs. The time-domain properties of these states were then examined for association with performance on the TASIT, a social perception test.
Results: We found 5 brain states across the two populations. The fractional occupancy of one of these states, characterized by co-activation of visual, attention, and theory-of-mind areas, was found to be lower in SzP ($p<0.05$ FDR-adjusted). The occurrence rate of this state was significantly correlated with TASIT performance in SzP ($r=0.51$, $p=0.008$) but not HC ($r=-0.14$, $p=0.6$). In this brain state SzP demonstrated strong reductions in the activation of the TPJm

(t(46)=-2.29, p=0.03) and TPJp (t(46)=-2.0, p=0.05). The time-course of the CAP States also differed between groups substantially (Spearman's r=0.41).
Conclusion: These results demonstrate not only the utility of temporal clustering-based approaches to identifying brain states in naturalistic studies, but also that previous differences in time-averaged data are the product of temporally isolated processing failures in SzP. Future studies using these methods will be able to isolate the neural substrates of momentary behavioral deficits associated with impaired social cognition.

Disclosures: D.J. Vieira: None. **S.A. Mirza:** None. **N.C. Foley:** None. **N.M. MacIlvane:** None. **J.K. Lee:** None. **G.H. Patel:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.04

Topic: H.06. Social Cognition

Support: Discovery Project 210101712 from the Australian Research Council (LJR)
Washington University in St Louis School of Medicine laboratory start-up funds (LJR)
Philanthropic funds from BICARE (Brain Injured Children Aftercare Recovery Endeavours)
Max Planck Society (PD) and the Alexander von Humboldt Foundation (PD)
GAR was supported by an Australian National Health and Medical Research Council Fellowship (APP1135769) and the Brazil Family Program for Neurology
LJR was supported by a Principal Research Fellowship from the National Health and Medical Research Council (GNT1120615)

Title: Bridging the divide: elucidating the social and cognitive impact of Corpus Callosum Dysgenesis

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Abstract: Corpus callosum dysgenesis (CCD) is one of the most common congenital neurological malformations. Despite being a clear and identifiable structural alteration in brain white matter connectivity, our understanding of the impact of CCD on cognition and behaviour

is incomplete. To address this, we administered a range of cognitive tasks to CCD and neurotypical (NT) participants, along with collecting psychometric measures of non-verbal abstract reasoning, trust, suggestibility, paranoia, and autistic-like traits. The tasks assessed metacognition and decision-making. Here we present our psychometric findings that better characterise the phenotype of CCD and the initial results of the cognitive tests. Using an unsupervised machine learning algorithm over all psychometric dimensions to estimate covariational differences between NT and CCD participants, we demonstrate that CCD participants are best defined by their propensity for suggestibility and gullibility after controlling for autistic-like traits, age, sex, and non-verbal abstract reasoning. Converging with prior evidence, we also found that CCD versus NT participants have a sharper, negative psychometric curve on increasingly difficult non-verbal abstract reasoning items; relative to their own performance, those with CCD find more difficult items even harder than NT participants. Finally, we present preliminary data on the impact of CCD on metacognition and decision-making versus NT participants, showing that those with CCD have lower metacognitive sensitivity, and are less able to consider increasing costs on exploratory behaviour. Taken together, our work provides an improved phenotypic characterisation of CCD and more broadly provides insight into the role of the corpus callosum on cognitive function.

Disclosures: **J. Barnby:** None. **H. Burgess:** None. **R. Dean:** None. **L. Mackenzie:** None. **G. Robinson:** None. **P. Dayan:** None. **L.J. Richards:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.05

Topic: H.06. Social Cognition

Support: ARO Grant W911NF-18-1-0244
NIH Grant T32DA028874

Title: Regulation of alcohol cue reactivity in a social context

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Abstract: Alcohol use is a leading and growing contributor to global disease burden. Young adults are more likely to engage in binge drinking than older adults and may be particularly susceptible to the deleterious effects of alcohol, including cognitive impairment, overdose, and unintentional injury. Exposure to alcohol cues in the environment drives alcohol consumption via engagement of cortico-striatal circuitry and can lead to significant increases in both the

frequency of alcohol drinking and the amount of alcohol consumed. Cognitive strategies with the potential to downregulate neural reactivity in response to alcohol cues could effectively reduce drinking behavior. In this study, we combine task and structural MRI data to investigate the neural mechanisms underlying peer perspective-taking as a cognitive intervention to reduce alcohol craving. Study participants underwent an fMRI scan in which they were instructed to react naturally ("natural-reacting" trials) or to take the perspective of a peer who drinks more or less than they do ("perspective-taking" trials) when presented with alcohol cues. During natural-reacting trials, participants were asked to rate their level of craving in response to each cue; during perspective-taking trials, they were asked to rate the level of craving that they imagined their high- and low-drinking peers would experience in response to the cue. We employed a control theoretic approach to operationalize the cognitive effort associated with transitioning from reacting naturally to taking the perspective of a peer while reacting to alcohol cues. We found that, on average, the cognitive effort associated with taking the perspective of a peer who drinks less is greater than that associated with taking the perspective of a peer who drinks more. Further, we identify a significant linear relationship between the control energy required to take a peer's perspective and the difference in cue-induced alcohol craving between self and peer, such that higher levels of peer craving are negatively associated with the energetic cost of perspective-taking, and lower levels of peer craving are positively associated with the energetic cost of perspective-taking. By investigating regional contributions to this effect, we determine that the Yeo somatomotor system significantly contributes to the higher energetic cost associated with shifting from taking one's own perspective to that of a peer who drinks less. Broadly, our study provides a framework to enable predictions about the influence of a person's social environment on their capacity to engage perspective-taking as a strategy for self-regulation of drinking behavior.

Disclosures: **J.K. Brynildsen:** None. **D. Zhou:** None. **D. Cosme:** None. **M. Jovanova:** None. **Y. Kang:** None. **X. He:** None. **K.N. Ochsner:** None. **D.M. Lydon-Staley:** None. **E.B. Falk:** None. **D.S. Bassett:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.06

Topic: H.06. Social Cognition

Support: NIH Grant MH124115

Title: Neural computations underlying social mood

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Abstract: Affective and social decision making are integral to cognition and mental wellness, and the disruption of these processes is often implicated in psychiatric disease. One element of healthy social functioning is the ability to encode and adapt to social norms. Often, social norms must be learned through experience, with norm prediction errors (NPEs) acting as a learning signal that updates internal norm expectations in a similar fashion to the role of reward prediction errors (RPEs) in updating reward expectations. These social signals have the potential to strongly impact mood. Recent computational models have been developed that formalize the impact of RPEs on mood (Rutledge et al, 2014), with neuroimaging studies implicating striatal and cortical activity in these processes. Here, we seek to expand on these models by examining the impact of social signals (NPEs) on mood as well as their neural signatures by leveraging invasive intracranial electrophysiology. Specifically, we collected invasive microelectrode recordings in deep brain stimulation surgery patients as they played a social exchange game. We recorded local field potentials from the substantia nigra pars reticulata (SNr), a subcortical nucleus implicated in emotion processing and decision-making. In one experiment, patients (n= 19 sessions, 10 subjects; males = 9; females = 1; mean age = 60 ± 6) played 30 trials of an ultimatum game, in which they were presented with a proposed split of $20, which they accepted or rejected. If the patient rejected, each party received $0. To estimate the impact of social reward on mood, we conducted a second experiment in which patients (n= 5 sessions, 4 subjects; males = 4; females = 0; mean age = 57 ± 24) self-reported their mood rating after 60% of choice trials and also played a nonsocial control condition, affording 60 total trials. We modeled subjective utility using a Fehr-Schmidt model of inequity aversion, and internal norm adaptation with a Rescorla-Wagner function, and we related obtained rewards and NPEs to mood using a general linear model. Lastly, we correlated the magnitude of neural activation to task events to examine the neural representation of social norm learning signals. We demonstrate that internal norm evolves over time as a result of cumulative NPEs, and SNr activity represents both the magnitude and direction of NPEs. We conclude that the SNr plays an integral role in social norm encoding and adaptation, thus identifying this region as an important structure in affective and social learning.

Disclosures: A. Neal: None. **O. Perl:** None. **B.H. Kopell:** F. Consulting Fees (e.g., advisory boards); Medtronic, Abbott Neuromodulation. **M. Heflin:** None. **S.E. Qasim:** None. **S. Na:** None. **K.T. Kishida:** None. **P. Montague:** None. **I. Saez:** None. **X. Gu:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.07

Topic: H.06. Social Cognition

Title: The Human Affectome and an Active Inference Model of Emotion Episodes

Authors: *A. N. C. YU[1], D. SCHILLER[2], R. SMITH[3], E. BILEK[4], S. N. GARFINKEL[5], L. LOWE[6], K. J. FRISTON[7];
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Abstract: We present here a unifying framework for affective phenomena: the Human Affectome, followed by a computational example. By synthesizing across perspectives, 173 authors have converged on definitions for terms ‘affect’, ‘feeling’, ‘emotion’, and ‘mood’. Under the enactive premise that affective mechanisms reflect goal-directed allostatic concerns, the human affectome is comprised of allostatic features (valence, motivation, and arousal) and allostatic concerns (extent of action required to alleviate allostatic load). Allostatic concerns often fall into three ranges: physiological (the most immediate), operational (intermediate to distal), and global (overall trajectory, general wellbeing, and self-identity). The human affectome allows vastly different scientific interests to reside within the same theoretical framework. We hope this framework serves as a common focal point for understanding affective mechanisms in the discipline’s collective research program. Furthermore, we demonstrate a computational example of this unifying approach: two prominent accounts of emotion episodes—the theory of constructed emotion (Barrett, 2017) and component process model (Scherer, 2001)—contradict each other on the semantic surface, but can be integrated in mechanistic terms. We present a computational account of emotion episodes from first principles by building central mechanisms from both accounts into a partially observable Markov decision process model under the neurocomputational process theory of active inference (Friston et al., 2017). Here, emotion episodes are hidden states of an internal generative model in the Bayesian brain, inferred as best explanations in the processing of multimodal sensory information. We develop and validate the model using simulations on learning sequences starting with no knowledge and across different rewards. We demonstrate that the model successfully learns emotions from synthetic childhood into adulthood. In addition, when highly motivated to be correct about its emotion, it favors exploitation earlier during trials instead of exploring all available sensory information. However, this leads to alexithymia, or low emotional granularity, when overly rewarded. In validating this integrative model’s capacity to formalize emotional phenomena of interest, we provide proof of principle that two accounts of emotion can be merged under active inference and within a common framework such as the Human Affectome. This unifying endeavor offers promising directions for the computational and empirical study of emotion and highlights theoretical implications for cross-disciplinary pluralism.

Disclosures: A.N.C. Yu: None. **D. Schiller:** None. **R. Smith:** None. **E. Bilek:** None. **S.N. Garfinkel:** None. **L. Lowe:** None. **K.J. Friston:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.08

Topic: H.06. Social Cognition

Support: F31

Title: Navigating social relationships: the role of the hippocampus

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Abstract: Background: The hippocampus represents places in both physical and non-physical spaces. Thus hippocampal function may be domain general, representing behaviorally relevant dimensions in map-like formats. Previous research probed perceivable spaces with instructed dimensions and reinforced locations, where the maps' use is explicitly required. Here we test hippocampal place coding's domain generality using a naturalistic social task with none of those properties. **Methods:** Functional magnetic resonance imaging (fMRI) was collected in two samples of healthy individuals (n=32, 17 female; n=18, 7 female) during a choose-your-own-adventure game where they interacted with fictional characters. Participants' relationships (i.e., decisions) with each character were modeled as sequences of locations in an abstract two-dimensional social space of power and affiliation. These locations were compared to brain patterns.
Results: A hippocampal place-like representation was observed in a representational similarity regression with both region-of-interest (ROI) and whole-brain searchlight approaches, as well as an ROI-based decoding probability analysis (all multiple comparisons corrected ps<0.05). The place effect was present in both samples, and not explained by other measures of task behavior or other kinds of task-based social information (e.g., character identity, familiarity), or by demographic variables (i.e., age, sex) (all ps>0.05).
Conclusions: Our findings show that hippocampus represents the others' latent locations in an abstract 2D social space. This is the first study to show a truly domain general place code in the hippocampus. Future work will ask how place representations combine into navigable maps and used for flexible behavior and how alterations in these representations may be implicated in disorders that feature both hippocampal and navigation-like dysfunction.

Disclosures: **M. Schafer:** None. **V. Sahani:** None. **K. Bachi:** None. **D. Schiller:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.09

Topic: H.06. Social Cognition

Support: NIH R01 Grant MH122611

Title: Impaired Neural and Behavioral Navigation of Dynamic Social Relationships in Autism Spectrum Disorder

Authors: *S. BANKER[1], M. SCHAFER[1], S. BARKLEY[2], J. TRAYVICK[2], X. GU[2], D. SCHILLER[2], J. H. FOSS-FEIG[2];
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Abstract: Autism spectrum disorder (ASD) is characterized by impairments in social functioning, including deficits in reciprocity and dynamic social interaction. Despite a multitude of neuroimaging studies investigating social dysfunction in ASD, the neural underpinnings of these impairments remain poorly understood. Utilizing a naturalistic task that probes dynamic aspects of social interaction in combination with functional magnetic resonance imaging (fMRI), we took an innovative computational psychiatry approach to understanding the neural underpinnings of social deficits in ASD. ASD participants (n=35; age: mean 26.5, range 18.4-41.5; sex: 60% male; gender: 57.1% male) completed a choose-your-own-adventure game in which they simulated interactions with virtual characters. Unbeknownst to the participant, each interaction shifted a given character's position in a behind-the-scenes plot of 'social space' framed by axes of social hierarchy and affiliation. Computational modeling approaches extracted parameters of interest based on the trajectory of decision-making in the task. Post-task questions assessed subjective opinions about characters. In a subset of participants (n=7; age: mean 23.5, range 18.2-31.9; sex: 85.0% male; gender: 85.0% male), general linear models with parametrically modulated regressors assessed activity in the hippocampus in association with characters' locations in social space. Correlations assessed relationships between task outcomes and symptom severity; Welch's t-tests assessed group differences in neural activity. Results showed that increased ASD symptoms were associated with reduced consistency along the affiliation dimension during the task ($r(33)=-0.43$, $p=0.011$). Additionally, participants with more ASD symptoms rated the characters as less similar to themselves ($r(33)=-0.41$, $p=0.015$) and reported that they liked the characters less overall ($r(33)=-0.55$, $p<0.001$). Compared to a matched sample of previously collected TD individuals (n=7; age: mean 27.6, range 24.0-32.0; sex: 85.0% male; gender: 85.0% male), individuals with ASD showed a reduction in hippocampal encoding of the angles of the vectors drawn between the participant's point of view and the characters' locations in social space (representing tracking of social relationships; ASD: mean=0.33, sd=0.47; TD: mean=0.90, sd=0.43; $t(11.84)=-2.36$, $p=0.036$). Together, these results suggest that individuals with ASD are inconsistent in their social interactions with virtual characters, feel distant from them, and do not utilize neural circuits known to track social relationships to the same extent as TD individuals.

Disclosures: **S. Banker:** None. **M. Schafer:** None. **S. Barkley:** None. **J. Trayvick:** None. **X. Gu:** None. **D. Schiller:** None. **J.H. Foss-Feig:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.10

Topic: H.06. Social Cognition

Support: NIH R01MH112927
R21MH124016
R21MH120789

Title: Altered sense of social control in adolescents with eating disorder

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Abstract: Adolescence is a critical period for learning to navigate the social world and exploit itscontrollability. As such, a diminished sense of social control is detrimental to mental health,such as observed in eating disorders (ED). Here, we examined social controllability inadolescents with (n = 27; age = 15.17 ± 1.34) and without (n = 28; age = 15.45 ± 1.62) ED asthey played an interpersonal exchange paradigm in which they could use their actions toinfluence the monetary offers from others. We applied computational modeling to estimate twokey parameters: estimated control (i.e., how much influence one had on future offers) andinitial norm (i.e., offer amount participants expected to receive prior to any interactions);participants also self-reported perceived control after the game. We found no group differencein estimated control (P = .66) or initial norm (P = .60), but a reduced sense of control in EDgroup (t (53) = - 2.18, p = .03). In healthy adolescents, perceived control was driven by model-estimated control (r = .62, p = .0004), but not initial norm (r = - .04, p = .85). Strikingly,adolescents with ED showed a completely reversed pattern in that their perceived control wasprimarily correlated with initial norm expectation (r = .47, p = .01) instead of model-estimatedcontrol (r = .05, p = .80). These findings suggest that a stable relationship between subjectiveawareness of controllability and one's actual behavioral influence protects against disorderedeating, while altered social norm expectation contributes to a diminished sense of control inadolescents with ED.

Disclosures: Q. Fu: None. **J. Harper:** None. **J. Palka:** None. **C. McAdams:** None. **X. Gu:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.11

Topic: H.06. Social Cognition

Support: Psychology Department Summer Research Award, CSUN

Title: Lights, camera, fatigue? Exploring the relationship of Zoom Fatigue with videoconferencing camera usage and social presence

Authors: *J. A. GLUCK, S. SHARMA, C. COUZIN, E. HERNANDEZ, L. E. KNOX, S. A. DREW;
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Abstract: The COVID-19 pandemic led to a transition from in-person to online learning, resulting in an increase in video conferencing usage. Given the number of academic and scientific relations conducted via online environments, it is imperative that we discuss the importance of social cognitive abilities, e.g. social connectedness, characterized by interactions with others online, as well as associated symptoms of "Zoom Fatigue". Related terms to this phenomenon are social presence, or feeling present with another person, and social co-presence, or the sense of awareness and inter-connection with others in virtual interactions. Previous literature on these phenomenon has shown that social presence in an online setting can affect course satisfaction and has emphasized the importance of social co-presence between teachers and peers. Additional research has shown that using a camera within an online environment has led to higher reports of fatigue. However, further investigation of the inter-relationships between these factors is required. This study investigated factors that relate to experiences of social presence and co-presence in online environments, including Zoom Fatigue and camera usage. We administered a study to students from California State University, Northridge, where participants completed an online survey that included measures of social presence, social co-presence, virtual meeting fatigue, and camera usage. We hypothesized that greater social presence and greater social co-presence would be associated with less virtual meeting fatigue. Additionally, we predicted that having your camera on would predict greater virtual meeting fatigue. Results of a one-way ANOVA test suggested that camera usage has a non-significant relationship to Zoom Fatigue. The multiple regression analyses revealed that social presence and social co-presence significantly predicted less virtual meeting fatigue. These data support our hypotheses that increased social presence and social co-presence are associated with fewer zoom fatigue symptoms.

Disclosures: J.A. Gluck: None. **S. Sharma:** None. **C. Couzin:** None. **E. Hernandez:** None. **L.E. Knox:** None. **S.A. Drew:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.12

Topic: H.06. Social Cognition

Support: Stony Brook Foundation Board of Trustees Dissertation Completion Endowed Fellowship
Dr. W. Burghardt Turner Dissertation Fellowship
Bridge to the Doctorate Research Grant
Stony Brook University Biopsychology Founders Endowed Fellowship

Title: Neuroimaging of Political Cognition: An fMRI Study on the Memory Retrieval of Negative Political Fake News

Authors: *B. GONZALEZ, T. CANLI;
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Abstract: Fake news often contains false information created to deceive the public for ideological and/or financial gain and can leave a lasting influence on reasoning even after it has been corrected. This study aims to investigate the neural processes underlying the memory retrieval of "real" and "fake" political news statements using functional magnetic resonance imaging (fMRI). fMRI measurements were performed on a Siemens PRISMA 3 Tesla MRI scanner, with a 64-channel head coil, and TR/TE of 2500/30ms. Data was later preprocessed, analyzed, and quantified using SPM12. Whole brain voxel wise analysis was conducted with a p-value set to .001 uncorrected, and a cluster level correction of 30 voxels. In this pilot study, human participants (N=54; mean age: 25.04; 46.3% female) were shown negative news statements in the form of a Twitter 'tweet' from two (fictional) political opponents in the scanner. Participants were initially asked to rate the news as probably real or fake, and then shown whether the news was in fact "real" or "fake". They were asked to remember the news label given for an immediate memory task. After the scan session, participants completed a set of questionnaires to assess their political orientation, attitudes, and beliefs, and were then debriefed. Preliminary results suggest that participants recruit different areas of the brain depending on whether the news label was congruent (matched) with their initial judgement of the news statement compared to when the label and judgement were incongruent (mismatched). Activation in these congruency conditions were found in regions of the default mode network (DMN) such as the precuneus (MNI coordinates 3, -43, 50; cluster size 116), cuneus (MNI coordinates -3, -79, 26; cluster size 100), and the medial prefrontal cortex (MNI coordinates 3, 50, 32; cluster size 66). These areas have been shown to be implicated in cognitive processes such as memory retrieval, decision-making, and emotional responses. One limitation to this study is the large number of liberal participants (n=30) and small number of conservative participants (n=7), resulting in an uneven distribution across the political spectrum. Understanding the cognitive processes that are recruited during the memory retrieval of political fake news can lead to more insight on political cognition, decision-making, and the continued influence effect.

Disclosures: B. Gonzalez: None. **T. Canli:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.13

Topic: H.06. Social Cognition

Support: The research leading to these results has received funding from the EEA Financial Mechanism 2014-2021. Project: 2019/35/J/HS6/03498.

Title: Are we willing to share what we believe is true? Cognitive processes, personality traits and information features influencing susceptibility to fake news.

Authors: *M. PIKSA[1], K. NOWORYTA[1], J. PIASECKI[2], P. GWIAźDZIńSKI[2], A. GUNDERSEN[3], J. KUNST[3], M. MORZY[4], R. RYGULA[1];
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Abstract: The contemporary media landscape is saturated with the ubiquitous presence of misinformation posing a serious threat to democracy, sociopolitical stability, and mental health. In our research, we investigated some of the mechanisms of fake news dissemination that eluded scientific scrutiny: the evaluation of the veracity and behavioral engagement with information in light of its factual truthfulness (true or false), cognitive utility (enforcing or questioning participants' beliefs), and presentation style (sober or populistic). Moreover, we also explored the nature of cognitive mechanisms and personality traits that contribute to the susceptibility to (mis)information. Both studies were conducted using online participants panels integrated with sophisticated cognitive tests and reliable personality questionnaires. In the first study, we found that the evaluation of veracity is mostly related to the objective truthfulness of a news item. However, the probability of engagement is more related to the congruence of information with participants' preconceived beliefs than the objective truthfulness or the presentation style of the information. In the second study, the participants completed a newly designed scale classifying people into one of four phenotypes of susceptibility to (mis)information. The four identified phenotypes, Doubters, Knowers, Duffers, and Consumers, showed that believing in misinformation does not imply denying the truth. Furthermore, the phenotypes significantly differed in levels of sensitivity to positive and negative feedback, cognitive judgment bias, extraversion, conscientiousness, agreeableness, emotional stability, grandiose narcissism, anxiety, and dispositional optimism. The obtained results constitute a basis for a new and holistic approach in understanding susceptibility to (mis)information as a psycho-cognitive phenotype. We also concluded that the common notion that the spread of fake news can be limited by fact-checking is flawed as people will share fake information as long as it reduces the entropy of their mental models of the world.

Disclosures: M. Piksa: None. **K. Noworyta:** None. **J. Piasecki:** None. **P. Gwiaździński:** None. **A. Gundersen:** None. **J. Kunst:** None. **M. Morzy:** None. **R. Rygula:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.14

Topic: H.06. Social Cognition

Title: Association of Face Processing with the Uncanny Valley Effect

Authors: I. ARORA[1], G. KAUR[1], A. SONI[1], M. CHAKRABARTY[2], T. TZVETANOV[3], ***S. RAY**[2];
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Abstract: Facial expressions are widely used for interpersonal communication as they reflect the internal affective or emotional state of an individual. However, humans react differently when they see a human, a humanoid or a mechanical bot. In 1970, Mori showed that humans respond emotionally to androids in a nonlinear manner as a function of androids' feature similarity to humans.
He called it the 'Uncanny Valley effect (UVE). UVE pertains to an eerie feeling when one sees or interacts with robots closely looking to humans. Given that facial cues alone also exhibit the UVE (Mathur & Reichling, 2016), we aimed to investigate the relation between face processing and the UVE. The Event-Related Potential (ERP) of N-170 is a robust marker associated with face processing. The amplitude of N170 component is found to be greater for human faces as compared to non-face stimuli. Therefore, we hypothesized that if the uncanny valley effect is related to face processing, then there would be differential characteristics of the N170 component elicited for human as compared to robotic face images. To test this hypothesis we asked participants to rate human and robotic face images presented on a computer monitor while recording EEG signals simultaneously. The rating was done on an analogue scale for each individual image on two metrics: Likeability and Mechano-humanness. The likeability defines how friendly is the face to look at and mechano-humanness indicates how mechanical does the face look like. Epochs of EEG aligned to the onset of face (human/robotic) stimulus were analysed offline to study the N170 ERP. The comparisons were made for N170 component between human and robotic faces when the participants were rating the presented images in mechano-humanness scale as compared to likeability scale. Results showed the presence of N170 component for both human and robotic faces. The magnitude of N170 was similar for human and robotic faces for mechano-humanness ratings. However, the magnitude of N170 was less for robotic as compared to human faces for likeability ratings. The difference in amplitude of N170 component was observed only when participants were performing likeability rating task suggesting the contribution of face processing towards the UVE.

Disclosures: I. Arora: None. **G. Kaur:** None. **A. Soni:** None. **M. Chakrabarty:** None. **T. Tzvetanov:** None. **S. Ray:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.15

Topic: H.06. Social Cognition

Support: Discovery Grant (Dr. Hayward)
Discovery Grant (Dr. Chapman)
NSERC CGS-M (Helen Ma)

Title: Take a guess: Implicit projection of goals via observed mouse-tracking across social contexts in a dyadic online game

Authors: *H. MA[1], J. K. BERTRAND[2], C. S. CHAPMAN[2], D. A. HAYWARD[1];
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Abstract: Social contexts and goals have been shown to influence basic cognitive processes and related behaviour. For example, when cooperating compared to competing with a partner in a visual search task, participants are slower but more accurate. However, most cognitive research relies on non-dynamic measures of accuracy and speed, wherein complex behaviour is compressed to a single number representing the endpoint of a behaviour. As a result, we understand that social context changes behaviour, but not how it does so. Thus, we sought to investigate whether participant performance changed based on changing goals using a combination of traditional cognitive measures (response time, accuracy), self-report measures (open form reporting of strategy), and data rich dynamic measures (mouse trajectories). Participants (n=48 dyads) played a two-player online card game, where the goal was to collect cards with a certain feature (e.g., triangles), and participant computer mouse movements were seen by both players. The task consisted of six games, three while cooperating and three while competing (e.g., Game mode; counterbalanced block-wise). Each game had eight turns, and points were awarded per turn for two decisions: (i) collecting a card that matched one's goal (ability to achieve personal goal) and (ii) correctly guessing the other player's goal (ability to guess intention), motivating participants to infer the goals of their fellow player. Each turn, one player (e.g. P1) looked at two cards and decided which to place face up. P2 then chose the face-up or face-down card; P1 received the unselected card. The data revealed: (1) Card scores didn't vary across Game Mode, as expected with the experimenter restricted decision space. (2) Guess scores did vary with Game mode, with more correct guesses when cooperating compared to competing - this was most pronounced for participants who competed first. (3) Looking at mouse trajectories, we saw increased durations and mouse distance travelled when competing compared to when cooperating, suggesting that better guess performance when cooperating is not due to explicit communication (i.e., circling desired cards), but instead due to an increased speed and confidence in decisions made. Conversely, poorer guess performance is due to slower movements and uncertainty in decisions made, reflected in increased mouse distance travelled. Overall, these results indicate people move differently depending on social context, and viewing movements of others can help (i.e., cooperate game mode) or hinder (i.e., compete game mode) our ability to successfully draw conclusions about others' goals.

Disclosures: H. Ma: None. **J.K. Bertrand:** None. **C.S. Chapman:** None. **D.A. Hayward:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.16

Topic: H.06. Social Cognition

Title: Characterizing gaze and movement behavior during dynamic virtual reality solo and two-player game play

Authors: *T. SIMMONS[1], J. SNIDER[3], L. CHUKOSKIE[2];
[2]Physical Therapy, Movement, and Rehabil. Sci., [1]Northeastern Univ., Boston, MA; [3]Inst. for Neural Computation, UCSD, La Jolla, CA

Abstract: Social interaction between humans requires a complex exchange of verbal and non-verbal signals. Effectively interpreting and responding to those signals requires accurate visual attendance to relevant stimuli and a corresponding response. For individuals with Autism Spectrum Disorder (ASD), differences in social interaction are part of the diagnostic criteria and contribute to major impacts in daily living. Gaze behavior and manual movements are both important components of social interactions and have also been shown to be individually impacted in autistic individuals; however, it is not completely understood how their interaction affects social interaction, and under what circumstances. Previous studies suggest that a temporally-modulated stimulus could be more difficult to orient to than one that is not temporally-modulated. Our experiment uses a fully immersive virtual reality (VR) video game to examine perception-action coupling in conditions where the stimulus is temporally-modulated and comparatively static. Loom is a 3-dimensional puzzle game where participants will either complete puzzles in a solo or two-player cooperative condition. The game, therefore, creates an opportunity to examine perception-action coupling with respect to temporal modulation in both solo and cooperative game play. The game requires players to recreate a pattern of blocks by catching individual falling blocks and placing them into their stationary positions. Using the HTC Vive Pro Eye VR headset and its built-in eye-tracking, we measured two perception-action coupling sequences. The first sequence starts when the participant visually attends to a falling cube and finishes when the participant successfully catches it (temporally-modulated condition). The second sequence starts when the participant visually attends to the stationary drop position for the caught cube and ends when they successfully place it (static condition). Our analyses characterize differences in gaze and manual action sequence execution between the temporally-modulated and static sequences and also across solo and cooperative conditions. Our preliminary results with non-autistic participants are consistent with prior research indicating fluent perception-action coupling with either static or temporally-modulated stimuli. Solo players were faster than cooperative players in temporally-modulated and static sequences. We imagine significant future implications for this work including an objective multi-modal assessment of social interaction and in the farther future, a move toward engaging and ecologically-valid interventions for motor aspects of social behavior.

Disclosures: **T. Simmons:** None. **J. Snider:** None. **L. Chukoskie:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.17

Topic: H.06. Social Cognition

Support: KAKENNHI 20K21562
JST Moonshot R&D JPMJMS2011
JST CREST

Title: Perception of social dominance hierarchy underlies social valuation

Authors: Z. QIANG, ***M. HARUNO**;
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Abstract: Social dominance hierarchy plays a critical role in human social behavior such as cooperation and aggression. However, it is poorly understood how its perception affects social valuation which is the core of social decision making. Social Dominance Orientation (SDO) is a personality trait which describes one's attitude towards social dominance and hierarchical society: a typical behavior of high SDO individual is to support the dominance and anti-egalitarianism. Here, we aim to clarify the relationship between SDO and social valuation: how valuation of the social context changes depending on their SDO and the relative position of the social partner in the social hierarchy. More specifically, we first collected personality trait scores including SDO from participants, and next asked them to play competitive games against the opponents with a different level of winning rate (i.e.., 75%, 50% and 25%), and confirmed that the participants successfully constructed a social dominance hierarchy. Then, in every trial in the main task, we provided a bonus for the participant and an opponent after a competitive game. We also asked the participants to rate the bonus distribution (which was advantageous, fair, or disadvantageous) by four different levels (i.e., 1 to 4). We analyzed how each participant rates bonus distributions depending on the contents of the bonus, the win or lose in the trials, the relative position of the opponents, and his/her SDO and other personality trait scores. Our results revealed several links between SDO and social valuation. First, participants rating of the bonus distribution has a significant correlation with the reward difference between the self and the opponent ($0.05<P$) and there was a significant interaction between SDO and the bonus difference on rating ($0.001<P$). More importantly, when we regressed the participant's bonus rating by using the bonus difference and the relative position, the beta coefficient for the bonus difference shows a negative correlation with the participant's SDO, suggesting that people with lower SDO disliked the bonus difference more when facing to the he same opponent and the same bonus distribution. In addition, when we considered the relative position of opponents, we found a negative correlation between beta coefficient for the reward difference and SDO became weaker when facing to a superior opponent, although the result did not reach a statistical significance ($P=0.10$). Thus, this study demonstrated that SDO captures individual differences in how the perception of one's social dominance hierarchy and relative positions affects social valuation.

Disclosures: **Z. Qiang:** None. **M. Haruno:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.18

Topic: H.06. Social Cognition

Support: IBS-R015-D1
NRF-2019M3E5D2A01060299
NRF-2019R1A2C1085566

Title: Not the same person I used to know : Social prediction error elicits updates in person representation

Authors: *J. RO[1,2], Y. SEO[1], W. SHIM[3,1];
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Abstract: For successful social interaction, people constantly predict others' actions and intentions based on their current social knowledge. In the predictive coding framework, prediction error (PE)—the difference between the prediction of our neural system and the actual observation— plays a central role in sensory processing. The neural PE signal, as a teaching signal to update the representation in higher brain regions, is believed to underpin surprise-based learning. Despite growing interest in identifying PE in social contexts, how social PE is processed in naturalistic social cognition and how it is linked to surprise-based learning remains unclear. Here we directly measured social PE during a movie with two-person conversations and investigated its relationship with the surprise rating and the evolution of person representations in the brain. We segmented the movie into scenes that contain the alternating character's utterances. After watching each scene, participants were asked to predict the response of the other character in the following scene on a continuous dimension of approaching versus avoiding. Then, after watching the scene they had previously predicted, participants rated the character's actual observed response on the same dimension. We calculated social PEs for each scene by comparing their action predictions with actual action assessments. Another group of participants rated how surprising each moment of the movie was. We found that the social PE was highly correlated with the surprise rating for each moment of the movie, which reflects the predictive process in perceiving social interactions. We further investigated the role of social PE in updating social information by comparing the neural representations of characters before and after experiencing social PE. We extracted the brain activity patterns while a separate group of participants (N=22) watched the same movie in an fMRI scanner and computed the neural pattern dissimilarity between the scenes that preceded (t-1) and followed (t+1) the current scene (t) separately for each character. We found that the neural pattern dissimilarity in the superior

temporal gyrus and the temporoparietal junction was correlated with the social PE measured for the current scene, indicating that, when social PE occurs, updates in the neural representation of a person follow. Taken together, our findings suggest that humans actively infer and learn about others through a predictive process that entails surprise-based learning.

Disclosures: **J. Ro:** None. **Y. Seo:** None. **W. Shim:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.19

Topic: H.06. Social Cognition

Support: EPSRC
Aston University, HLS

Title: "are you looking at me?" a novel joint attention paradigm with a virtual human in vr.

Authors: *C. KELLY[1], U. BERNARDET[1], J. ZUMER[1], T. MEESE[1], K. KESSLER[2];
[1]Aston Univ., Birmingham, United Kingdom; [2]Univ. Col. Dublin, Dublin, Ireland

Abstract: A key to building social relationships is the alignment of mental representations through joint attention; however the details are poorly understood. Successful joint attention aids communication and subsequently builds stronger social relationships. Using virtual reality, we can simulate these social dyads and explore non-verbal behaviours which comprise joint attention. We investigated the role of two such behaviours: eye-contact and collaborative gaze between real and virtual humans (VH) in a series of seven online and one in-person neuro-Virtual Reality (VR) experiments.Our task required participants to work with a VH to complete two puzzles. On each trial, a puzzle piece, hidden from the participant, was presented to the VH and the participant observed the VH's gaze behaviour derived from human recordings. In a 2x2 design the conditions were, *Collaboration:* where the VH's behaviour either directed the participants' attention to which of the puzzle boards the piece belonged or was uninformative and *Gaze Type:* where the VH either established eye-contact or did not. With this behaviour as a prompt, participants responded as quickly and accurately as possible by indicating to which board they felt they were being directed. Online Experiments 1-5 manipulated a variety of parameters, including: VH gaze speed, VH construction (with or without body), number of trials (80 vs. 160) and gaze control (recorded human vs. computer generated). Robust main effects of Collaboration were observed, with response times significantly faster and generally more accurate for collaborative trials; however, little to no effect was found from the other parameters. However, Experiments 6 and 7 optimally matched the number and timings of gaze shifts between conditions and indeed revealed a significant main effect of Gaze Type, with faster response times when the VH engaged in eye-contact. The final Experiment 8 was run in-person, using a virtual reality head-mounted display, eye-tracking and EEG to investigate the neural

underpinnings of responding to joint attention with a VH. Analysis of these results explores the role of alpha and theta frequencies within the 'social network' i.e. the temporo-parietal junction and the medial frontal lobe. Here we present our findings from these eight experiments and the insight they provide to improve our understanding of joint attention within the human brain. The integration of VR, eye-tracking and EEG, also demonstrates the power of multimodal monitoring in elucidating complex cognitive behaviours.

Disclosures: C. Kelly: None. **U. Bernardet:** None. **J. Zumer:** None. **T. Meese:** None. **K. Kessler:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.20

Topic: H.06. Social Cognition

Support: JSPS KAKENHI 22H04855

Title: The neural correlate of self-evaluation and their correlations with social acceptance and rejection

Authors: *Y. DING[1], K. OBA[1], R. ISHIBASHI[1], S. SUZUKI[2], M. SUGIURA[1];
[1]Inst. of Development, Aging and Cancer, Tohoku Univ., Sendai, Japan; [2]The Univ. of Melbourne, Melbourne, Australia

Abstract: Negative self-evaluation (i.e., people tending to think of themselves as worse than others) has been associated with social acceptance and rejection. This association is suspected to stem from a psychological process as the pursuit of humility to gain social acceptance and avoid social rejection. Although positive bias is frequently identified in self-evaluation (i.e., people think they are better than others), recent research has reported negative bias in some contexts. It has been shown that negative self-evaluation in the context of competence may be robust in general. However, it is unclear how social acceptance and rejection are associated with the neural mechanism of self-evaluation. We hypothesize the psychological process involved in gaining social acceptance and avoiding rejection is possibly associated with brain areas for inhibiting undesirable self-relevant information. To test this hypothesis, we recruited 45 participants (20 ~ 30 years old) who were instructed to rate themselves and a celebrity during an fMRI session using personality adjectives that were controlled for two basic social values (morality and competence) and valences (positive and negative). To measure individual differences in social acceptance and rejection, participants completed the sense-of-acceptance and rejection scale, which measured the feeling of being accepted and rejected by others. The behavioral results showed a negative self-evaluation in the negative competence condition, i.e., participants thought they were more incompetent than others. However, the difference between self- and other-evaluation scores was not significantly associated with social acceptance or rejection in all four

conditions. The neural analysis revealed a significant positive correlation between sense-of-rejection and activation in the inferior frontal gyrus and a negative correlation between sense-of-acceptance and activation in the ventral medial prefrontal cortex during the self-referential processing ([self > other]) of negative competence adjectives ($p < 0.05$ FWE-corrected cluster-wise). These results support our hypothesis that inhibition is associated with the psychological process of gaining social acceptance during self-referential processing. They suggest that when solving the situation facing negative competence words, those who feel less social acceptance might inhibit undesirable information, while those who feel more social rejection were speculated to regulate their emotions.

Disclosures: Y. Ding: None. **K. Oba:** None. **R. Ishibashi:** None. **S. Suzuki:** None. **M. Sugiura:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.21

Topic: H.06. Social Cognition

Support: IBS R015-D1
NRF-2019M3E5D2A01060299
NRF-2019R1A2C1085566

Title: Tracking social relationships and personality traits in the default mode network

Authors: *D. KWON[1,3], K. HEO[1,3], W. SHIM[2,3,1];
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Abstract: Understanding the personalities of individuals and their interpersonal relationships plays a crucial role in social interaction in the real world, such as knowing with whom to form a social group. To understand them, humans need to acquire the structured knowledge of relational social information. Previous studies have shown that the structures of knowledge about spatial, semantic, and social space are represented in the brain. However, it remains elusive how humans update the dynamic changes in the structured knowledge of social information over time. In this study, we investigated and modeled how neural representations of individuals and their social relationships are constructed and updated using behavioral and fMRI data. During an fMRI scan, subjects watched a movie with rich and dynamically varying social interactions and later rated the personalities of each fictional character and pairwise directional social relationships between characters in multiple dimensions (Q&A task). First, we built models to track social information that unfolds over time in the movie. The co-occurrence of characters and the sentiment scores of their interactions from a Korean sentiment word dictionary were used for a model to track

interpersonal relationships between characters, and the characters' action and emotion extracted from movie annotations were used for a model to track personality traits of each character. The model outputs were robustly correlated with subjects' behavioral ratings on characters' relationships and personalities, respectively. Then we performed a representational similarity analysis on the Q&A task data, which showed that the knowledges of characters' relationships and individual personalities were represented in the subregions of the default mode network (DMN) and hippocampus, respectively. Furthermore, the neural response pattern in the DMN as well as the functional connectivity between the sensory and DMN, and the sensory and dorsal attention network (DAN) represents the social relationship information between the characters, which constantly changes over time during movie watching. These results suggest that the structured knowledge of the social interaction, which comprises multifaceted information on individuals and their relationships, is dynamically updated through the interaction between multiple functional brain networks centered on the DMN.

Disclosures: D. Kwon: None. **K. Heo:** None. **W. Shim:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.22

Topic: H.06. Social Cognition

Title: Lonely brains at rest: A population neuroscience approach to understanding resting-state functional connectivity in lonely individuals

Authors: K. MANOLI, ***R. RAMSEY**;
Macquarie Univ., Macquarie Univ., Sydney, Australia

Abstract: Humans are inherently social beings whose lives are centered around interactions with others. Because of that, loneliness - a discrepancy between the perceived and desired quality of social connections - has been associated with a range of negative health outcomes, such as higher morbidity and mortality. Although loneliness is having an increasing influence on many aspects of everyday life, the neurobiological basis of loneliness is far from clear. In light of this, the current project systematically examined how resting-state functional connectivity (RSFC) patterns vary as a function of loneliness using a large secondary dataset (N>35k from the UK Biobank). Approximately 20% of the UK Biobank sample reported being currently lonely when given yes-no response options. In two pre-registered analyses, we used a Bayesian estimation analytical framework to assess how RSFC varies across large-scale brain networks as a function of self-reported loneliness. We performed two separate analyses to build replication into our analytical approach. The first analysis used a subsample of participants, before the second, more confirmatory analysis was run on a new sample of participants. Across both analyses the results showed that loneliness was associated with small increases and decreases in RSFC between a widespread and distributed set of brain networks, including coupling between visual, affective,

attentional, and default-mode resting-state networks. The magnitude of these effects was relatively small and in the order of a 0.1 change in the correlation coefficient between brain networks. However, the effects were widespread and spanned approximately 20 different connections between brain circuits that have been previously associated with a wide range of sensory-motor, cognitive and affective functions. As such, the results support the inference that loneliness is underpinned by widespread reorganisation across many brain circuits, which include a range of functions, rather than a narrow set of brain systems and functions. In the short term, the results provide novel insight into the nature of functional re-organisation that occurs between major brain networks when individuals experience loneliness. In the longer term, by developing a richer mechanistic understanding of loneliness at a population neuroscience level, such findings can also inform interventions that aim to alleviate the persistent consequences of loneliness.

Disclosures: K. Manoli: None. **R. Ramsey:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.23

Topic: H.06. Social Cognition

Support: UC Berkeley internal funds

Title: Simultaneous mapping of five types of social information across human cerebral cortex

Authors: *C. TSENG, S. SLIVKOFF, J. L. GALLANT;
Univ. of California Berkeley, Berkeley, CA

Abstract: Successful social interactions require using knowledge about other individuals, groups, and their relationships. Previous neuroimaging studies identified regions of the human cerebral cortex that may represent each of these types of social information. However, because it is difficult to compare statistically significant results across studies, it is unclear whether each region represents only one type of social information, or whether each region represents multiple types of social information. Here we simultaneously map the cortical representation of individual traits, interpersonal relationships, social groups, social networks, and subjective judgements. To do this, we used functional MRI to record blood-oxygen-level-dependent (BOLD) responses from six subjects while they answered questions about these five types of social information for a fictional social network. The questions were presented one word at a time using rapid serial visual presentation, and subjects responded to each question by rating 1 (low/disagree) to 5 (high/agree). Each subject answered 1120 unique questions spread across eight ~10-minute scanning runs. To identify voxels that represent each type of social information, we fit a linearized encoding model to every voxel in every subject. The linearized encoding model consisted of five feature spaces that captured the five types of social information, and nine

feature spaces that captured other information in the experiment. To avoid overfitting, the model was trained on seven runs of BOLD data, and the estimated model weights were used to predict the eighth test run of BOLD data. This was done for every split of seven training runs and one test run. Model prediction accuracy was computed as the coefficient of determination (R^2) between the model-predicted BOLD responses and the actual BOLD responses for the test run. In all subjects, we find that voxels in the left temporal parietal junction (TPJ), left precuneus, and left superior frontal gyrus (SFG) represent individual traits. We find that a separate set of voxels in bilateral TPJ, bilateral precuneus, bilateral SFG, and bilateral inferior frontal gyrus represent both individual traits and interpersonal relationships. Finally, we find that voxels in the left medial prefrontal cortex represent subjective judgements. In contrast, we find that the representations of social networks and social groups are highly variable and inconsistent across subjects. These results suggest that different types of social information have overlapping representations in the brain, and they highlight the need for experiments that probe many types of social information simultaneously.

Disclosures: C. Tseng: None. **S. Slivkoff:** None. **J.L. Gallant:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.24

Topic: H.06. Social Cognition

Support: NIH Grant R25 NS 80686

Title: The Role of Conversation in Shared Moral Judgment: A Neuropsychological Perspective of Shared Reality Theory and the Alignment of Moral Evaluation

Authors: *S. RIVERA[1], D. REINERO[2], P. PARNAMETS[3], M. ROSSIGNAC-MILON[4], J. J. VAN BAVEL[5];
[1]Hunter Col., New York, NY; [2]Princeton Univ., Princeton, NJ; [3]Karolinska Inst., Solna, Sweden; [4]Columbia Univ., New York, NY; [5]New York Univ., New York, NY

Abstract: Conversation is one way we can express our inner states to one another. Language allows us to share our personal perceptions of the world with those around us, and at times share the same inner states (e.g., beliefs, feelings, etc.) as others, building a sense of a shared reality. Yet our subjective realities are not always aligned. When it comes to questions of right or wrong, people may hold different moral values or political views that prevent their realities from aligning. In this research, we explore how linguistic aspects of conversation can elicit shared realities of moral scenarios. Specifically, we recruit strangers to have conversations over Zoom video calls and examine how these conversations shape their own private moral views and their sense of shared reality. We explore this through speech dynamics, vocal synchronicity, language content, perceived interpersonal coherence, evaluation change, and shared reality theory. We will

further interpret these results in line with the emerging research in both social psychology and neuroscience. Implications for future research and societal application are discussed.

Disclosures: **S. Rivera:** None. **D. Reinero:** None. **P. Parnamets:** None. **M. Rossignac-Milon:** None. **J.J. Van Bavel:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.25

Topic: H.06. Social Cognition

Support: iTHRIV Scholars Program
NCATS of the NIH UL1TR003015
NCATS of the NIH KL2TR003016

Title: Dance on the Brain: Examining the ability for dance to enhance social skills through modifications in behavioral and neural synchrony

Authors: *A. J. SMITH[1], N. TASNIM[2], D. GYAMFI[3], D. F. ENGLISH[1], J. C. BASSO[4,1,5]; [1]Neurosci., [2]Translational Biol., [3]Human Nutrition, Foods, and Exercise, [4]Human Nutrition, Foods and Exercise, [5]Ctr. for Transformative Res. on Hlth. Behaviors, Virginia Tech., Blacksburg, VA

Abstract: Interpersonal coordination, which includes both mimicry and synchrony, has been evolutionarily selected for its important role in social bonding. Inter-brain synchrony or the coordinated brain activity between individuals has been proposed as a neural mechanism underlying such social interactions. Dance enhances interpersonal coordination, and we have recently hypothesized that dance can be used as a tool to enhance inter-brain synchrony (i.e., The Synchronicity Hypothesis of Dance). In this randomized control trial, we examined the hypothesis that dance enhances social skills/cognition and behavioral and neural synchrony in healthy adults (n=16; age range 18-45; 87.5% female). Neurotypical participants were assigned to participate in either 4-weeks of improvisational dance training (n=7) or dance movie watching (n=9) (twice per week for 90 minutes each session). Using self-reported questionnaires and neurocognitive tasks, we assessed mood state, quality of life, mindfulness, social skills, and social cognition before and after the intervention. Additionally, electroencephalography (EEG) hyperscanning was conducted (both before and after the intervention) between teacher and student, using BrainVision's LiveAmp 32, during a variety of 5-minute interactive experiences including: 1) eye gaze, 2) verbal conversation, 3) movement mirroring, and 4) movement conversation. Body physiology was also recorded during these experiences using Emotibit, a wearable sensor that captures over 16 biosignals including photoplethysmography and electrodermal activity. Motion tracking was captured during all experiences using DeepLabCut. All data were synchronized using an arduino-based platform. We will analyze these

simultaneous recordings at the level of body, brain, and behavior and correlate these data with the longitudinal psychological outcomes. Findings from this research will add to our understanding of how the brain supports social interactions, and specifically the utility of dance as a method to support social skills and underlying neurophysiology. Hypothesized results of dance-induced modifications to neural oscillations would suggest a broad utility of dance as a clinical modality in conditions with oscillatory activity impairments such as Autism Spectrum Disorder.

Disclosures: A.J. Smith: None. **N. Tasnim:** None. **D. Gyamfi:** None. **D.F. English:** None. **J.C. Basso:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.26

Topic: H.06. Social Cognition

Support: The iTHRIV Scholars Program is supported in part by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Numbers UL1TR003015 and KL2TR003016

Title: Flow state in dance: an exploratory analysis of psychological state and electroencephalography hyperscanning with members of Memphis Jookin': The Show

Authors: *N. TASNIM, A. SMITH, D. GYAMFI, D. F. ENGLISH, J. C. BASSO; Virginia Tech., Blacksburg, VA

Abstract: Flow is the psychological stage of being completely immersed in the task at hand. Previous work has shown that flow is associated with positive effects such as improved focus and performance, enhanced happiness, stronger sense of presence, and increased interoception. Most of this work has focused on sport, art, science, and daily tasks, but little has been done to study flow in the context of dance. We used a combination of qualitative and quantitative measures to examine trait and state elements of flow during performance of Memphis Jookin' by professional dancers, including Charles "Lil Buck" Riley (N = 6, age: 19 - 33, 5 male and 1 female, 10+ years of dance training). Memphis Jookin' is a dance style that originated in Memphis, Tennessee in the 1980's and consists of elegant steps, slides, glides, toe spins, and footwork. Participants were asked to describe their experience with flow while dancing in general and during a performance at Virginia Tech through the Dispositional Short Flow Scale (Median = 4.94; Range: 4.33 - 5) and Short Flow Scale (Median = 4.89; Range: 4.67 - 5), respectively. Dancers reported high levels of flow and its manifestation did not differ between performance and general practice of dance (paired Wilcoxon test: p = 1). We recently developed and validated the Multidimensional Impacts of Movement Scale (Lynn & Basso, In Review), which we utilized to ask dancers how the movement associated with their performance at

Virginia Tech made them feel physically and psychologically through subscales concerning body, contentment, energy, intuition, and mind. Dancers (Mean = 215.5, Range: 194-225) reported relatively higher levels (Mann-Whitney U Tests) of impact relative to participants whose primary movements were running (N = 28, Mean = 165, Range: 123 - 223, $p < 0.05$), weightlifting (N = 38, Mean = 181.4, Range: 100 - 225, $p < 0.05$), and yoga (N = 37, Mean = 181.8, Range: 132 - 225, $p < 0.05$). Two dancers wore electroencephalography caps (Brain Products GmbH, Germany) and were hyperscanned during several interactive movement experiences, namely choreographed movement, improvisational mirroring, and dance battling. We will compare alpha, beta, and theta bands between participants and assess intra- and inter-brain synchrony. We expect our results to support our hypothesis that dance enhances neural efficiency by promoting synchrony (Basso, Satyal, & Rugh, 2021). Preliminary findings show an association between flow and heightened levels of interoception. Our continued analysis of the dancers' neurophysiological data will help further understand the manifestation of flow and the possible beneficial impacts of dance on socioemotional health.

Disclosures: **N. Tasnim:** None. **A. Smith:** None. **D. Gyamfi:** None. **D.F. English:** None. **J.C. Basso:** None.

Poster

738. Emotion and Behavior in Human Social Interaction

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 738.27

Topic: H.05. Working Memory

Support: Zuckerman STEM leadership program

Title: Establishing the functional independence between face perception and face memory

Authors: *J. KADLEC[1], C. WALSH[2], J. RISSMAN[2], M. RAMOT[1];
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Abstract: Our ability to recognize faces is fundamental to our daily functioning and is comprised of the interaction of many different processes. In particular, there is a long-debated issue of the relationship between face perception and face memory, and whether the two are intrinsically linked and inseparable, or whether they are distinct underlying processes which can be teased apart. In most experimental paradigms, these two processes are coupled. Nevertheless, a large body of evidence suggests that they might be independent. The divergence of face memory and face perception has been noted in the acquired prosopagnosia literature, autism, and, most importantly, in development. However, direct evidence that face memory and perception are independent has been sparse. In this study, we address the challenge of disentangling face memory and perception through the design of a novel paradigm: the Face Memory and Perception (FMP) task. The FMP parametrically modulates perceptual difficulty

using face morphs of real face images while independently modulating the demands on short-term memory. This design allows us to directly test the dissociation between particular aspects of these two processes. Our behavioural data, collected on a large sample (N=224), shows that while there are robust main effects for both perception and memory difficulty levels, there is no interaction between them. The additive nature of these effects indicates that we successfully manipulated perceptual difficulty independently from memory load. Our data thus argue for the functional independence of face memory and face perception. These findings set the stage for fMRI investigations of the putatively distinct neural correlates that underlie these processes.

Disclosures: **J. Kadlec:** None. **C. Walsh:** None. **J. Rissman:** None. **M. Ramot:** None.

Poster

739. Emotion and Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 739.01

Topic: H.06. Social Cognition

Support: R01 MH071916
R01 DA043535

Title: Unsupervised quantification of undirected human behavior for bipolar disorder analysis

Authors: *Z. ZHANG[1], H. ROSBERG[5], W. PERRY[2], J. YOUNG[2], A. MINASSIAN[2], G. MISHNE[3], M. C. AOI[4];
[1]Computer Sci., [2]Psychiatry, [3]Data Sci., [4]Neurobiology, Data Sci., Univ. of California San Diego, San Diego, CA; [5]San Diego State Univ., San Diego, CA

Abstract: The organization of undirected behavior reflects motor, cognitive, and motivational processes and may be utilized as a window for understanding and diagnosing psychiatric conditions such as bipolar disorder (BD). Video recordings of human behaviors are typically manually annotated by a human observer, which can be time-consuming, biased, and unstandardized (Torres et al, 2016). Automated, computer vision-based methods of behavioral annotation can help mitigate some of these shortcomings. We demonstrate a semi-supervised quantification of undirected human behavior to differentiate patients with BD and healthy control participants (CP) using approaches from machine learning, computer vision, and topological data analysis. We collected videos of BD (n=12) and CP (n=12) freely moving in an unexplored room using a top-down camera and each video was manually annotated into 6 behavior categories, e.g. walking. We tracked the spatiotemporal postures of the subjects in each video using DeepLabCut (Mathis et al, 2018) with 20 markers placed on the skeleton of human subjects, e.g., shoulders, elbows, and legs. Then, we used the VAME latent variable model (Luxem et al, 2021) coupled with DeepLabCut to encode the human pose sequences into latent vectors. The latent vectors of the entire dataset were clustered into 30 fine-resolution behavioral motifs, such as “standing then turning”, and “standing still”. To inspect the transitions between motifs, we constructed a

bidirectional graph for every video using a transition matrix between motifs. Using topology-based condensation algorithms (Sharir, 1981), we combined similar motif nodes into super-nodes representing behavior categories, e.g. standing. The motif distributions between BD and CP are significantly different (asymptotic and bootstrap multinomial test, p-value: 0.04, 0.02). However, such significance was not found in the manually annotated categories. The transition matrix of the BD group reflected more stereotypical motifs with smaller transition probabilities. In contrast, there was less variety of motifs in CP, and higher transition probabilities from one motif to another. Our preliminary unsupervised analysis identifies fine-resolution behavioral motifs that can distinguish BD and CP from undirected human behavior. With further analysis, we can quantify higher-order behavioral characteristic features of BD for clinical assessment.

Disclosures: Z. Zhang: None. **H. Rosberg:** None. **W. Perry:** None. **J. Young:** None. **A. Minassian:** None. **G. Mishne:** None. **M.C. Aoi:** None.

Poster

739. Emotion and Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 739.02

Topic: H.06. Social Cognition

Title: Analysis of intergroup and interpersonal mental image differences in social reverse correlation studies without using external raters

Authors: *Y. WEI[1], S. WANG[2], L. ZHANG[3], E. P. LEMAY, Jr.[1];
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Abstract: Reverse correlation (RC) is a data-driven technique that has been applied in social psychology to visualize mental representations based on judgments of randomly varying stimuli (typically faces). In a typical RC experiment, participants are presented with a pair of facial stimuli superimposed by random noises and are asked to choose the one that most resembles a certain mental representation (e.g., a trustworthy face). Mental representations are visualized by classification images (CI) that are generated from participants' accumulated choices.
Recently, there has been growing interests in using RC to study how mental representations are modulated by social and clinical factors like personality traits or psychiatric traits. These studies conventionally adopted a two-phase procedure. In phase 1, participants perform a RC experiment. In phase 2, an independent group of raters are asked to rate the CIs generated in Phase 1. The correlation between the CI ratings and traits are then analyzed. Previous research suggested that this procedure requires potentially large amounts of ratings of individual CIs to avoid an inflation of Type-I error.
In this study, we proposed three alternative methods to evaluate the correlation between mental images and traits without relying on phase-2 ratings. These methods assessed trait-CI correlations at the level of choices, group CIs, and individual CIs, respectively. The first method

analyzed the independence of traits and choice compliance (i.e., the degree to which a participant's choice aligns with the majority of participants). Less compliance indicates more deviance of an individual's CI from the group. Statistical significance can be obtained by the Cochran-Mantel-Haenszel Chi-Squared test. The second method used a permutation test to analyze the differences between sub-group CIs of participants with different trait levels. We repeatedly shuffled the trait levels among participants and computed the differences among sub-group CIs to obtain the null distribution. The real sub-group CI differences were then tested against the null distribution. This method was carried out at the pixel level and could serve as a tool for identifying diagnostic facial regions. The third method aimed at assigning an indigenous score to the individual CI in place of the phase-2 ratings. Specifically, we calculated the inner product between the individual CIs and the group CI by comparing pixel-by-pixel luminance. This score measures the relative bias each individual has in the mental representation relative to the group. All three methods were validated using synthetic data and will be further evaluated using data from published studies.

Disclosures: Y. Wei: None. **S. Wang:** None. **L. Zhang:** None. **E.P. Lemay:** None.

Poster

739. Emotion and Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 739.03

Title: WITHDRAWN

Poster

739. Emotion and Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 739.04

Topic: H.06. Social Cognition

Support: R01AG069976

Title: Parameterizing aperiodic and oscillatory electrophysiological activity in subcortical nuclei of patients with Parkinson's Disease

Authors: *A. VALENTINE, S. QASIM, A. LUND, B. KOPELL, A. CHARNEY, I. SAEZ; Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Electrophysiological neural activity follows a 1/f power law wherein power exponentially decreases with increasing frequency. The slope of this relationship is called the

power-law exponent and reflects scale-free aperiodic activity across frequencies. In turn, neuronal oscillations reflect periodic activity, and appear as increases in power across specific frequency-bands over aperiodic activity. The Fitting Oscillations & One Over F (FOOOF) package is an established tool to parameterize oscillations and the power-law exponent. Implementations with surface EEG data have found that oscillations are implicated in cognitive, motor, and sensory processes and may reflect brain pathology; for example, beta (13-30 Hz) power increases in Parkinson's Disease (PD) patients. However, the role of periodic/aperiodic components in subcortical nuclei activity has not been systematically decomposed. Here, we carried out microelectrode (MER) recordings from awake patients (N = 79) during deep brain stimulation (DBS) surgery for treatment of PD. We analyzed electrophysiological activity (local field potentials, LFPs) recorded from MERs during functional mapping in either the subthalamic nucleus (STN; N = 56) or globus pallidus internal (GPi; N = 23). LFPs were parameterized with FOOOF to extract aperiodic/periodic components. Recordings with a duration below 5s, model fit of $R^2 < 0.8$, or an aperiodic slope < 0 were excluded from analysis. A total of 213 recordings were then analyzed, with a mean of 2.7 recordings per patient. For each recording, we examined oscillatory peaks in the theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and low gamma (30-50 Hz) frequency ranges. We found that beta peaks were predominant in both the STN and GPi, such that ~95% of patients expressed a beta oscillation. In the STN, beta peaks had significantly higher power than theta, alpha, and low gamma peaks (p's < 0.01, t-test). Similarly, the GPi showed higher beta peak power compared to theta and alpha (p's < 0.001, t-test). Yet, the GPi had more powerful low gamma peaks than the STN ($p < 0.001$, t-test), as well as its low gamma peaks had higher power than alpha and theta peaks (p's < 0.001, t-test). The average slope of aperiodic activity was 1.16 (SD = 0.57) with no significant difference between the STN and GPi ($p = 0.7$, t-test). These findings demonstrate that basal ganglia structures express similar scale-free aperiodic activity but varied oscillatory activity. Future work should aim to understand how aperiodic/periodic components differentially contribute to PD pathology, thus identifying biomarkers of disease and DBS treatment outcomes.

Disclosures: **A. Valentine:** None. **S. Qasim:** None. **A. Lund:** None. **B. Kopell:** None. **A. Charney:** None. **I. Saez:** None.

Poster

739. Emotion and Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 739.05

Topic: H.06. Social Cognition

Support: NIH Grant R01DA043695

Title: A Computational Account for Momentary Craving in Eating and Substance Use Disorders

Authors: *K. R. KULKARNI, L. BERNER, V. G. FIORE, X. GU;
Ctr. for Computat. Psychiatry, Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: *Background:* Craving is a core feature and a key target of investigation in understanding compulsion-related disorders such as drug addiction and eating disorders. However, to date, the computational mechanisms underlying craving remain largely unknown. In this study, we developed a novel computational approach to test the hypothesis that momentary craving across addictive disorders arises from discrepancies between expected and received rewards, i.e., stimulus-related prediction error (PE).
Methods: We recruited heavy alcohol and cannabis users, and binge-eaters (n=40 for each group) through a web-based research platform (Prolific). Participants completed a modified two-armed bandit task with either alcohol, cannabis, or food rewards, and intermittent self-reports of craving. Four candidate temporal difference reinforcement learning (TDRL) models were utilized to track values, and prediction error signals were then used to generate predictive models of momentary craving.
Results: Across all groups, the standard TDRL model with a static learning rate was overall the best fit for participant choices (DIC_{best} ~ 96.6; DIC_{alt} ~ 98-108). There were significant differences in parameter estimates for learning rates between the two blocks. Importantly, we found that the best performing craving model (DIC_{best} ~ 65; DIC_{alt} ~ 70-175) included both tracked choice values and PEs, and also outperformed the alternative model incorporating only cue-induced effects. PE was found to track positively with craving, such that increased PE predicted higher craving.
Conclusions: Our results provide the empirical evidence supporting a computational hypothesis that momentary craving evoked during a decision-making task is best accounted for by a domain-general mental model that computes the deviations of outcomes from one's expectations about addictive rewards. The computational model proposed here thus provides a concrete, mechanistic link between subjective craving state and addictive decision-making.

Disclosures: K.R. Kulkarni: None. **L. Berner:** None. **V.G. Fiore:** None. **X. Gu:** None.

Poster

739. Emotion and Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 739.06

Topic: H.06. Social Cognition

Title: The neural basis of representation learning in the human prefrontal cortex

Authors: *C. MAHER, X. GU, A. RADULESCU, I. SAEZ;
Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Much of the human brain's ability to support flexible behavior depends on representation learning: the process of mapping high-dimensional observations to states to achieve a goal. For example, when deciding what to order on a menu, each item can be classified along multiple dimensions (e.g., size, price, flavor, spiciness), but only some predict whether we will enjoy the meal. Efficient representation learning involves selective attention for relevant

dimensions, which allows us to use limited experience to generalize behavior to novel contexts. For instance, we may only attend to flavor and spiciness when ordering from a different menu. Previous work has primarily used fMRI to study the role of different prefrontal regions in human representation learning (Niv et al., 2015; Leong & Radulescu et al., 2017; Niv 2019). However, how activity in these discrete regions is integrated to support the learning and maintenance of state representations remains an open question. To address it, we recorded local field potentials (LFP) using stereotactic EEG (sEEG) electrodes implanted in prefrontal and hippocampal regions of neurosurgical patients (n=3) while they played an adapted multidimensional decision-making task ('Gem Hunters'). This approach provides high temporal and spatial resolution previously unavailable through human neuroimaging methods. In the 'Gem Hunters' task, participants choose between 3 'gem' options that vary in shape and color. Within each block, one target feature (e.g., red) within the relevant dimension (e.g., color) predicts reward with 80% probability, while all other features predict reward with 20% probability. Participants can maximize reward by selectively attending to the relevant dimension and choosing the option that contains the target feature. Replicating previous findings by Saez et al. (2018), we found that transient high-frequency activity (HFA, 70-200 Hz) in the orbitofrontal cortex encoded reward-outcome information ($p < 0.05$ across overlapping choice and outcome epochs, n=2). Additionally, we found that transient HFA and low-frequency activity in the theta-alpha bands (8-13 Hz) in orbitofrontal and lateral prefrontal cortices was related to selective attention within relevant dimensions ($p < 0.05$ across overlapping choice and outcome epochs). Further, selective attention within relevant dimensions biased reward-outcome dependent HFA ($p < 0.05$ across post-outcome epoch, n=1). Together, these results provide evidence for a role of the human orbital and lateral prefrontal cortex in deploying selective attention in service of representation learning.

Disclosures: C. Maher: None. **X. Gu:** None. **A. Radulescu:** None. **I. Saez:** None.

Poster

739. Emotion and Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 739.07

Topic: H.06. Social Cognition

Support: NIMH Grant F32MH108311
Hilda and Preston Davis Foundation

Title: Emotion regulation in Bulimia Nervosa: a potential central role for the Inferior Parietal Cortex

Authors: *C. SUN[1], A. SIMMONS[3], T. VIRANDA[2], J. CHEN[4], A. KRUEGER[3], W. H. KAYE[3], L. A. BERNER[2];
[1]Neurosci., [2]Psychiatry, Icahn Sch. of Med. At Mount Sinai, New York, NY; [3]Psychiatry, UCSD, San Diego, CA; [4]Psychology, Drexel Univ., Philadelphia, PA

Abstract: Bulimia nervosa (BN) is characterized by uncontrolled episodes of binge eating and purging. These defining behaviors are associated with self-reported difficulties with regulating emotions. However, the underlying neural mechanisms of this emotion dysregulation have not yet been established.
In the current study, 29 women with BN and 29 matched healthy controls (HC) were scanned using functional magnetic resonance imaging during an emotion regulation task and at rest. During the task, participants were instructed to down regulate or maintain their emotions in response to a sequence of negatively valanced or neutral images. The same subjects were told to keep focus on a fixation cross for an eyes-open resting-state scan.
Task-based BOLD signals for each group were compared for two main contrasts: emotion regulation (Decrease Negative - Maintain Neutral) and emotion reactivity (Maintain Negative - Maintain Neutral). We applied a network analysis approach known as Group Iterative Multiple Model Estimation (GIMME) to compare groups' resting-state connectivity within an emotional regulation network.
During the task, participants with BN showed reduced activation as compared to HC in the left inferior parietal cortex when down regulating in response to negative affect (voxelwise $p < 0.001$, clusterwise alpha = 0.05). Groups did not differ on emotion reactivity. At rest, the BN group had fewer unique connections within the emotion regulation network as compared to HC. During attempted emotion regulation, women with BN showed deficient activation in a region critical for managing multiple mental states, the L PFC, as compared to controls when decreasing the intensity of their negative affect. At rest, women with BN showed fewer connections to this same region. Similar results have been found in other clinical populations with emotion regulation disturbances. The results suggest dysfunction and dysconnectivity in the emotion regulation network that may be useful targets for BN treatment.

Disclosures: C. Sun: None. **A. Simmons:** None. **T. Viranda:** None. **J. Chen:** None. **A. Krueger:** None. **W.H. Kaye:** None. **L.A. Berner:** None.

Poster

739. Emotion and Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 739.08

Topic: H.06. Social Cognition

Support: 1 R01 MH124763
NSF GRFP

Title: Investigating the neurophysiological basis of subjective wellbeing in humans using intracranial electroencephalography

Authors: *A. FINK[1], J. OVERTON[2], L. NUNEZ[2], X. GU[3], I. SAEZ[2];
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[2]Nash Family Dept. of Neurosci., [3]Ctr. for Computat. Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Depression is a debilitating psychiatric disease that is highly prevalent but remains poorly understood. Two hallmark symptoms of depression are chronic depressed mood and altered reward processing, which arise from dysfunction in prefrontal and limbic brain structures. Though mood and reward processing have been studied independently, there has been limited work investigating the relationship between mood and reward processing in humans with depression and how that relationship is represented in neural activity. Providing a mechanistic explanation for the link between altered mood and reward computations in depression is crucial for understanding its pathophysiology. We investigated the impact of reward signals on mood in patients with depression by adapting a decision-making paradigm from computational psychiatry and recording intracranial EEGs in humans with intractable epilepsy. Importantly, these patients suffer from a high (~40%) comorbidity rate with depression, and therefore provide a unique opportunity to probe mood and reward computations across depression states while simultaneously recording neurophysiology data from limbic brain structures rarely available in humans. Patients played a monetary gambling task where they chose between a safe bet or risky gamble that had a 50% probability of resulting in a better or worse outcome. After each trial, patients were shown both how much money that earned, and how much they would have earned had they chosen the alternative option. This provided two important quantitative metrics for reward computations: reward prediction errors (expected outcome - actual outcome) and counterfactual prediction errors (regret or relief from the difference in actual reward - maximum potential reward). Patients also numerically rated their mood state throughout the game, allowing for an explicit quantitative estimation of their momentary subjective well-being. Using computational modeling, we related self-assessed mood states with recent reward outcomes. We hypothesized that patients with comorbid depression would have altered emotional responses to and neural representations of reward computations. We show that our computational model successfully captured the emotional impact of reward choices and outcomes. Building on earlier results that showed that regret signals are encoded in high frequency activity in the orbitofrontal cortex, we examined the neural representation of regret signals. These data provide new insights into the neural correlates of disrupted representations of reward value through the novel combination of intracranial recordings and computational modeling of reward and mood.

Disclosures: A. Fink: None. **J. Overton:** None. **L. Nunez:** None. **X. Gu:** None. **I. Saez:** None.

Poster

739. Emotion and Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 739.09

Topic: H.06. Social Cognition

Support: KAKENHI 18H03612

Title: Functional connectivity of human risk decisions: Cognitive control and systematic deviation from risk neutrality

Authors: *T. ASAMIZUYA[1], J. KATO[2], H. TAKESUE[4], S. OTA[5], Y. KUNIYOSHI[3]; [2]Grad. Schools of Law and Politics, [1]Univ. of Tokyo, Bunkyo, Tokyo, Japan; [3]Grad. schoold of information science and technology,Department of Mechano Inf, Univ. of Tokyo, Tokyo, Japan; [4]Fac. of Law, Tokyo Metropolitan Univ., Hachioji, Tokyo, Japan; [5]Sch. of Law, Meiji Univ., Chiyoda, Tokyo, Japan

Abstract: Human rational decision-making is often considered based on an objective evaluation of probabilities and outcomes. Prospect theory challenges this presumption and illuminates the systematic deviation of human decisions, i.e., risk aversions and risk-seeking, respectively when outcomes are framed as gain and loss. The psychological principles have attracted much attention from cognitive scientists, but the underlying brain mechanism is still unknown. This fMRI study estimated the value functions of risk decisions when subjects drew the lotteries both in the gain and loss framings and examined the functional connectivity across activated regions. Activation was found when making risk decisions in the BA 10, BA 32, the bilateral, ventral anterior insula, and the precuneus. When decisions were made along with prospect theory, i.e., risk aversion to gain outcomes and risk-seeking of loss outcomes, the functional connectivity was strengthened from BA32 to BA10. The result implies that systematical deviation from risk-neutral choices results from the connectivity of the regions implicated with cognitive control. Moreover, stronger connectivity from BA10 to BA32 was specific to risk-seeking in expectation of losses, but the bilateral connectivity between the right anterior insula and BA32 was strengthened only by risk aversion expecting gains. Connectivity between the precuneus and the left anterior insula was just the opposite, i.e., strengthened from the precuneus in risk aversion for gains but from the left anterior insula in risk-seeking to avoid losses. Overall, our functional connectivity analyses imply that the systematic deviation from risk neutrality results from the working of cognitive control. Social cognition might play a role in risk aversion in gain framing, but metacognition, that is, high executive control, in risk-seeking in loss framing.

Disclosures: T. Asamizuya: None. **J. Kato:** None. **H. Takesue:** None. **S. Ota:** None. **Y. Kuniyoshi:** None.

Poster

739. Emotion and Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 739.10

Topic: H.06. Social Cognition

Support: National Natural Science Foundation of China 31922089

Title: Frontal gamma but not alpha frequency band transcranial alternating current stimulation (tACS) modulates immediate and delayed optimism biases

Authors: *Z. YAO[1], J. WEI[2], G. HUANG[2], L. LI[2], Z. LIANG[2], L. ZHANG[2], Z. ZHANG[2], X. HU[1];
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Abstract: When forecasting the future, people tend to underestimate the chances of experiencing adverse events, i.e., optimism bias. This bias is believed to be driven by valence-dependent motivational processing, such that people preferentially incorporate desirable but not undesirable information into belief systems. A common cortical activity depicting motivational processing is the frontal alpha asymmetry (FAA, right-minus-left alpha power), with higher FAA (more significant left frontal activity) indicating a stronger approach motivation toward positive stimuli or a stronger withdrawal motivation from negative stimuli. To investigate whether electric brain stimulation over the right frontal cortex could modulate motivational belief updating, we conducted a randomized, single-blind between-subjects experiment in which participants received a single session of individualized alpha frequency (IAF)-tACS (N = 31), 40 Hz-tACS (gamma band, N =30), or sham-tACS (N = 31) over right frontal regions. We assessed optimism bias using the classic belief update paradigm, with the tACS administered after half of the experimental trials when participants were during rest. To understand how brain stimulation may influence long-term biases, participants completed the task again in 24 hours. Replicating prior findings, we found that participants showed larger updates for desirable than for undesirable feedback (i.e., update bias). We also observed enhanced updates for both desirable and undesirable feedback in the 40 Hz-tACS group in the immediate session. Importantly, after 24 hours, participants in the 40 Hz-tACS group showed increased long-term optimistic updating biases, suggesting that the frontal gamma stimulation may induce delayed effects via a valence-dependent offline consolidation process. When examining EEGs, we observed no significant changes in frontal alpha power for the IAF-tACS group compared to the other groups. The findings indicate that IAF-tACS did not significantly change FAA or optimism bias in a single session. Notably, in the 40 Hz-tACS group, we found a positive correlation between the delayed update for undesirable feedback and the frontoparietal phase connectivity during post-stimulation trials. Thus, impaired online working memory maintenance after the gamma stimulation (i.e., the smaller phase connectivity) might contribute to the delayed neglect of undesirable feedback (i.e., smaller update). Taken together, these findings suggested that while the single-session frontal alpha stimulation may not influence motivated belief updating, the frontal gamma tACS bears promises in modulating optimistic belief updating.

Disclosures: Z. Yao: None. **J. Wei:** None. **G. Huang:** None. **L. Li:** None. **Z. Liang:** None. **L. Zhang:** None. **Z. Zhang:** None. **X. Hu:** None.

Poster

739. Emotion and Human Behavior

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 739.11

Topic: H.06. Social Cognition

Support: R01AG058817
R01AG022983
2018-A-006- NET

Title: Contrasting Two Models of Utilitarian Reasoning

Authors: *R. ANTONIOU[1], H. ROMERO-KORNBLUM[2], C. YOUNG[1], M. YOU[3], J. H. KRAMER[1], K. P. RANKIN[1], W. CHIONG[1];
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Abstract: <META NAME="author" CONTENT="Ρέα Αντωνίου">**Contrasting Two Models of Utilitarian Reasoning**Rea Antoniou[1], Heather Romero-Kornblum[1, 2], J. Clayton Young[1], Michelle You[1,3] Joel H.Kramer[1], Katherine P. Rankin[1], and Winston Chiong[11]Memory and Aging Center, Department of Neurology, University of California San Francisco.[2]Rady School of Management, University of California San Diego.[3]School of Medicine, New York Medical College
One influential framework for examining utilitarian judgments has been a dual process model, inwhich utilitarian judgment (e.g., infliction of harm for the greater good) is typically associated with deliberate cognitive control processes, while non-utilitarian (e.g., avoiding such harms) judgment is associated with emotional, automatic processes. Another paradigm framework of moral cognition, the two-dimensional model of utilitarian psychology, posits that utilitarian choices may reflect either instrumental harm, i.e., inflicting harm on an individual for the greater good; or impartial beneficence, i.e., impartially and altruistically acting for the benefit of the overall welfare. We evaluated preregistered (https://osf.io/m425d) hypotheses derived from these models of moral cognition in a sample of 275 neurologically healthy older adults. Our results suggest that both the dual process and two-dimensional models provided insights regarding utilitarian reasoning. The dual process-based model was partially supported by our findings, with higher emotionality associated with decreased endorsement of utilitarian judgments (b = - 0.12, p <.001). Relevant to the second paradigm emphasizing the two-dimensional nature of utilitarianism, we found that the dimensions of instrumental harm and impartial beneficence are positively associated across certain moral categories (r = .26, p <.001). Thus, moral cognition models may be more complementary than competitive, contrary to contemporary moral reasoning literature.*Keywords:* utilitarian judgments, moral cognition, dual process model, two-dimensional model, instrumental harm, impartial beneficence

Disclosures: R. Antoniou: None. **H. Romero-Kornblum:** None. **C. Young:** None. **M. You:** None. **J.H. Kramer:** None. **K.P. Rankin:** None. **W. Chiong:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.01

Topic: H.08. Learning and Memory

Support: NIA K01AG066847
NIA P30AG066530-02S1

Title: Single molecule gene expression for identification of cell types within the mouse ventral subiculum

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Abstract: The subiculum (SUB) is the major output of the hippocampal formation and is classically divided into a 'cognitive' dorsal region and 'limbic' ventral region (Fanselow and Dong, 2010). Previously, as part of the mouse Hippocampus Gene Expression Atlas (HGEA; Bienkowski et al, 2018), we identified four relatively distinct gene expression layers that are differentially expressed across the entire SUB longitudinal axis. Based on each layer's distribution, we defined five new SUB subregions and demonstrated how SUB laminar connectivity within each subregion are parts of larger networks related to distinct hippocampal function. Within this new perspective, the classic ventral SUB is split into two subregions (SUBv and SUBvv) which both contain different representations of the same three gene expression layers. While the three SUBv/SUBvv gene expression layers appear spatially discrete, multiplexed spatial transcriptomics approaches are needed to determine how distinct each layer is at the single cell-type level. Using RNAscope single molecule fluorescent *in situ* hybridization (smFISH), we triple-labeled mouse coronal tissue sections of the SUBv/SUBvv using RNAscope probes targeted to three marker genes expressed by each layer (*Dlk1*, *Teddm3*, *Tle4*). Within each tissue section, three gene expression layers were clearly labeled within the SUB pyramidal layer with no dorsal/ventral gradient of expression. Using QuPath analysis software, we then quantified the single molecule expression of each RNA fluorescent probe across thousands of cells within the SUBv and SUBvv regions and mapped their spatial distribution within the tissue. Using varying degrees of thresholding for each probe, we identified cell-type classes based on the combinatorial expression of the three marker genes, including some individual cells at layer boundaries which strongly co-expressed multiple marker genes. Our results identify new cell-types within the SUBv/SUBvv regions and demonstrate quantification and classification of cell-types using smFISH for identified HGEA marker genes.

Disclosures: **N. Khanjani:** None. **M. Pachicano:** None. **M.S. Bienkowski:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.02

Topic: H.08. Learning and Memory

Support: HHMI funding

Title: Formation of hippocampal cognitive maps revealed by longitudinal cellular imaging during multi-task learning

Authors: *W. SUN[1], J. WINNUBST[1], M. MICHAELOS[1], C. LAI[1], J. X. WANG[2], K. L. STACHENFELD[2], Z. KURTH-NELSON[2], X. ZHAO[1], G. MICHEL[1], D. FLICKINGER[1], V. GONCHAROV[1], S. DILISIO[1], S. E. LINDO[1], C. STRINGER[1], M. PACHITARIU[1], J. E. FITZGERALD[1], N. SPRUSTON[1];
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Abstract: The hippocampal formation is essential for an animal's ability to navigate and forage effectively in complex environments. It contributes by forming structured representations of the environment, often called cognitive maps. While many experimental and theoretical aspects of learned hippocampal cognitive maps are well established, the exact learning trajectories for their formation and usage remain unknown. We performed large-scale 2-photon calcium imaging of more than 5,000 neurons in mouse CA1 and tracked neural activity of the same neurons over 30 days, while the animals learned multiple versions of a linear two-alternative choice task in virtual reality (VR) environment. We used various manifold discovery techniques to visualize the high-dimensional neural data over the entire learning period and found that each animal went through a stereotyped transition of learning stages, demarcated by distinct low-dimensional embeddings and decorrelations of neural activity at key positions along the VR track, which correlated with task performance. Our results indicate that the evolution of hippocampal representations during learning reflects the extraction of task-related features that correlate temporally with the animal's evolving performance. Furthermore, the learned structures appear to be reused in novel tasks, suggestive of transfer learning. By designing and simulating artificial agents based on reinforcement learning, we found that some architectures reproduced key features of both animal behavior and neural activity. The ability to monitor the formation of cognitive maps over weeks-long periods of learning provides a platform for developing and testing hypotheses regarding the underlying plasticity mechanisms, cell types, circuits, and computational rules responsible for adaptive learning.

Disclosures: W. Sun: None. **J. Winnubst:** None. **M. Michaelos:** None. **C. Lai:** None. **J.X. Wang:** None. **K.L. Stachenfeld:** None. **Z. Kurth-Nelson:** None. **X. Zhao:** None. **G. Michel:** None. **D. Flickinger:** None. **V. Goncharov:** None. **S. DiLisio:** None. **S.E. Lindo:** None. **C. Stringer:** None. **M. Pachitariu:** None. **J.E. Fitzgerald:** None. **N. Spruston:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.03

Topic: H.08. Learning and Memory

Support: Children's Health Research Institute (CHRI) Trainee Award

Title: Subcortical function and structure features in fetal memory systems

Authors: *S. CORREA[1], E. S. NICHOLS[2], M. MUELLER[2], B. DE VRIJER[3], R. EAGLESON[4], C. A. MCKENZIE[5], S. DE RIBAUPIERRE[6], E. G. DUERDEN[2];
[2]Fac. of Educ., [3]Obstetrics & Gynaecology, Schulich Sch. of Med. & Dent., [4]Biomed. Engin., [5]Med. Biophysics, Schulich Sch. of Med. & Dent., [6]Clin. Neurolog. Sciences, Schulich Sch. of Med. & Dent., [1]Univ. of Western Ontario, London, ON, Canada

Abstract: ***Objective:*** Learning and memory difficulties impact 6-10% of school-aged children, and many of these cognitive difficulties have their origins in utero due to alterations in the development of key memory-related brain regions, including the hippocampus and the thalamus[1]. Despite the continuous nature of environmental insults impacting the developing fetal subcortical structures and subsequent cognitive impairments, little research is available on fetal memory systems due to the technical challenges of studying the brain and behavior in utero[2]. ***Methods:*** We recruited women with singleton pregnancies (n=10). Single-shot fast spin-echo images were acquired using a 3T GE Discovery scanner and 32-channel torso coil at Western University. Images were reconstructed into a single 3D volume using NiftyMic. Subcortical volumes (hippocampus, basal ganglia, thalamus) were automatically segmented. Activation time courses were extracted from the default mode networks (DMN) and medial temporal lobe (MTL) networks. Generalized linear models were used to examine the association between functional connectivity strength in DMN and MTL and subcortical volumes, adjusting for gestational age. ***Results:*** Increased functional connectivity strength in the DMN-MTL networks positively associated with hippocampal (B=0.004, p=<0.001), thalamic (B=0.005, p= <0.001) and basal ganglia volumes. Decreased functional connectivity strength presented a relationship with putamen (B=-0.12, p=<0.001), globus pallidus (B=-0.16, p=<0.001), and amygdala (B=-0.30, p=<0.001), volumes. Increased functional connectivity strength was also associated with caudate volumes (B=0.012, p=<0.001). ***Conclusion:*** In investigation of subcortical volumes, we found the thalamus to be an important mediator, this result implicates that thalami-cortical networks play a key role in memory systems. Developing sensitive MRI- biomarkers enables the formation of a normative model of fetal memory systems[3]. These biomarkers are critical in establishing normative functional and volumetric data in the fetal brain.

Disclosures: S. correa: None. **E.S. nichols:** None. **M. Mueller:** None. **B. de Vrijer:** None. **R. Eagleson:** None. **C.A. Mckenzie:** None. **S. De Ribaupierre:** None. **E.G. Duerden:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.04

Topic: H.08. Learning and Memory

Support: NSF CAREER IOS-1844935

Title: Temporal context and hidden state inference in the hippocampal "splitter" signal

Authors: *M. VAN DER MEER, R. M. GRIEVES, E. DUVELLE;
Dept. of Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: The hippocampus is thought to enable the encoding and retrieval of ongoing experience, the organization of that experience into structured representations like contexts, maps, and schemas, and the use of these structures to plan for the future. A central aim is to understand what the core computations supporting these functions are, and how these computations are realized in the collective action of single neurons. A potential access point into this issue is provided by so-called “splitter cells” which, unlike classical place cells, encode not only current location, but also the previous and/or future trajectory. However, the literature on splitter cells has been fragmented and confusing, owing to differences in terminology, behavioral tasks, and analysis methods across studies.
In this work, we synthesize consistent findings from the splitter cell literature, establish a common set of terms, and translate between single-cell and ensemble perspectives. Most importantly, we examine the combined findings through the lens of two major theoretical ideas about hippocampal function: (1) representation of temporally graded traces of the recent past and expectations of the future, as instantiated in the temporal context model (TCM) and the successor representation (SR), and (2) and hidden state inference, as instantiated, among others, in nonparametric Bayesian models.
We find that unique signature properties of each of these models are necessary to account for the data, but neither theory, by itself, explains all of its features. Specifically, the temporal gradedness of the splitter signal is strong support for temporal context models, but hard to explain using hidden state inference, while its flexibility and task-dependence is naturally accounted for using state inference, but poses a challenge otherwise. These theories suggest a number of avenues for future work, and we believe their application to splitter cells is a timely and informative domain for testing and refining theoretical ideas about hippocampal function.

Disclosures: M. van der Meer: None. **R.M. Grieves:** None. **E. Duvelle:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.05

Topic: H.08. Learning and Memory

Title: The dysconnectome in Schizophrenia represented as sets of lost features

Authors: *H. AMOURI, A. CHOWDURY, J. KOPCHICK, J. STANLEY, V. DIWADKAR;
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Abstract: Schizophrenia (SCZ) a chronic psychiatric condition is seen as a classic dysconnection syndrome (Friston et al., 2014) and a loss of network features have been

characterized using a multiplicity of analytic techniques (Silverstein et al., 2016). Here, in characterizing patterns of dysconnections as sets of lost features, we characterized dysconnectomic profiles that were common across four conditions of memory formation and that were unique to each of the four conditions. fMRI data (3.0T Siemens Verio) were collected from 55 participants (24 patients). The learning task alternated between four distinct conditions: Encoding (learning associations between nine object-location pairs), Post- Encoding Consolidation (passive task-free epochs), Retrieval (cued retrieval of memoranda), and Post-Retrieval Consolidation (passive task-free epochs). The sub-figures represent each of the five derived sets as connective rings with chords representing pathways with reduced uFC in SCZ (all effects were SCZ < HC). Two effects appear as salient: First, the most loquacious set, is that associated with Post-Retrieval Consolidation (Figure 1a, bottom right), a stimulus free rest interval during which participants are passively recapitulating associative memories (Ravishankar et al., 2019). Evidently, schizophrenia is characterized by a specific loss of functional connectivity across frontal, parietal and hippocampal nodes. A second loquacious set, reflects the intersection across all four conditions (Figure 2b) suggesting condition independent loss of connectivity in SCZ. This set spans all the sub-parts of the dys- connectome. The dysconnectome in schizophrenia is not a “thing” but a “process”: Accordingly, it should be expected to follow dynamic principles of task-modulated network function (Park and Friston, 2013). As we demonstrated, thinking of dysconnectomes as sets of lost features provides a lucid framework for thinking of how these features generalize across or are specific to task-related processes.

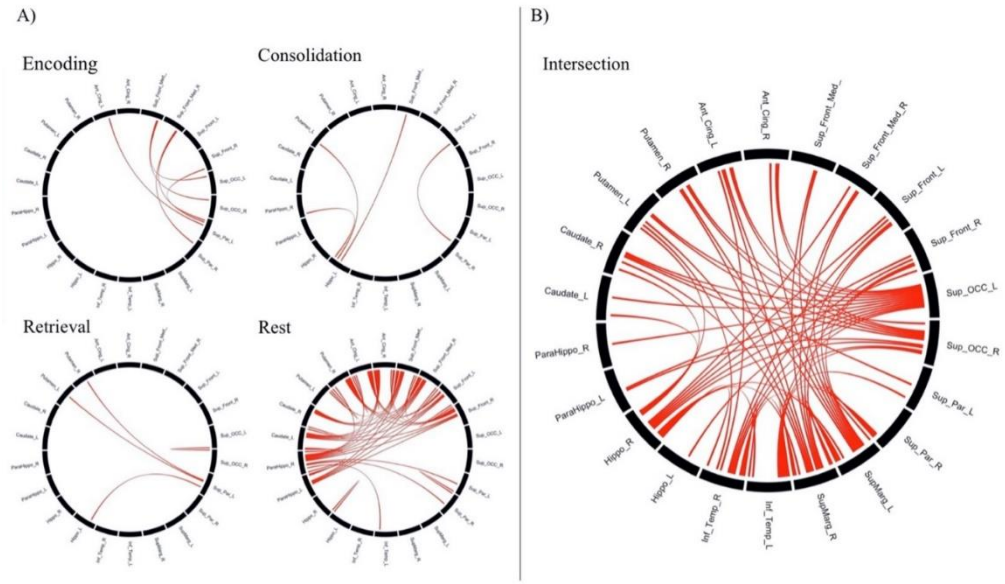

Figure 1: The connectomic rings depicts all 22 nodes organized in a clockwise direction starting with posterior and proceeding to anterior. Each chord represents a pathway, in which the uFC was significantly greater in (a) HC (red chords) or in (b) SCZ (blue chords). A) The four connectomic rings are: Encoding, Consolidation, Retrieval, and Rest. The consolidation period separated Encoding from Retrieval and is characterized as a state of memory retention. A chord in one of these four rings defines the chord as a unique feature during that state. B) The Intersection connectogram illustrates the common features, significant differences in the uFC, across all four states.

Disclosures: **H. Amouri:** None. **A. Chowdury:** None. **J. Kopchick:** None. **J. Stanley:** None. **V. Diwadkar:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.06

Topic: H.08. Learning and Memory

Support: Canadian Institutes of Health Research (CIHR)
Natural Sciences and Engineering Research Council of Canada (NSERC)

Title: Novelty-modulated activity of hippocampal VIP interneurons in freely behaving mice

Authors: *S. TAMBOLI[1,2], D. TOPOLNIK[1,2], P. YASHCHUK[1,2], S. SINGH[1,2], A. GUET-MCCREIGHT[3], L. TOPOLNIK[1,2];
[1]Neurosci. Axis, CRCHUQ-CHUL, Quebec city, QC, Canada; [2]Dept. of Biochemistry, Microbiology and Bio-informatics, Univ. Laval, Quebec City, QC, Canada; [3]Krembil Ctr. for Neuroinformatics, Univ. of Toronto, Toronto, ON, Canada

Abstract: In the CA1 hippocampus, vasoactive intestinal polypeptide expressing (VIP) interneurons make complex connectivity motifs by targeting GABAergic cells and pyramidal neurons. The resulting inhibitory and disinhibitory circuit interactions can regulate memory encoding, but the specific roles of VIP cell types in this process remain poorly understood. Here we used a series of behavioral tasks to study various facets of episodic memory and simultaneously performed *in vivo* calcium imaging of VIP/calretinin (CR) co-expressing axons within CA1 oriens-alveus using wireless fiber photometry in freely moving mice. First, consistent with previous studies conducted on head-restrained mice, we found that VIP/CR calcium transients (CaTs) were strongly modulated by changes in the animal locomotion speed. Second, a higher level of VIP/CR activity was detected when mice were placed in a novel context, at the beginning of the context re-visit trial and following a context switch. Third, when mice were allowed to explore different objects, CaTs were significantly higher in the object zone than in the neutral zone, revealing the object-related modulation of VIP/CR interneuron activity. Furthermore, the object modulation was higher in relation to novel objects or spatially displaced objects in the object-recognition and object-location tests, respectively. Taken together, these data indicate that VIP/CR interneurons respond to changes in the environment by increasing their activity and may therefore aid in the encoding of episodic-like memory and adaptive behaviors.

Disclosures: S. Tamboli: None. **D. Topolnik:** None. **P. Yashchuk:** None. **S. Singh:** None. **A. Guet-Mccreight:** None. **L. Topolnik:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.07

Topic: H.08. Learning and Memory

Support: NRF 2018R1A4A1025616
NRF 2019R1A2C2088799
NRF 2021R1A4A2001803
NRF 2022M3E5E8017723
NRF 2022R1I1A1A0106975611
BK21 program

Title: Subicular neurons represent multiplex task information by using theta rhythm in a hippocampal-dependent visual scene memory task

Authors: *S.-M. LEE[1], J. SEOL[2], I. LEE[1];
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Abstract: The subiculum has long been considered a critical brain region through which the hippocampal information is transmitted to various cortical areas, but little is known about its exact roles in hippocampal-dependent memory tasks. Most hippocampal place cells tend to have single place fields, and they can represent visual scene or behavioral choice information via rate remapping. On the other hand, subicular place cells exhibit very different firing properties by showing broad and spatially invariant firing fields. Such discrepancies make it difficult to compare the two regions by using the traditional rate-based analytical methods. To address this issue, we adapted spiking-phase methods to parse multiple subfields from the single broad firing field of a subicular neuron. Specifically, we trained five male Long-Evans rats to make a behavioral choice to either left or right arm in a T-maze according to visual scene stimulus presented on LCD monitors. During the task, single-unit spiking activities and local field potentials were recorded simultaneously in the dorsal subiculum and hippocampal CA1 by an implanted multi-electrode drive equipped with 24 tetrodes. Among the putative complex spiking cells (CA1, n=270; subiculum n=151), two-thirds of subicular cells had multiple place fields after the field parcellation based on the spiking-phase method, and those cells showed enhanced rate remapping for task-related information (i.e., visual scene and choice response). Notably, multiple subfields of a single subicular neuron could carry different types of task variables respectively, which was rarely observed in the CA1. Combining these results, we conclude that subicular neurons may facilitate associative learning by multiplexing hippocampal-dependent information so that downstream structures receive more associative information between the critical task variables. Furthermore, since it has recently been reported that the neuronal population in the subiculum has a finer representation of navigational factors compared to the CA1, we aim further to investigate whether the subicular neurons recorded in the scene memory-based task also generate better populational decoding accuracy than the CA1 neurons in terms of animal's position and task variables. We also plan to examine the contribution of temporal codes to the decoding performance, which is expected to be significant for the position rather than task variables.

Disclosures: S. Lee: None. **J. Seol:** None. **I. Lee:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.08

Topic: H.08. Learning and Memory

Title: The effects of long-term oral tamoxifen administration on brain derived neurotrophic factor (BDNF) expression in the hippocampus of female Long-Evans hooded rats

Authors: *A. R. HALLIDAY, S. M. BLOSSOM, E. M. BIEN, A. G. BERNHARD, L. E. BEEN, M. E. KELLY;
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Abstract: Many patients are prescribed tamoxifen as a long-term adjuvant therapy to prevent recurrence of estrogen-positive breast cancers. People who take this selective estrogen receptor modulator (SERM) often report significant psychological side effects, including depression, anxiety, brain fog, and memory impairments. However, the neurobiological mechanisms underlying these cognitive changes are unknown. We therefore developed a novel rodent model of long-term oral tamoxifen treatment: 34 middle-aged, adult Long-Evans Hooded female rats were fed tamoxifen food pellets or standard chow for 10-13 weeks ad-lib. Body weight and condition were monitored throughout the drug administration period. Long-term oral tamoxifen administration resulted in clinically-relevant levels of tamoxifen in plasma, demonstrating it to be a robust model. At the conclusion of the study, animals were sacrificed by intracardial perfusion and brains were processed for immunohistochemical localization of brain derived neurotrophic factor (BDNF) in the hippocampus. Hippocampal BDNF was chosen as a target because it influences dendritic spine density, spinogenesis, synaptogenesis, and long term potentiation. Estrogen mediates BDNF transcription via an estrogen-response element on the BDNF gene, and the effects of estrogen on BDNF density are particularly salient in the hippocampus, specifically in the dentate gyrus (DG) and CA3. Coronal sections containing the rostral-caudal extent of the hippocampus were imaged using a Brightfield microscope and analyzed with background-subtracted densitometry in the DG and CA3. We found that long-term oral tamoxifen administration decreased BDNF density in the DG ($p < .002$) and dorsal CA3 ($p < .001$), but not the ventral CA3, of Long-Evans hooded female rats, suggesting a potential mechanism for tamoxifen's effects on psychological health.

Disclosures: A.R. Halliday: None. **S.M. Blossom:** None. **E.M. Bien:** None. **A.G. Bernhard:** None. **L.E. Been:** None. **M.E. Kelly:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.09

Topic: H.08. Learning and Memory

Support: K01AG054729
P20GM113131-7006
R15MH126317
R15MH125305

Title: Identification of Memory-eligible Primed Neurons Based on In vivo Neuronal Activity Hierarchy and Memory-associated Burst Synchronization

Authors: *Y. ZHOU[1], L. QIU[1], M. LYON[2], X. CHEN[3];
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Abstract: Memory is thought to be encoded by sparsely distributed memory-eligible neurons in memory-related regions. Thus far, there is no reliable method to distinguish memory-eligible neurons from other neurons in real time. We utilized a fiber-optic confocal florescence endoscope to visualize single neuron activity in the hippocampal CA1 region in free-moving mice. Instant imaging using a fiber-optic microprobe allows for free-behaving memory tests (such as trace fear conditioning) and avoids hippocampal inflammation and pathological neuroexcitation. Here we report a numerical method, which is based on principal component analysis (PCA) of *in vivo* neuronal activity and trace memory-associated burst synchronization, to quantitatively define memory-eligible neurons (namely primed neurons). The neurons with high activity levels and high synchronization are identified as primed neurons, which are preferentially engaged in trace fear memory formation. We also found that the first principal component of PCA is mostly mediated by primed neurons during repetitive training and successful recall. Interestingly, the first principal component fails to predominate when animals are not actively engaged in mnemonic activities. In animals with severe learning deficits, the percentage of primed neurons is drastically reduced, and the predominant major component of PCA fails to emerge. This work presents a novel method to reliably define memory-eligible primed neurons. Implement of this method to study memory-eligible neurons will advance our understanding of hippocampal memory formation.

Disclosures: Y. Zhou: None. **L. Qiu:** None. **M. Lyon:** None. **X. Chen:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.10

Topic: H.08. Learning and Memory

Support: Wellcome Trust Grant (100154/Z/12/A)
BBSRC DTP
Wellcome Trust Felowship (206682/Z/17/Z)
Isaac Newton Trust/Wellcome Trust ISSF/University of Cambridge Joint Research Grant

Title: Real-time formation of the hippocampal-medial entorhinal cognitive map

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Abstract: How fast does an animal learn its environment? Does it matter if the learning occurs all at once or is spread across different sessions over multiple days? It was reported that stable place cells become evident during the first exposure to an enclosure, while the formation of stable grid cells typically occurs within several days. The formation of both types of spatial patterns was typically studied in discontinuous recordings over multiple trials with significant breaks outside the novel enclosure. Hence the learning process may have included encoding as well as recall and comparison phases. To determine the true place encoding dynamics, we simultaneously recorded from the hippocampal place cells, the medial entorhinal grid cells and boundary cells while a rat was performing a 3-hour-long continuous exploration of a novel 1x1m2 enclosure. Our results show that place cells mature before grid cells, whose individual fields emerge independently. Conversely, co-localized fields of simultaneously recorded grid cells show correlated movements and the same relative convergence rates, invariant across distinct grid modules, animals and environments. Finally, grid patterns do not show consistent anchoring points or higher stability at the borders despite relatively stable border cells, suggesting that border cells do not generally act as an anchor at the onset. Together, these results suggest that in novel enclosures, place cells evolve first and may provide local inputs to grid cells, whose convergence is globally controlled by the internal entorhinal neural network.

Disclosures: M. Bauza: None. **M. Krstulovic:** None. **J. Krupic:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.11

Topic: H.08. Learning and Memory

Title: Exercise training modulates CS-GAG expression in hippocampal perineuronal nets and alleviates memory impairments induced by the overexpression of Chst11 in the hippocampus.

Authors: *N. E. DOODY[1], E. C. AKAM[2], G. N. ASKEW[1], J. C. F. KWOK[1,3], R. M. ICHIYAMA[1];
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Abstract: Studies exploring the effects of exercise training in the healthy central nervous system (CNS) mainly focus on the increase in neurotrophic factors that facilitate plasticity. However, much less is known regarding whether exercise training modulates structures that restrict neural plasticity such as perineuronal nets (PNNs). PNNs are lattice-like structures that enwrap subsets of neurons, restrict synaptic plasticity, and are implicated in learning and memory. This project investigated whether exercise training modulated the expression of PNNs in the hippocampus and whether this led to improvements in novel object recognition memory. Male Wistar rats (~200g) underwent six weeks of either moderate intensity continuous training (MICT) or high intensity interval training (HIIT) on a motorised treadmill and were compared to a sedentary control group (SED). Immunohistochemistry was used to label PNNs with anti-aggrecan and Wisteria floribunda agglutinin (WFA) to visualise aggrecan core protein and chondroitin-sulphate glycosaminoglycan (CS-GAG) chains, respectively. All analyses were completed blinded to experimental groupings. MICT increased the proportion of aggrecan positive/WFA negative PNNs in the CA1 (SED: 2.43%, MICT: 11.36%, HIIT: 2.82%, $\chi2 = 11.16$ $p<0.05$), CA2 (SED: 9.36%, MICT: 36.51%, HIIT: 34.73%, $\chi2 = 23.72$ $p<0.0001$) and CA3 hippocampal regions (SED: 0.48%, MICT: 6.33%, HIIT: 1.54%, $\chi2 = 7.19$ $p<0.05$) (n=3). It was then investigated whether the MICT-induced modulation of CS-GAGs in hippocampal PNNs improved novel object recognition. Either GFP (control group) or Chst11 (a chondroitin 4-sulfotransferase that makes CS-GAGs more inhibitory to plasticity) was overexpressed in the hippocampus. Hippocampal Chst11 overexpression impaired short-term object recognition memory in sedentary and MICT animals at a three hour delay (MICT-GFP: 0.541 ± 0.141 discrimination index; SED-Chst11: 0.213 ± 0.249 discrimination index, p=0.044; MICT-Chst11: 0.200 ± 0.264 discrimination index, p=0.034; F(3,28)=5.092, p=0.006). However, MICT increased the number of trials with preference for the novel object after 24 hours in both the GFP and Chst11 animals ($\chi2= 11.68$, p=0.009). These results suggest that exercise training improves recognition memory by modulating CS-GAG expression in hippocampal PNNs. These results provided a novel insight into how exercise training can be implemented to alter the biochemical composition of hippocampal PNNs and alleviate deficits of novel object recognition memory.

Disclosures: **N.E. Doody:** None. **E.C. Akam:** None. **G.N. Askew:** None. **J.C.F. Kwok:** None. **R.M. Ichiyama:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.12

Topic: H.08. Learning and Memory

Support: NIH U19NS104590
NIH NINDSR01NS99457

NIH K99NS117795
Lundbeck Foundation R273-2018-212

Title: Ripple-selective hippocampal TORO cells controlling local and extra-hippocampal interneurons

Authors: *G. G. SZABO[1], J. S. FARRELL[1], B. DUDOK[1], W.-H. HOU[2], A. L. ORTIZ[1], C. VARGA[1], P. MOOLCHAND[1], C. I. GULSEVER[1], T. GSCHWIND[1], J. DIMIDSCHSTEIN[3], M. CAPOGNA[2], I. SOLTESZ[1];
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Abstract: Sharp wave-ripples (SPW-Rs) are short, high-frequency electrographic events critically involved in learning and memory. However, the in vivo circuit mechanisms coordinating ripple-related activity among local and distant neuronal ensembles are not well understood. In particular, it is not clearly established whether SPW-R-associated hippocampal inhibitory dynamics is relayed to extra-hippocampal areas through long-distance GABAergic projections. In this study, we identify and characterize in behaving mice a GABAergic cell population that selectively fires immediately before and during SPW-Rs and provides inhibition to certain hippocampal interneuron subtypes including parvalbumin- and cholecystokinin expressing cells. Unlike other GABAergic neurons, these cells reduce their firing frequency during running due to a combination of septo-hippocampal theta-ON GABAergic inputs and activation of inhibitory cholinergic receptors. The unique behavior of such cells (i.e. theta-OFF, ripple-ON or “TORO”) remains unchanged across sleep-wake brain states. In addition, these TORO cells project beyond the hippocampus, forming a substantial fraction of long-range GABAergic projections originating from the CA1. Our findings outline a functional circuit element ideally positioned to broadcast ripple-related disinhibitory activity both within and beyond the hippocampus.

Disclosures: G.G. Szabo: None. **J.S. Farrell:** None. **B. Dudok:** None. **W. Hou:** None. **A.L. Ortiz:** None. **C. Varga:** None. **P. Moolchand:** None. **C.I. Gulsever:** None. **T. Gschwind:** None. **J. Dimidschstein:** None. **M. capogna:** None. **I. Soltesz:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.13

Topic: H.08. Learning and Memory

Support: AG052258
AG028740
AG037984
AG068205

CA211963
CA219836
AG03801

Title: Peripheral senolytic treatment alleviates age-associated cognitive impairments and improves NMDA-receptor mediated synaptic function

Authors: *A. KUMAR[1], V. BUDAMAGUNTA[1], A. RANI[2], D. ZHOU[3], T. C. FOSTER[4]; [1]Univ. of Florida, Gainesville, FL; [2]Univ. of Florida Med. Col., Gainesville, FL; [3]Univ. of Texas Hlth. Sci. Ctr., San Antonio, TX; [4]Dept Neurosci., Evelyn F. and William L. McKnight Brain Inst. Univ. Florida, Gainesville, FL

Abstract: Age-related cognitive impairment is a common detriment for the elderly population, with noticeable deficits experienced by over 40% of people aged over 65 years. With the global population of people aged over 65 projected to reach 1.5 billion within the next 30 years, it is imperative to find ways to conserve the vitality of humans as they age. Though cellular senescence has revealed itself to be a prominent therapeutic target that has been linked to several brain related pathologies and pathology-associated cognitive decline, there is very little understanding as to the impact of peripheral senescence on cognitive functioning. Starting at middle age (12 months), F344 male rats were treated orally for 5 consecutive days every 2 weeks, for 6 months, with either vehicle (n=36), Dasatinib + Quercetin (D+Q, 1.2 mg/kg+12 mg/kg, n=28) a senolytic that crosses the blood brain barrier (BBB), or ABT-263 (12 mg/kg, n=22), a senolytic that does not cross the BBB. At 18 months of age, rats were subjected to a battery of behavioral tests followed by tissue collection for electrophysiological characterization of CA3-CA1 hippocampal synaptic function and transcriptomic sequencing. Young male rats (6 months) were used as a control group. Results from water maze and inhibitory avoidance tests demonstrate that the older vehicle treated rats had 24 hr memory deficits compared to young and older ABT-263 and D+Q treated rats ($p < 0.01$). Senolytic treatment improved grip strength ($p < 0.05$). Results from the electrophysiological assessment revealed that older vehicle treated rats exhibited a significant decrease in the N-methyl-D-aspartate receptor mediated excitatory postsynaptic potential compared to young and older ABT-263 and D+Q treated rats ($p < 0.01$), and senolytic treatment increased the total synaptic response compared to aged vehicle treated ($p < 0.05$). Transcriptomic sequencing revealed that senolytic treated rats exhibited a marked reduction in the expression levels of senescent genes (*Cdkn2a* and *Cdkn1a*, $p<0.005$) in the periphery (e.g. lung) and dentate gyrus genes associated with neuroinflammation. These results of the current study suggest that peripheral senescent cells can drive brain aging and cognitive impairments. Current studies are examining the effects of treatment on the integrity of the BBB.

Disclosures: **A. Kumar:** None. **V. Budamagunta:** None. **A. Rani:** None. **D. Zhou:** Other; Co-founder and stock holder of Unity Biotechnology. **T.C. Foster:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.14

Topic: H.08. Learning and Memory

Support: AG052258
AG028740
AG037984
AG068205
CA211963
CA219836
AG03801

Title: Senolytic treatment alleviates chemotherapy-induced cognitive impairments and NMDA-receptor mediated synaptic dysfunction

Authors: *V. BUDAMAGUNTA[1], A. KUMAR[2], A. RANI[3], D. ZHOU[4], T. C. FOSTER[5]; [2]Dept Neuroscience, McKnight Brain Inst., [1]Univ. of Florida, Gainesville, FL; [3]Univ. of Florida Med. Col., Gainesville, FL; [4]Univ. of Texas Hlth. Sci. Ctr., San Antonio, TX; [5]Dept Neurosci., Evelyn F. and William L. McKnight Brain Inst. Univ. Florida, Gainesville, FL

Abstract: Chemobrain is defined as a decline in cognitive function observed as an adverse side-effect of chemotherapy, with annual reports of over 1.5 million and 700,000 chemotherapy receiving Americans experiencing signs of chemobrain during and long after the treatment, respectively. Despite knowing that several chemotherapeutic agents trigger the accumulation of senescent cells, the role of chemotherapy associated senescence accumulation in the pathophysiology of chemobrain is very poorly understood. To address this, we utilized young (6 months) F344 male rats and split them into 3 groups. One group received vehicle (n=22), another one received doxorubicin (Dox, once a week intraperitoneally for 4 weeks, 2 mg/kg, n = 13) while the last group received ABT-263 (ABT, 12 mg/kg, 5 consecutive days of oral treatment during the 2nd and 4th weeks of Dox treatment, n=14), a senolytic that does not cross the blood brain barrier (BBB), in addition to dox. Following treatment completion, rats were subjected to behavioral tests to assess their learning and long-term (24 hr) memory retention capabilities. The rats were then euthanized for electrophysiological characterization of CA3-CA1 hippocampal synaptic function and transcriptomic sequencing. Our results show that Dox rats exhibit an impaired learning on the spatial water maze task, as measured by a significantly ($p < 0.05$) reduced discrimination index (DI) score on acquisition probe trial, when compared to vehicle treated and Dox+ABT treated rats. Long-term memory deficits were observed in Dox treated rats, as measured by a significantly reduced DI score on the 24-hour retention probe trial of the spatial water maze, when compared to vehicle ($p < 0.001$) and Dox+ABT ($p < 0.05$) treated rats. Dox treatment also impaired memory on the inhibitory avoidance (IA) task, as measured by a significantly ($p < 0.05$) reduced average latency to enter the dark chamber on the retention testing day of IA, when compared to vehicle and Dox+ABT treated rats. Furthermore, electrophysiological characterization of the hippocampal synaptic function revealed a significant ($p < 0.01$) decrease in N-methyl-D-aspartate receptor (NMDAR) mediated excitatory post synaptic potentials in Dox treated relative to vehicle and Dox+ABT treated rats. These results provide strong evidence that ABT mediated senescence clearance alleviates chemobrain, in part *via* mitigating the chemotherapy induced NMDAR-mediated synaptic dysfunction. Current studies are assessing the change in transcriptomic profile of hippocampal subregions, levels of

circulating inflammatory cytokines and chemokines, and the effect of treatment on the integrity of BBB.

Disclosures: V. Budamagunta: None. **A. Kumar:** None. **A. Rani:** None. **D. Zhou:** Other; Co-founder and stock holder of Unity Biotechnology. **T.C. Foster:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.15

Topic: H.08. Learning and Memory

Support: AG068205
AG028740
AG037984
AG052258

Title: Expression profile of serine racemase in the Prefrontal Cortex and the Hippocampal subfields over the course of aging

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Abstract: Aging is associated with a decrease in N-methyl-D-aspartate (NMDA) receptor function. NMDA receptors play a critical role in synaptic plasticity, learning and memory. Activation of NMDAR requires glutamate and either co-agonist, glycine or D-serine. The catalysis of D-serine from L-serine is due to the enzyme serine racemase (SR). Thus, age-related changes in the expression of SR could contribute to decreased NMDA receptor function. However, age-associated changes in the expression of SR in the hippocampus and in the medial prefrontal cortex (mPFC) have not been elucidated. Therefore, the current studies are designed to determine SR expression profile in the mPFC and hippocampal subfields, CA1, CA3, and dentate gyrus (DG). Hippocampal subregions and mPFC were collected from young (4-6 mo, n=5) and aged (24-26 mo, n=5) male Fischer-344 rats and were stored at -80 ^{o}C. For Western blot analysis, sample lysate (10 µg/well) was loaded into TGX-stain-free gels. Following electrophoresis, gels were activated for 1 minute and proteins were transferred to LF-PVDF membranes then imaged for total protein prior to blocking. Membranes were probed for SR antibody (Santa Cruz sc-365217) and B-actin (Abclonal AC026) overnight at 4°C. Licor secondary antibodies were applied for 1 hr at room temperature and membranes were scanned on the Licor Odyssey Clx. Data were generated using Image Studio (Licor), Image Lab (Bio-Rad) software and Microsoft Excel. SR expression was normalized to B-actin and to total protein. Technical replicates, randomly positioned, were run on the same gel. To compare across blots,

signals were first normalized to total protein, and then compared to a control master mix consisting of equal concentrations of each sample. Values are reported as fold-change from young control group. ANOVA across age group indicates a significant decrease [$F(1, 8) = 24.62$; $p < 0.001$) in SR expression in mPFC. *Post hoc* tests demonstrate a significant reduction ($p < 0.005$, n = 5/age) in SR expression in mPFC in aged rats when compared with young. ANOVAs across CA3 [$F(1, 8) = 29.06$; $p < 0.001$) and CA1 [$F(1, 8) = 6.73$; $p < 0.03$) hippocampal subfields suggest a significant decrease in SR expression. *Post hoc* tests demonstrate a significant decline in the CA3 ($p < 0.001$, n=5/age) and in the CA1 ($p < 0.05$, n=5/age) of aged rats when compared to young. These results illustrate that a decrease in SR expression during aging might contribute to a reduced NMDA receptor function.

Disclosures: **L.A. Bean:** None. **A. Rani:** None. **T.C. Foster:** None. **A. Kumar:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.16

Topic: H.08. Learning and Memory

Support: CIHR
NSERC

Title: Imaging Context-Specific Memory Recall in the Hippocampus

Authors: *A. MOCLE[1], C. A. COELHO[2], A. I. RAMSARAN[3], S. A. JOSSELYN[4], P. W. FRANKLAND[5];
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Abstract: The encoding specificity principle states that episodic memories are linked to the context in which they are formed, such that encountering a context similar to the encoding context increases the likelihood of recalling the corresponding memory. Animals can also use context to disambiguate cues that have multiple associations or meaning across different contexts. To study the neural basis of context-dependent memory we developed a discriminative context-odor pair association task, in which mice learn that in one context (A), digging in a peppermint-scented (odor 1), but not carvone-scented (odor 2), bedding is reinforced. Concurrently, these mice learn in a second context (B) that digging in carvone-scented (odor 2) but not peppermint-scented (odor 1), bedding is reinforced. Using the RAM-tagging approach in the dentate gyrus (DG) of the hippocampus, we captured the engram of one of the initial context exposures. Following training, mice underwent unrewarded memory probes in both contexts, where digging at each odor was measured to determine the whether the context-odor was learned. We show that activating the engram of one context using optogenetics or DREADDs is

sufficient to reverse the learned context-odor association in the untagged context. Furthermore, when probed in a novel context, activating the DG engram of the tagged context promoted digging at the scent that was rewarded in the tagged context. Next, we used a custom-built miniature endoscope to image neuronal activity in CA1 during the training and probe sessions of the task. We found that activity in CA1 at long timescales (~10s of seconds) reliably distinguishes between contexts during the training sessions. Furthermore, activating the tagged-context DG engram in the untagged context disambiguates cues by re-instating the activity patterns in CA1 that correspond to the tagged context, resulting in an observed reversal of the context-odor association. These results suggest that engrams serve as a neural representation of context, which the hippocampus uses to disambiguate cues that have multiple, context-dependent associations.

Disclosures: A. Mocle: None. **C.A. Coelho:** None. **A.I. Ramsaran:** None. **S.A. Josselyn:** None. **P.W. Frankland:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.17

Topic: H.08. Learning and Memory

Support: CIHR
NIH F31MH120920-01

Title: Maturation of CA1 inhibitory circuitry regulates the ontogeny of episodic-like memory

Authors: *A. I. RAMSARAN[1], Y. WANG[1], B.-R. A. YEUNG[1], A. GOLBABAEI[1], J. LAU[1], M. DE SNOO[1], A. RASHID[1], A. AWASTHI[1], L. M. N. TRAN[1], A. ABBEGG[1], L. DUAN[1], C. MCKENZIE[1], J. GALLUCCI[1], M. AHMED[1], T. K. LIU[1], R. KAUSHIK[4], A. DITYATEV[5], S. A. JOSSELYN[2], P. W. FRANKLAND[3];
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Abstract: In humans and other mammals, event memories are imprecise until the emergence of episodic or episodic-like memory sometime during childhood. The onset of episodic-like memory has been associated with the maturation of the hippocampus, yet precisely when and how this occurs remains unknown. Using a combination of optogenetic, chemogenetic, and viral gene transfer approaches in developing mice, we identified a series of cellular and molecular events in the neurodevelopment of the hippocampus that underlies the ontogeny of precise, episodic-like memories. First, we found that hippocampus-dependent spatial memories increase in precision at the beginning of the fourth postnatal week (between P20 and P24) following a transient period of elevated neuronal activity in CA1. Moreover, the emergence of precise,

episodic-like memories during the fourth postnatal week involved a shift in excitatory-inhibitory balance in CA1 that was initiated by the formation of the extracellular matrix around parvalbumin (PV)-expressing interneurons. The maturation of PV interneurons by perineuronal nets (PNNs) in the developing CA1 subsequently allowed experiences encoded by older mice to be allocated to sparse neuronal ensembles that support precise, episodic-like memories. In summary, our studies indicate that the development of episodic-like memory requires adult-like neuronal allocation mechanisms that are controlled by the maturation of the extracellular matrix surrounding inhibitory circuitry in CA1. Although the onset of episodic-like memory has historically been equated with the 'coming online' of the hippocampus, our work instead suggests that the hippocampus passes through multiple stages of functional development distinguished by distinct neural and mnemonic phenotypes.

Disclosures: **A.I. Ramsaran:** None. **Y. Wang:** None. **B.A. Yeung:** None. **A. Golbabaei:** None. **J. Lau:** None. **M. de Snoo:** None. **A. Rashid:** None. **A. Awasthi:** None. **L.M.N. Tran:** None. **A. Abbegg:** None. **L. Duan:** None. **C. McKenzie:** None. **J. Gallucci:** None. **M. Ahmed:** None. **T.K. Liu:** None. **R. Kaushik:** None. **A. Dityatev:** None. **S.A. Josselyn:** None. **P.W. Frankland:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.18

Topic: H.08. Learning and Memory

Support: CIHR postdoctoral fellowship

Title: Neurogenesis-mediated circuit remodeling reduces engram reinstatement and promotes forgetting

Authors: A. AWASTHI[1], S. KO[1], A. GUSKJOLEN[1], J. DHALIWAL[1], J. DE LA PARRA[1], J. R. EPP[2], E. CHAHLEY[3], M. L. DE SNOO[1], M. SOLARI[1], P. PANESAR[1], J. S. SNYDER[4], X. DUAN[5], J. R. SANES[6], S. A. JOSSELYN[1], P. W. FRANKLAND[1];
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Abstract: Post-training increases in hippocampal neurogenesis are associated with forgetting of hippocampus-dependent memories in adult mice. This form of forgetting might be due to increased numbers of new neurons, remodeling of hippocampal circuitry or some combination of both. Here we tested the hypothesis that neurogenesis-mediated forgetting is caused by remodeling of hippocampal circuits by engineering mice in which adult-generated granule cells

hypo- or hyper-integrate into hippocampal circuits. Using gene deletion, opto- and chemogenetic strategies, we find that hypo-integration of newborn neurons prevents post training exercise-induced forgetting of contextual fear memories. Conversely, inducing hyper integration of newborn neurons following contextual fear conditioning is sufficient to produce forgetting. Ex vivo patch clamp recordings from these gene deleted adult-generated granule cells confirmed hypo- or hyper-integration into the perforant path. Recording optogenetically evoked EPSCs from the same cells in downstream CA3 cells also established hypo- or hyper-integration at their output synapses. Because these interventions did not affect survival of newborn neurons, these findings suggest that neurogenesis-mediated remodeling of hippocampal circuits represents a continuous and active form of interference that alters accessibility of engrams underlying hippocampal memories. Consistent with this, using engram-labeling approaches, we found that exercise-induced forgetting was associated with reduced engram reactivation.

Disclosures: **A. Awasthi:** None. **S. Ko:** None. **A. Guskjolen:** None. **J. Dhaliwal:** None. **J. de la Parra:** None. **J.R. Epp:** None. **E. Chahley:** None. **M.L. De Snoo:** None. **M. Solari:** None. **P. Panesar:** None. **J.S. Snyder:** None. **X. Duan:** None. **J.R. Sanes:** None. **S.A. Josselyn:** None. **P.W. Frankland:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.19

Topic: H.08. Learning and Memory

Support: CIHR

Title: Engram specific synaptic potentiation is important for fear memory formation and expression in-vivo

Authors: *M. SADERI[1,4], A. AWASTHI[4], S. A. JOSSELYN[4,2,3], P. FRANKLAND[4,2,3]; [1]Dept. of Physiology,, [2]Dept. of Physiol., [3]Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada; [4]Program in Neurosciences & Mental Hlth., The Hosp. for Sick Children (SickKids), Toronto, ON, Canada

Abstract: Memories are thought to be encoded in the brain via synaptic strengthening among memory engram cells. While this idea is widely assumed to be true, direct evidence has remained out of reach. It has not been possible to observe if learning potentiates synaptic connections (i.e., measure synaptic strength before and after learning) and simultaneously show that these changes are causally related to memory expression (i.e., they occur in engram neurons). Here, we used a novel engram allocation-based approach to observe synaptic changes in engram neurons upon learning in-vivo. Using optogenetics, we assigned selected Medial Entorhinal Cortex (MEC) neurons to a context dependent fear memory in a mouse model. This takes advantage of the fact that neurons with more excitability are preferentially allocated to engrams. To do this, we

expressed an adeno-associated virus with both excitatory (blue light) and inhibitory (red light) opsins in MEC and implanted an optrode above MEC terminals in the Dentate Gyrus (DG). Briefly increasing the excitability of infected MEC terminals in mice that underwent fear conditioning (by shining blue light immediately before training) allocated the fear memory to virus-infected neurons. This was evidenced by the fact that, 24 hours after conditioning, during red light exposure, mice showed a reduced memory expression demonstrated by decreased freezing behaviour. In a separate cohort of animals, we used in-vivo electrophysiology to record pre- and post-learning strength of MEC to DG allocated neurons' synapses. Remarkably, we found that synapses originating from allocated MEC neurons were potentiated 24 hours after learning. Finally, to assess a causal relationship between engram-specific synaptic potentiation and memory, in the same animals, we used optogenetics to induce synaptic depression 24 hours after learning in the terminals of allocated neurons. We observed that synaptic strength reversed to pre-learning levels. Additionally, when animals were tested again in the training context, they showed decreased freezing behavior (i.e., weaker memory) compared to control animals. Using a within-subject in-vivo design, this work supports the hypothesis that engram-specific synaptic potentiation is a key mechanism for memory encoding and storage.

Disclosures: **M. Saderi:** None. **A. Awasthi:** None. **S.A. Josselyn:** None. **P. Frankland:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.20

Topic: H.08. Learning and Memory

Title: Neurogenesis-mediated rewiring of hippocampal episodic engram circuitry drives memory generalization

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Abstract: Episodic information is allocated to the hippocampal engram cells, embedded within DG-CA3-CA1 circuitry. However, it is unclear whether the hippocampal engram fidelity for an episode is maintained or remodeled over time. Adult-born new granule cells (abGCs) are continuously integrated into the existing hippocampal circuits throughout the lifetime and potentially interact with engram cells. Here, we attempted to rewire episodic engram circuits by modulating adult hippocampal neurogenesis *after* the memory formation. We first examined the impact of manipulating overall levels of adult neurogenesis. Our results show that reducing post-learning neurogenesis retains episodic fidelity (i.e., prevents memory generalization). Conversely, increasing post-learning neurogenesis reduces episodic fidelity (i.e., accelerating memory generalization) in both contextual fear conditioning and watermaze. Next, we evaluated the impact of altering how abGCs integrate into hippocampal circuits on episodic fidelity.

Conditional knockout of the cadherin-9, a cell adhesion protein, only in abGCs blocked abGCs structural integration into the DG-CA3 after the memory formation and prevented the degradation of episodic fidelity. This suggests that post-learning structural changes in DG-CA3 circuitry mediates neurogenesis-mediated fidelity degradation. In addition, we investigated whether the addition of abGCs directly induces structural changes of the DG-CA3 engram circuitry. Using engram-specific whole-neuron synaptic connectivity visualization (i.e., enhanced green fluorescent protein reconstitution across synaptic partners; eGRASP technique) and engram projection visualization, we found that post-learning neurogenesis modulation rewires DG-CA3 engram connectivity, including both excitatory (i.e., large mossy fiber terminal structure) and inhibitory (i.e., filopodial contacts to parvalbumin-positive interneurons) connections. Consequently, the output of the CA3 engrams (i.e., CA3-CA1 engram connectivity) is maintained when neurogenesis is ablated in the post-learning window, whereas CA3-CA1 engram connectivity is reduced when neurogenesis level is elevated. Regardless of neurogenesis-mediated rewiring, optogenetic suppression of neurotransmitter release at presynaptic terminals of the CA3 engrams (i.e., CA1 region) using eOPN3 functionally interferes with both episodic and generalized memory retrieval. Together, our study suggests that adult hippocampal neurogenesis transforms episodic engram circuitry into generalized engram circuitry in the hippocampus, which reflects fidelity changes.

Disclosures: S.Y. Ko: None. **S.A. Josselyn:** None. **P.W. Frankland:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.21

Topic: H.08. Learning and Memory

Support: NWO Rubicon
Niels Stensen fellowship
CIHR postdoctoral fellowship

Title: Disruption of memory allocation by stress: a role for parvalbumin interneurons and endocannabinoid signaling

Authors: *S. L. LESUIS[1], B. J. WALTERS[2], M. N. HILL[3], P. W. FRANKLAND[1], S. A. JOSSELYN[1];
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Abstract: AIMS: The ability to remember which cues in a particular environment predict threat, and which do not, is imperative for survival. Overgeneralization of threatening cues, such that also neutral cues are perceived as threatening, may result in excessive anxiety-like behavior, and is a core symptom in many anxiety-related disorders and PTSD. Stress may promote such

overgeneralization of memory, and hence may instigate or amplify anxiety-disorders. The overarching objective of these studies is to decipher the key pathways that underlie stress-induced memory generalization at the level of behavior, network dynamics and the cellular level, with a focus on inhibitory interneuron signaling. METHODS: Mice were exposed to corticosterone injections or acute restraint stress, and the specificity of memory during fear conditioning and reward learning was assessed. Using *in vivo* fiber photometry, opto- and chemogenetics and iDISCO we establish the underlying cell types and networks mediating these effects. RESULTS: After stress, mice show stronger memory generalization, both for memory with a positive and negative valence. In parallel, the lateral amygdala ensembles encoding for these memories are enlarged, and these enlarged ensembles were responsible for the generalized expression of the memories. Stress suppresses the activity of parvalbumin $(PV)^+$-interneurons, and indeed the effects of stress on memory generalization and ensemble size could be prevented by activation of PV^+-interneurons, while inhibition of PV^+-interneurons mimicked the effects of stress. We next show that endocannabinoid signaling within the lateral amygdala, which is directly modulated by stress, underlies the stress effects on interneurons and memory generalization. CONCLUSIONS: Stress results in generalized memory expression, and disrupted memory allocation, which is prevented by modulating PV^+-interneuron activity. We propose that endocannabinoid signaling mediates these effects. Understanding these neurobiological mechanisms of stress-induced memory generalization may be a first step towards the development of novel treatment strategies for anxiety-related pathologies.

Disclosures: S.L. Lesuis: None. **B.J. Walters:** None. **M.N. Hill:** None. **P.W. Frankland:** None. **S.A. Josselyn:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.22

Topic: H.08. Learning and Memory

Support: Ontario Graduate Scholarship
CIHR
NSERC

Title: Imaging the dynamics of a multi-trial engram

Authors: *A. JACOB[1], A. MOCLE[1], C. YUAN[1], P. W. FRANKLAND[2], S. A. JOSSELYN[3]; [1]Univ. of Toronto, Toronto, ON, Canada; [2]PGCRL - NMH 5th floor, [3]Neurosci. & Mental Hlth., The Hosp. For Sick Children, Toronto, ON, Canada

Abstract: Engrams are subpopulations of neurons whose activity is both necessary and sufficient for memory recall. To date, most investigations of engrams in different brain regions have examined memories formed after only a single trial. Single-trial learning provides an appealing

experimental model in which the precise moment of memory encoding can be easily determined. Studies using this model have identified a neuronal allocation process in which cells with high excitability immediately prior to the learning event become core components of a subsequently formed memory. While this allocation process is well understood in single-trial learning, a broad class of memories - especially appetitive memories - arise only after multiple learning trials. It remains unclear what circuit processes govern engram formation under these conditions. Previous research has identified the lateral nucleus of the amygdala (LA) as a key site for appetitive memory engrams. Therefore, we observed and manipulated the activity of principal neurons (PNs) in the LA as mice learned a multi-trial reward association task to understand the mechanisms of engram formation and recall. Using two-photon microscopy, we imaged the activity of a stable population of LA PNs across two weeks as head-fixed mice learned a tone-reward relationship. We observed robust coding of reward consumption in both the LA and a nearby control striatal region. However, only in the LA, we identified a sparse ensemble of PNs whose activity was linked with successful recall during a memory test. Interestingly, this memory-relevant ensemble showed significantly elevated excitability during only the first day of learning, before mice fully acquired the tone-reward contingency. These results indicate that while behavioural performance may require multiple days to reach asymptotic levels, the cellular constituents of the engram may be determined much earlier than this - during the first few exposures to the learned stimulus. Together, these data imply that an allocation process may occur during multi-trial learning and may have similar dynamics to those observed in single-trial learning.

Disclosures: **A. Jacob:** None. **A. Mocle:** None. **C. Yuan:** None. **P.W. Frankland:** None. **S.A. Josselyn:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.23

Topic: H.08. Learning and Memory

Support: Restracomp, Sickkids
CIHR

Title: The supramammillary nucleus (SuM) transforms environmental signals into effects on cognition and mood via regulation of hippocampal neurogenesis

Authors: *J. DHALIWAL[1], S. KO[2], M. SADERI[1], A. VALLAZZA[1], M. SOLARI[1], S. A. JOSSELYN[3], P. W. FRANKLAND[4];
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Abstract: Adult neurogenesis in the dentate gyrus (DG) of the hippocampus represents an important form of neuroplasticity that regulates both mood and cognition. Adult neurogenesis is bidirectionally regulated by environmental stimuli, including enrichment (which promotes neurogenesis) and stress (which suppresses neurogenesis). However, how these signals reach the DG to regulate neurogenesis is unknown. To address this, we used anatomical tracing to identify input projections to the DG from cortical, basal forebrain, midbrain and hypothalamic regions. We found that the activity of many of these regions was regulated by environmental enrichment and stress. In particular, the activity of one hypothalamic region, the supramammillary nucleus (SuM), was downregulated by chronic enrichment and upregulated by chronic restraint stress. The SuM sends both excitatory and inhibitory projections to the DG. We found that chronic chemogenetic inhibition of SuM excitatory (but not inhibitory) projections increased neurogenesis, similar to enrichment. Conversely, chronic activation of these same SuM projection neurons suppressed neurogenesis, similar to stress. Subsequent experiments established that these effects are mediated by an SuM (excitatory neuron) to DG (granule cell) to DG parvalbumin (PV) interneuron circuit, and that chemogenetic interventions targeting this circuit can mimic or block the effects of environmental signals on neurogenesis. Finally, we show that direct manipulation of SuM has bidirectional effects on mood and cognition, similar to enrichment and stress manipulations. Together, these studies identify the SuM as a key region that translates environmental signals into effects on mood and cognition via regulation of hippocampal neurogenesis.

Disclosures: J. dhaliwal: None. **S. Ko:** None. **M. Saderi:** None. **A. Vallazza:** None. **M. Solari:** None. **S.A. Josselyn:** None. **P.W. Frankland:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.24

Topic: H.08. Learning and Memory

Title: Examining the Engram encoding specificity hypothesis in mice

Authors: *J. JUNG[1], Y. WANG[1,2], A. MOCLE[1,2], A. Y. CHUNG[3], S. KOHLER[4], P. W. FRANKLAND[1,2,5], S. A. JOSSELYN[1,2];
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Abstract: Memories are thought to be stored in sparse groups of neurons (engrams); retrieval cues reactivate the engram to induce memory recall. According to a long-standing theory, memory is best recalled by retrieval cues that overlap with training cues (encoding specificity hypothesis). Although human behavioral and imaging studies generally support this hypothesis, they cannot examine encoding specificity at the level of the neuronal ensemble. Here we used

engram visualization tools in mice to test directly whether retrieval cues that closely overlap with training cues produce robust memory recall via high engram reactivation. Using variations of cued fear conditioning tasks in which a tone conditioned stimulus (CS) is paired with footshock, we manipulated encoding and retrieval conditions along multiple domains, including pharmacological state, external sensory (varying tone CS and retrieval cue) and internal (varying optogenetic CS and retrieval cue) cue. Maximal engram reactivation and memory recall occurred when retrieval closely matched training conditions. These findings provide a biological basis for the encoding specificity hypothesis and highlight that memory recall involves an interaction between stored information (engram) and information available at retrieval (memory retrieval cue).

Disclosures: J. Jung: None. **Y. Wang:** None. **A. Mocle:** None. **A.Y. Chung:** None. **S. Kohler:** None. **P.W. Frankland:** None. **S.A. Josselyn:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.25

Topic: H.08. Learning and Memory

Support: Mohammad Khazali, Andreas Schulze-Bonhage, Armin Brandt, Lukas Kunz, Josh Jacobs: NIH/NINDS grant U01 NS113198-01
Peter Reinacher: Fraunhofer Society (Munich, Germany), Else Kröner-Fresenius Foundation (Bad Homburg, Germany)
Lukas Kunz: German Research Foundation (DFG); KU 4060/1-1

Title: Single neuron representations of temporal order in the human medial temporal lobe

Authors: *M. F. KHAZALI[1], A. BRANDT[1], P. C. REINACHER[1], A. SCHULZE-BONHAGE[1], J. JACOBS[2], L. KUNZ[2];
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Abstract: Cellular activity in the medial temporal lobe contribute to fundamental neural mechanisms underlying episodic memory. A key component of episodic memory is the temporal organization of single events that form an entire episode. Here, using invasive single-neuron recordings in human epilepsy patients (n = 17), we asked whether neurons in the human medial temporal lobe encode the serial position of events that are sequentially organized. To examine this question, patients performed an episodic memory task, in which they freely navigated a virtual environment in order to explore and remember the locations of various different objects (Kunz et al., Neuron, 2021). During each exploration period, the patients sequentially encountered two or three different objects that were placed in different locations. This allowed us to examine single-neuron firing rates as a function of the serial position in which the objects were presented. Our results show that a significant number of single neurons in the human

medial temporal lobe are tuned to the serial position of the objects during the exploration period—for example, by activating most strongly whenever the subject is presented with the first object, independent of the identity of the object itself. Overall, about 10% (n=95 out of 945) of human medial temporal lobe neurons exhibited such tuning to serial position in our dataset, which is similar to another recent human single-neuron study (Tsitsiklis et al., Current Biology, 2020). More detailed analyses revealed that some of these neurons represented serial order on top of a visual response to object presentation, whereas other neurons encoded serial position independent of a visual response. Classifying our neurons as putative interneurons (with narrow spike waveform) or putative pyramidal neurons (with wide spike waveform) showed that both cell types exhibited tuning to serial position. Our study thus underlines the presence of temporal order coding in the human medial temporal lobe, which may help humans to correctly recall the temporal structure of episodic memories.

Disclosures: **M.F. Khazali:** None. **A. Brandt:** None. **P. C. Reinacher:** None. **A. Schulze-Bonhage:** None. **J. Jacobs:** None. **L. Kunz:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.26

Topic: H.08. Learning and Memory

Support: BMBF; 01GQ1705A
NIH/NINDS grant U01 NS113198-01
DFG; KU 4060/1-1
Fraunhofer Society (Munich, Germany)
Else Kröner-Fresenius Foundation (Bad Homburg, Germany)

Title: Human associative memory is linked to single-neuron activity during hippocampal ripples

Authors: *L. KUNZ[1], B. STARESINA[2], P. C. REINACHER[3], A. BRANDT[4], A. SCHULZE-BONHAGE[4], J. JACOBS[1];
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Abstract: The medial temporal lobe is critical for forming and retrieving associations between previously unrelated items. Hippocampal sharp-wave ripples may play a key role in these cognitive operations by inducing and activating synaptic connections between neurons. Sharp-wave ripples are a neural network phenomenon that has been studied most extensively in the rodent hippocampus (Buzsaki, Hippocampus, 2015). They occur preferentially during immobility or sleep, when the activity sequences of single neurons replay the content of previous

experiences (Colgin, Nat Rev Neurosci, 2016). Recent studies in both rodents and humans indicate that ripples also play a role in wake behaviors such as the planning of future navigation trajectories (Diba & Buzsaki, Nat Neurosci, 2007) as well as the encoding and retrieval of episodic memories (Norman et al., Science, 2019; Vaz et al., Science, 2020). The relevance of hippocampal ripples for human associative memory remains poorly understood, however. In this study, we therefore examined the dynamics of single-neuron activity in the medial temporal lobe during hippocampal ripples using invasive neural recordings in human epilepsy patients. During the recordings, the patients performed an associative object-location memory task in a virtual environment (Kunz et al., Neuron, 2021). In this task, the patients first learned the locations of several different everyday objects in the virtual environment. During each of multiple test trials, the patients were then asked to remember the location of a given object, navigated to the remembered object location, received feedback about their response accuracy, and collected the object from its correct location to continuously improve their associative memories. Following previously established techniques (Staresina et al., Nature Neuroscience, 2015), we identified human ripples in the local field potentials of bipolar recordings from the left and right hippocampus. We show that hippocampal ripples trigger a state of increased excitation across the human medial temporal lobe. Furthermore, increased ripple rates precede successful and follow unsuccessful retrieval of associative memories. Stimulus-specific neurons encoding specific objects or locations activate together during hippocampal ripples when the represented objects and locations are part of associative memories. These results help translate the functional role of ripples in the rodent hippocampus to the human brain and contribute to a growing body of evidence that ripples in the human hippocampus play a role in human memory.

Disclosures: L. Kunz: None. **B. Staresina:** None. **P.C. Reinacher:** None. **A. Brandt:** None. **A. Schulze-Bonhage:** None. **J. Jacobs:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.27

Title: WITHDRAWN

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.28

Topic: H.08. Learning and Memory

Support: Ser Cymru II 80762-CU-143 (East)
Cardiff University

Title: The role of the dorsal subiculum in spatial reference memory

Authors: *C. FRANCESCHI, J. WILSON, S. KANG, J. O'NEILL;
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Abstract: The dorsal subiculum (dSub), a major output region of the hippocampus, has been shown to be involved in spatial working memory, but its involvement in reference memory has not been established. This study investigated the role of dSub in both spatial working and reference memory by inhibiting its activity using the GABA-A agonist muscimol at different stages of a radial arm maze task, in which rats learned the position of three rewards over the course of multiple days (20 trials per day). We first tested whether disrupting subiculum function impaired acquisition of the task by administering either muscimol (test group) or saline (control group) prior to learning. We found that the test group performed worse on the days muscimol was delivered, exhibiting an increased number of errors. Given that both working and reference memory were impaired during acquisition, we tested whether a disruption of subicular activity immediately after learning would impact the performance over the following days. Inhibiting after acquisition, we hypothesised, would disrupt the consolidation process and will then reflect a disruption of reference memory only, leaving working memory intact. Rats receiving muscimol exhibited an increased number of errors compared to controls, which included an increase in reference memory errors. This result is consistent with a role for the dSub in reference memory formation. Lastly, we sought to characterise changes in dSub activity over the course of learning by recording cell activity across days using silicon probes and neuropixels. Our recordings show that a subset of subicular neurons exhibited spatial remapping over the course of learning, indicating that the subicular population spatial code undergoes partial remapping, as performance in the task improves. In conclusion, this data provides supporting evidence of the subiculum's role in spatial working memory, as previous studies have shown, as well as providing a first indication of its involvement in reference memory.

Disclosures: C. Franceschi: None. **J. Wilson:** None. **S. Kang:** None. **J. O'Neill:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.29

Topic: H.08. Learning and Memory

Support: NIH Grant NS113557

Title: Sharp-wave ripples occur selectively during replay of particular locations and paths in an open field maze.

Authors: J. WIDLOSKI[1], ***D. FOSTER**[2];
[1]Neurosci., Univ. of California Berkeley, Berkeley, CA; [2]Univ. of California, Berkeley, Berkeley, CA

Abstract: One of the most prominent signals in the mammalian brain is the sharp wave ripple. Ripples, which are brief high frequency oscillations in the local field potential, originate in the hippocampus and often herald the emergence of sequenced behavior-like reactivations of place cells, called replay, that are believed to subserve memory consolidation and planning. Previous work has shown that the timing of sharp-wave ripples during replay is not random. On linear tracks, ripples have been tied to the replay of specific track segments, suggesting that ripples form a rigid backbone for the formation and possible elongation of replay. Whether the same is true for replay in more open environments (where each location can be approached from many different angles) and with goal-directed task components is unknown. To address this, we utilized a large, previously published data set of 7273 replays across 37 sessions from 3 rats navigating an open field with sparsely-placed barriers that changed from session to session. We found that ripples occurred reliably, and in a spatially restricted manner, as a function of replay location, independent of the rat location or the time since the start of the replay. Indeed, these ripple accumulation zones, or "ripple fields" when normalized by replay occupancy, were found to have above chance levels of spatial information and within-session stability (shuffles were computed by circularly permuting the ripple power across the full set of replay events). Strikingly, ripple fields tended to avoid the maze periphery and occupied rather the interior of the maze, usually along corridors that represented the more efficient routes through the maze, even though ripple-less replays appeared readily outside these zones. Ripple fields were largely conserved across tetrodes and hemispheres, independent of the number of cells detected on each tetrode. Population bursting was also reliable and spatially restricted and showed the same accumulation zones as ripples, confirming that global CA1 spiking and ripples are tightly yoked during replay. Indeed, this yoking, together with the spatially restricted nature of the ripple/burst fields, explains a previous perplexing finding of how some replays can contain neither ripples nor population bursts by seemingly avoiding the ripple/burst fields. In sum, our results confirm and extend previous work on linear tracks by showing that ripples are exquisitely timed to occur selectively during the replay of certain locations and paths in an open field maze.

Disclosures: **J. Widloski:** None. **D. Foster:** None.

Poster

740. Learning and Memory: Hippocampal: Formation Circuitry

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 740.30

Topic: H.08. Learning and Memory

Support: HHMI Hanna Gray Fellowship
NIMH: R01 MH103325

Title: Medial entorhinal cortex is necessary for intact reverse hippocampal replay

Authors: C. S. MALLORY[1], D. J. FOSTER[2];
[1]Univ. of California Berkeley, Berkeley, CA; [2]Psychology, Univ. of California, Berkeley, Berkeley, CA

Abstract: During awake immobility, direct input from medial entorhinal cortex (MEC) to hippocampal area CA1 is required to sustain spatially-extended replay trajectories (Yamamoto & Tonegawa, 2017). Yet, whether the MEC plays a broader role in shaping the content of hippocampal replay remains unknown. Additionally, the previous work examined hippocampal replay under chronic inactivation of the temporoammonic pathway, leaving uncertain the specific time point at which MEC input is required. To examine the contribution of MEC to the content of hippocampal replay, we recorded CA1 place cell activity from three rats as they traversed a linear track, and optogenetically inactivated the bilateral MEC on alternating laps, solely during periods of immobile reward consumption. To investigate replay content, we applied a memoryless Bayesian decoder to compute the posterior probability of the hippocampal representation over space given spiking activity. We defined replays as spike density events in which the posterior probability traveled smoothly across space and time (based on jump distance and weighted correlation). We restricted analysis to replays classifiable as either forward or reverse. We defined long replays as replays spanning >50% of the track length. Many features of hippocampal activity were unaltered by MEC inactivation, including the rates of sharp wave ripples, spike density events, and replays. Strikingly, however, we found that reverse replays were shorter with MEC inactivation, while forward replays were unaffected. Moreover, the rate of long reverse- but not long forward- replays was significantly reduced by MEC inactivation. How might MEC drive or sustain reverse replay? A recent study identified a subset of CA1 neurons that preferentially participate in reverse replay (Wang et al., 2020). These 'bimodal cells' fire strongly at both the peak and trough of the LFP theta oscillation, and share a number of features associated with deep CA1, which receives strong MEC input. Consistently, we found that during laser-OFF trials bimodal cells participated more strongly in reverse versus forward replays. However, this bias was eliminated in laser-ON trials. These data suggest that MEC activation of bimodal cells may be required to sustain long reverse replays in the hippocampus. Together, our findings indicate that different mechanisms drive forward and reverse replay and point to a critical role of MEC in the latter.

Disclosures: C.S. Mallory: None. **D.J. Foster:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.01

Topic: H.09. Spatial Navigation

Support: NIMH R56 MH106475
Simons Foundation Collaboration on the Global Brain
James S McDonnell Foundation
Vallee Foundation
NIMH U19 MS118284-01

Title: Learning map alterations in the medial temporal lobe

Authors: *S. LEVY[1], L. M. GIOCOMO[2];
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Abstract: Self-localization within an environment requires assessing one's position at multiple scales, both the precise location relative to nearby cues and the global layout of such cues within the larger environment. The hippocampus (HPC) and medial entorhinal cortex (MEC) play distinct roles in memory and navigation. While neurons in both of these structures have firing patterns modulated by an animal's spatial position and trajectory and can each produce a map of the environment, patterns of spatial tuning are distinct and reflect divergent local circuitry. We trained mice to run in linear virtual reality environments composed of distinct landmarks encountered in multiple specific orders. This task has the benefit in that it creates a demand for unique representations of each cue order. We then used Neuropixels probes to record the neural activity of large populations of neurons in HPC and MEC. In ongoing work, we are studying how HPC and MEC each encode maps of novel environments and the differences across these structures in how these maps are transformed when local cues are rearranged. This paradigm will allow us to address a tension in the hypotheses for remapping: on the one hand, it is expected that there is a low degree of remapping would be expected in the MEC since the environment should be highly familiar and grid cells remap coherently and support a global metric of the environment, while more remapping is expected in the hippocampus to encode novel transitions through space between re-ordered cues; on the other hand, HPC and MEC are synaptically coupled and produce cognitive maps jointly, so novel maps produced through remapping should be tightly linked across structures.

Disclosures: S. Levy: None. **L.M. Giocomo:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.02

Topic: H.09. Spatial Navigation

Support: NIMH R56 MH106475
NIDA P50 DA042012

Title: Ketamine disrupts and restructures entorhinal and hippocampal spatial coding

Authors: *F. MASUDA[1], Y. SUN[2], E. A. JONES[3], L. M. GIOCOMO[4];
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Abstract: Ketamine is a commonly used rapid-acting dissociative anesthetic that has been used in clinics since the 1970s. Recently, ketamine has received significant clinical and scientific attention due to its ability to acutely treat depression a subanesthetic doses. Unfortunately, ketamine has a plethora of undesirable side effects: out-of-body experiences, dissociation, and cognitive spatial memory impairments (Wilkins et. al 2012, Krystal et. al 1994, Malhotra et. al 1996, Vesuna et. al 2020). Yet despite the scientific and clinical attention, ketamine's effect on neurological circuitry remains poorly understood. After confirming that ketamine disrupts spatial memory consolidation in mice, we examined how ketamine affected the entorhinal-hippocampal spatial memory circuit in mice navigating virtual reality environments using Neuropixels probes. We found that ketamine reliably affects behavior in VR and induces an acute disruption and longer term remapping of spatial maps in the entorhinal cortex. Ketamine's acute disruption of spatial maps appears to be driven by its aberrant up-regulation of entorhinal excitatory neural firing rates which results in an acute decoherence period. Interestingly this acute disruption seems to be a driven by a breakdown in the typically robust cell pair connectivity. Using calcium imaging we recorded ketamine's effect on hippocampal coding, and found that ketamine also disrupts hippocampal coding but does so by depressing pyramidal cell firing rates and significantly decreasing place cell activity. Ketamine's acute disruption of spatial maps appears to be driven by its actions on NMDA channels, while its restructuring effects seem to be dependent on its actions on HCN1 channels. This finding suggests potential avenues for reducing the pharmacological off-target effects of ketamine that impair memory and navigation during clinical use.

Disclosures: F. Masuda: None. **Y. Sun:** None. **E.A. Jones:** None. **L.M. Giocomo:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.03

Topic: H.09. Spatial Navigation

Support: NIDA P50 DA042012

Title: Neural circuit dynamics of drug-context associative learning in the hippocampus

Authors: *Y. SUN[1], L. M. GIOCOMO[2];
[1]Stanford Univ., [2]Neurobio., Stanford Univ., Stanford, CA

Abstract: The environmental context associated with previous drug consumption is a potent trigger for drug relapse. However, the mechanism by which neural representations of context are modified to incorporate information associated with drugs of abuse remains unknown. Using

longitudinal calcium imaging in freely behaving mice, we find that different from the associative learning of natural reward, drug-context associations for psychostimulants and opioids are encoded in a specific subset of hippocampal neurons. These neurons showed distinct activity patterns before drug exposure and were selected based on drug-spatial experience. After drug conditioning, these neurons weakened their spatial coding for the nondrug-paired context, with their spatial coding predictive of drug-seeking behavior. Furthermore, ketamine dissociated the formation of drug-context association and thus blocked the corresponding drug-seeking behavior. Together, this work reveals how drugs of abuse alter the hippocampal circuit to encode drug-context associations and points to the possibility of targeting drug-associated memory in the hippocampus.

Disclosures: Y. Sun: None. **L.M. Giocomo:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.04

Topic: H.09. Spatial Navigation

Support: Simons Foundation Collaboration for Plasticity & the Aging Brain
NIMH R56 MH106475
James S McDonnell Foundation
Vallee Foundation
NIMH U19 MS118284-01

Title: From Molecules to Behavior: Understanding How Aging Impacts Entorhinal-Based Navigation

Authors: *C. HERBER[1], L. M. GIOCOMO[2];
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[2]Stanford Univ., Stanford Univ., Stanford, CA

Abstract: As the most significant risk factor for Alzheimer's disease (AD) and other dementias, aging causes the gradual decline of specific cognitive abilities, like spatial memory, reducing quality of life. However, the neurobiological mechanisms underlying aging-mediated cognitive decline remain unclear, limiting the development of therapies that extend the brain's healthspan. Here, we aim to enrich our mechanistic understanding of healthy neural aging by simultaneously characterizing and then correlating molecular, cellular, and network changes in a well-studied brain region. Across species, medial entorhinal cortex (MEC) facilitates goal-directed navigation, which is important for mobility and independence. Neurons in MEC represent self-motion cues like speed and head direction, environmental landmark locations, and maps of space within their electrical firing patterns, helping us integrate our location in space as we move. In young and old mice (n = 8, n = 7) navigating an unchanging virtual reality (VR) environment, we

identified a significant, age-dependent degradation in the firing patterns of spatially-tuned MEC neurons recorded *in vivo* at high density with Neuropixels 1.0 silicon probes. In addition, we observed that the short-term stability of MEC spatial cell firing is significantly compromised in aged mice. Efforts to analyze how aging impacts the coordination of MEC network activity by theta rhythm are ongoing. We will also interrogate MEC spatial coding dynamics during a spatial memory VR task that challenges mice to acquire and track a hidden, landmark-associated reward as it moves. Finally, in these same mice, we are characterizing single neuron transcriptomic changes in MEC neurons to identify candidate genes underlying the observed changes in MEC circuit function and spatial memory during aging.

Disclosures: C. Herber: None. **L.M. Giocomo:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.05

Topic: H.09. Spatial Navigation

Support: A.P. Giannini Postdoctoral Research Fellowship
Stanford School of Medicine Dean's Postdoctoral Fellowship
Stanford Interdisciplinary Graduate Fellowship
NIMH R56 MH106475
Simons Foundation Collaboration on the Global Brain
James S McDonnell Foundation
Vallee Foundation

Title: Investigating How Medial Entorhinal Cortical Sequences Support Spatial Navigation and Learning

Authors: *E. A. AERY JONES, I. I. C. LOW, L. M. GIOCOMO;
Neurobio., Stanford Univ., Stanford, CA

Abstract: Our brains represent how events unfold over time and space through sequences. When an animal explores its environment, neurons in the hippocampus fire to represent its previous, current, and future location, paced by theta rhythm (theta sequences). When an animal rests, neurons fire to represent time-compressed trajectories (replays). Recent evidence suggests neurons in a related region, the medial entorhinal cortex (MEC), may also fire in theta sequences and replays. MEC encodes several variables necessary for navigating space - such as location, speed, and head direction - and thus provides a unique system in which to study these phenomena. However, we know little about the content encoded by MEC theta sequences and replays, the relationship between these two sequence types, and how both sequence types adapt over learning. To address this, we developed a technique to chronically implant a Neuropixel electrode into mouse MEC. This enabled stable recording of hundreds of simultaneously

recorded neurons during freely moving behavior over several weeks. We next developed a directed alternation task which mice could reliably learn and rapidly perform during neural recording. In ongoing work, we are identifying theta sequences during movement and replays during rest, comparing classic detection methods to novel classification and unsupervised detection methods to best capture how MEC represents spatial variables through sequential ensembles. Our findings will uncover how MEC sequences could encode current trajectories, consolidate past trajectories, and adapt these representations to support learning.

Disclosures: E.A. Aery Jones: None. **I.I.C. Low:** None. **L.M. Giocomo:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.06

Topic: H.09. Spatial Navigation

Support: Helen Hay Whitney Foundation
NIMH R56 MH106475
Simons Foundation Collaboration on the Global Brain
James S McDonnell Foundation
Vallee Foundation
NIMH U19 MS118284-01

Title: Sequential novel experiences reconfigure the hippocampal map

Authors: *M. SOSA[1], M. H. PLITT[1,2], L. M. GIOCOMO[1];
[1]Neurobio., Stanford Univ., Stanford, CA; [2]Mol. & Cell Biol., Univ. of California, Berkeley, Berkeley, CA

Abstract: To learn and remember where to find reward in an environment, the brain must maintain an accurate spatial map of the entire environment while updating that map with predictive information. This complex spatial memory process relies on the hippocampus. Hippocampal place cells fire in specific locations in space and “remap” (i.e. change their preferred firing locations) in novel environments, creating a unique map of each new experience. As reward locations are learned within an environment, hippocampal place cells tend to further remap their firing fields to overrepresent the reward location at the population level. How this reward “overrepresentation” develops over the course of experience is not well understood. Here, we provide insight into this question with two-photon (2P) imaging of calcium activity in hippocampal area CA1 as head-fixed mice navigate multiple virtual environments with changing hidden reward locations. Leveraging 2P imaging to track the activity of the same large neural population across days, we investigate how novelty and reward interact to shape the place cell code across successive novel experiences. Specifically, we ask whether meta-learning (i.e. learning to learn) impacts the dynamics of place field remapping and the development of the

reward overrepresentation. We find behavioral evidence of meta-learning in our virtual reality task. In parallel, the hippocampal reward overrepresentation develops across days and is amplified by novel reward locations and experience with novel environments. After a novel environment is introduced in which animals must perform context-dependent licking behavior, the reward locations become overrepresented both in the novel environment and in the familiar environment, more so than during the single-environment condition. Our results suggest that hippocampal reward representations are shaped by changing cognitive demands as animals learn the task structure.

Disclosures: M. Sosa: None. **M.H. Plitt:** None. **L.M. Giocomo:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.07

Topic: H.09. Spatial Navigation

Support: NSERC

Title: Functional differentiation along the rostocaudal axis of the Japanese quail hippocampus

Authors: *C. DAMPHOUSSE, N. MILLER, D. F. MARRONE;
Wilfrid Laurier Univ., Wilfrid Laurier Univ., Waterloo, ON, Canada

Abstract: The mammalian hippocampus (Hp) can be functionally segregated along its septotemporal axis (also called the dorsoventral axis), with involvement of septal (dorsal) hippocampus in spatial memory and temporal (ventral) hippocampus in stress responses and emotional behaviour. In the present study, we investigate comparable functional segregation in proposed homologues within the avian brain. Using Japanese quail (Coturnix Japonica), we report that bilateral lesions of the rostral hippocampus (rHp) produce robust deficits in a spatial Y-maze discrimination (YMD) test while sparing performance during contextual fear conditioning (CFC), comparable to results from lesions to homologous regions in mammals. In contrast, caudal hippocampus (cHp) lesions failed to produce deficits in either CFC or YMD, suggesting that, unlike mammals, both cHp and rHp of birds can support emotional behavior. These observations demonstrate functional segregation along the rostrocaudal axis of the avian Hp that is comparable in part to distinctions seen along the mammalian hippocampal septotemporal axis.

Disclosures: C. Damphousse: None. **N. Miller:** None. **D.F. Marrone:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.08

Title: WITHDRAWN

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.09

Title: WITHDRAWN

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.10

Topic: H.09. Spatial Navigation

Support: Max Planck Society
Human Frontier Research Grant (RGY0072/2018-302)
European Research Council ('NavigationCircuits' GA714642)

Title: A spatial map in the orbitofrontal cortex can be formed independently of the hippocampus.

Authors: I. BÖLÜKBAşı, R. BASU, *H. T. ITO;
Max Planck Inst. for Brain Res., Frankfurt, Germany

Abstract: Spatial navigation requires the brain to form a detailed representation of the locations in the environment. Many lines of evidence suggest that this ability is supported by the brain's spatial representation system in the hippocampus and the medial entorhinal cortex (MEC), where neurons such as place cells or grid cells increase their firing rates depending on the animal's position in space. A recent study reported the existence of another spatial map located in the orbitofrontal cortex (OFC) that encodes the animal's goal destination during navigation (Basu et al., 2021). In an environment with multiple reward sites, OFC neurons exhibit target-location specific firing, enabling accurate prediction of the animal's destination from the ensemble activity of OFC neurons. As the hippocampus is implicated in providing spatial information to other cortical areas (Esteves et al., 2021, Bota et al. 2021, Wikenheiser et al., 2017), here we investigated if the spatial representations observed in the OFC depend on the hippocampus or not. We performed ibotenic acid mediated lesions in the entire dorsoventral axis of bilateral

hippocampi of rats and subsequently trained them in a navigation task on a linear maze equipped with ten equally spaced reward locations as previously described (Basu et al, 2021). Briefly, rats were required to visit two given locations alternately to obtain a reward, and this pair of rewarding locations was changed multiple times during a behavioral session. While the rats performed this task, we recorded the activity of hundreds of OFC neurons simultaneously using a tetrode drive. We observed that, in spite of hippocampal lesions, OFC neurons continued to exhibit target-location specific firing, which allowed for successful decoding of the destination of the animal in individual trials. Furthermore, we discovered that OFC neurons in intact animals exhibited a topologically-organized coding of well positions in the maze, such that the spatial tuning of OFC neural ensembles was similar between nearby positions whereas it was separated incrementally as the spacing between encoding positions became larger. Notably, this relational structure of spatial coding in the OFC developed normally even in animals with hippocampal lesions. These results together suggest that spatial tuning of OFC neurons as well as its relational organization corresponding to the maze geometry can be formed independently of a spatial map in the hippocampus.

Disclosures: I. Bölükbaşı: None. **R. Basu:** None. **H.T. Ito:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.11

Topic: H.09. Spatial Navigation

Support: Max Planck Society
Human Frontier Research Grant (RGY0072/2018-302)
European Research Council ('NavigationCircuits' GA714642)
Alexander von Humboldt Foundation (Postdoctoral fellowship)

Title: Topological schema of space in the orbitofrontal cortex

Authors: *R. BASU, I. BÖLÜKBASI, C. WERT-CARVAJAL, H. T. ITO;
Max Planck Inst. for Brain Res., Frankfurt am Main, Germany

Abstract: Animals in nature are often required to choose the best navigational strategy in a constantly changing environment. This ability is likely supported by the generalization of prior navigational experiences across similar contexts so that spatial memories can be reused in a given context. Previous research has identified place cells and grid cells in the hippocampus and the parahippocampal cortices that fire specifically when an animal visits a particular location. The spatial representations formed by these cells are sensitive to the difference in a behavioral context. For example, the change in a behaving room or maze shape elicits global remapping, whereby place cells and grid cells shift their spatial tuning, resulting in a new map orthogonal to the previous one. Such a phenomenon raises the question of how animals can maintain a

consistent navigation strategy across environments where the underlying brain's map changes completely. Here we report a new kind of spatial map in the orbitofrontal cortex (OFC) that preserves topological relationships of encoding positions in space. Rats were trained to alternate between two given locations on a linear track with ten equally spaced reward wells (Basu et al., 2021). While the rats performed this task, we observed that OFC neural ensembles exhibited distinct firing patterns depending on the animal's target location. Further analysis revealed that the difference in the ensemble firing patterns representing two locations is proportional to the distance between these locations in physical space. Hence, OFC neurons formed a spatial map preserving topological relationships of positions in a behaving arena. Next, to examine the similarity of the OFC map between contexts, we trained rats to perform the same task in the identical mazes located in two distinct rooms. In contrast to the hippocampal spatial map, the OFC neurons retained their location-specific activity across the two rooms, and at a neural ensemble level, the OFC map remained largely unchanged. Finally, to test if the OFC maps can be generalized across mazes with different geometry, we trained animals in two tracks with different shapes, either linear or circular, but with identical spacing between reward locations. We observed that the OFC neural ensembles formed a spatial map preserving topological relationships of positions in both mazes, which could further be aligned using a linear transformation. Taken together, the OFC forms a task-relevant schema of spatial positions by maintaining their topological relationships across environments, pointing to the OFC as a potentially crucial brain region for planning context-invariant navigational strategies.

Disclosures: R. Basu: None. **I. Bölükbasi:** None. **C. Wert-Carvajal:** None. **H.T. Ito:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.12

Topic: H.09. Spatial Navigation

Support: Max Planck Society
Human Frontier Research Grant (RGY0072/2018-302)
European Research Council ('NavigationCircuits' GA714642)

Title: Behavior-dependent interference between theta oscillators in the medial septum and the supramammillary nucleus

Authors: *M. MOZAFFARILEGHA, H. T. ITO;
Max Planck Inst. for Brain Res., Frankfurt am Main, Germany

Abstract: Cortical synchrony has been considered to play a key role in integrating distributed information across the brain. During trajectory decisions in goal-directed navigation, theta oscillations are dynamically coordinated between the prefrontal cortex and the hippocampus, but how the brain can modulate this inter-regional synchrony desirably depending on behavioral

demands remains largely unclear. Previous studies described that the brain has two major subcortical theta oscillators in the supramammillary nucleus (SUM) and the medial septum (MS), and we hypothesize that these two oscillators may create interference patterns by changing phases and amplitudes in projection areas, which may help dynamic inter-regional coupling during navigation. To test this idea, we performed simultaneous recordings from SUM, MS, and area CA1 of the hippocampus. We first examined spectral coherence between these structures while the rat performed random foraging exploration in an open-field arena. We found that, despite high theta coherence between CA1 and SUM or MS, theta coherence between SUM and MS was rather low, indicating that these two oscillators appear to generate the theta rhythm independently. We next asked whether the theta interference between MS and SUM changes depending on behavioral demands. To address this question, we performed recordings while the rat performed a continuous alternation task in a modified T-maze. We then divided the animal's behaviors into two phases; one is when the animal runs toward the upcoming T-junction on the maze ('stem'), and the other is when the animal runs along the track without a requirement of trajectory decision ('non-stem'). We found that the theta spectral coherence between SUM and MS changed dynamically and systematically, expressing higher coherence on the stem overall. This result was further confirmed at the level of individual neurons. We found that spike-phase locking of a subset of SUM and MS neurons relative to CA1 theta increased particularly before trajectory decisions on the stem, and the proportion of neurons showing such modulation is significantly higher in SUM compared to MS. Finally, we confirmed that spike-time relationships between a pair of theta-rhythmic SUM and MS neurons changed systematically between the stem and non-stem parts of the maze, supporting the idea of oscillatory interference in their projection area. Together, our findings suggest that theta rhythms in SUM and MS are differentially modulated depending on the demand of trajectory decisions, which may create oscillatory interference in their projection regions to support dynamic functional coupling between cortical regions.

Disclosures: M. Mozaffarilegha: None. **H.T. Ito:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.13

Topic: H.09. Spatial Navigation

Support: Max Planck Society
Human Frontier Research Grant (RGY0072/2018-302)
European Research Council ('NavigationCircuits' GA714642)
JSPS Overseas Research Fellowships

Title: Decision-invariant coding of memory traces of spatial goals in the dopamine-striatum system

Authors: *N. TAKAKUWA, H. T. ITO;
Max Planck Inst. for Brain Res., Frankfurt, Germany

Abstract: For an animal to navigate to a desired destination, the brain must estimate the direction and distance of the destination relative to the animal's position at the beginning of the journey. While a recent study discovered that neurons in the orbitofrontal cortex point to the animal's subsequent destination during navigation (Basu et al., 2021), how the brain can choose this goal location from numerous positions across the environment is still largely unclear. Previous studies have suggested a key role for the dopamine-striatum system in evaluating available choice options to maximize the expected reward. During goal-directed navigation, the dopamine release in the ventral striatum (vStr) has been shown to increase toward the next destination (Howe et al., 2013; Kim et al., 2020), and this signal is thought to help the animal's navigation by indicating the spatial proximity to the destination. However, it is still unknown whether this goal-dependent dopamine release can flexibly change depending on the animal's goal choice, and if so, when and how this activity can influence the animal's subsequent goal-directed journey. To address this question, we recorded the dopamine release and spiking activity in the vStr during a spatial navigation task in which an animal is required to update start and goal locations multiple times in daily sessions. By using this task, we confirmed that the dopamine release in the vStr, measured by a dopamine sensor dLight, increased toward a goal location and changed flexibly following the change of start and goal location pairs. The same flexible goal-dependent coding was also observed in the spiking activity of a subpopulation of vStr neurons. We then asked whether the goal-dependent spiking activity in the vStr can be used for the animal's goal decision. We compared the spiking activity between trials when the animal targeted two different goal destinations and found that the neural activity at the initial phase of the journeys was almost identical. A decoder constructed from ensemble activity of vStr neurons could not discriminate between two trials targetting different goals either, suggesting that the vStr activity is unlikely to be able to support goal decisions at navigation onset. Furthermore, when the animal was required to run over a location where a reward was provided in previous trials, the activity of vStr neurons increased not only to the goal of ongoing trials, but also to the previous goals where a reward was no longer provided. Our results together suggest that the goal-dependent activity of vStr neurons does not simply reflect the animal's goal decision, but rather represents the memory of spatial goals from previous experiences.

Disclosures: **N. Takakuwa:** None. **H.T. Ito:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.14

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIDA Drug Supply Program
TCU SERC grant # 210321

Program in Neuroscience and Behavior, Mount Holyoke College
Curtis Smith Neuroscience Award
HUM-642, Junta de Andalucia, Spain
SCAI, UJA, Spain

Title: Flexible behavioral adjustment to frustrative nonreward in anticipatory behavior, but not in consummatory behavior, requires the dorsal hippocampus

Authors: C. HAGAN[1], S. GUARINO[1], M. HOXHA[2], A. O. WHITE[2], A. SANCHEZ-BLANCO[3], A. NAVARRO-EXPOSITO[3], A. D. R. AGUERA[3], C. TORRES[4], ***M. R. PAPINI**[1], M. SABARIEGO[2];
[1]Texas Christian Univ., Texas Christian Univ., Fort Worth, TX; [2]Mount Holyoke Col., South Hadley, MA; [4]Univ. of Jaen, [3]Univ. of Jaen, Jaen, Spain

Abstract: Remembering and acting on memories evoked by reward signals is crucial for survival and the hippocampus is key for the representation of such appetitive memories. However, goal-directed behavior requires reward representations to be accurate, reflect current reward value, and be updatable. Previous studies showed that the hippocampus supports behavioral adjustment to reward shifts, but its specific function in appetitive behavior remains unclear. Here we examined the role of the hippocampus in situations involving negative discrepancies between obtained and expected rewards—frustrative nonreward. First, we evaluated the effects of hippocampal lesions using an instrumental task in the 8-maze. In this task, turning in one direction led to 12 pellets, whereas turning in the opposite direction led to 2 pellets. Full hippocampal lesions did not affect preference for the large reward before reward devaluation. However, rats with lesions continued to prefer that arm after a 12-to-2 pellet downshift. Next, and due to the critical role of the dorsal hippocampus in reward coding, we focused our manipulation on this area. Rats were infused with inhibitory designer receptors exclusively activated by designer drugs (DREADDs) in the dorsal hippocampus and found that chemogenetic inhibition did not affect preference for a 12-pellet lever in an anticipatory autoshaping task, but a 12-to-2 pellet downshift in one lever led to a similar perseverance of the preshift preference. Hippocampal disruption (1) could have impaired the ability to anticipate a reward downshift event or (2) could have disrupted the ability to alter previously learned responses. To explore these hypotheses, we used a task that required the development of a consummatory response without demanding the anticipation of a reward downshift event. Inhibition of the dorsal hippocampus led to consummatory suppression similar to that found in controls after a 32-to-2% sucrose downshift. Similarly, systemic administration of lipopolysaccharide did not affect consummatory behavior after reward downshift but it induced perseverance of the preshift preference in an autoshaping task. There was no evidence that a 32-to-2% sucrose downshift in the consummatory task led to increased activation in the dorsal or ventral hippocampus, in terms of c-Fos reactivity, relative to unshifted controls. Together, these results suggest that reward memories can be initially formed and also retrieved after a change in value without a functional hippocampus. However, disruptions of this circuitry impair behavioral flexibility in situations requiring anticipation of reward downshift events.

Disclosures: C. Hagan: None. **S. Guarino:** None. **M. Hoxha:** None. **A.O. White:** None. **A. Sanchez-Blanco:** None. **A. Navarro-Exposito:** None. **A.D.R. Aguera:** None. **C. Torres:** None. **M.R. Papini:** None. **M. Sabariego:** None.

Poster

741. Hippocampus and Entorhinal Cortex

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 741.15

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Mount Holyoke College

Title: Reward loss drives drug-seeking behavior during dorsal hippocampal inactivity

Authors: E. VOGIATZOGLOU[1], S. CHITALE[1], G. WALLSINGER[1], O. ARIES[1], K. MILLER[1], L. ANDERSON[1], H. NAWAID[2], N. AHMED-ADEDOJA[1], A. WHITE[2], M. SABARIEGO[1];
[1]Neurosci. and Behavior, [2]Biol. Sci., Mount Holyoke Col., South Hadley, MA

Abstract: Reward loss triggers an aversive emotional state called frustration that derives from the comparison between the present and the memory of past rewards. The adaptive value of frustration resides in its ability to cause a rapid change in learning and performance, preventing perseverance on no-longer rewarded responses. Thus, frustrative nonreward facilitates a switch from responses that do not yield rewards to a search mode that may result in the discovery of needed resources. Previously, we have demonstrated that animals without a functional hippocampus show behavioral impairments to adjust to frustrative nonreward. However, it is unclear whether the impairment is due to a lack of emotionality (i.e. hippocampal lesioned/inactivated rats not feeling frustrated after reward loss) or a lack of cognitive flexibility (i.e. hippocampal lesioned/inactivated rats unable to modify previously learned goal-directed responses). Because negative states powerfully increase drug value even after extinction, we reasoned that if hippocampal-inactivated rats did not feel frustration then drug-seeking behavior would not change after reward downshifts. In order to investigate this question, we exposed rats (with active and inactive dorsal hippocampi) to a reward-loss paradigm alongside a conditioned place preference (CPP) task. In particular, animals were first infused with inhibitory designer receptors exclusively activated by designer drugs (DREADDs). After recovering from surgery, rats were conditioned to acquire a drug associated place preference. Subsequently, they were trained to recognize two reward sites on a figure-8-maze: one site containing 12 sugar pellets (large reward) and the other containing two sugar pellets (smaller reward). Each day--following this training phase in the figure-8-maze--animals were exposed to cocaine CPP extinction sessions. Once animals extinguished their preference for the cocaine-paired side, all rats were injected with clozapine-N-oxide and the large reward in the figure-8-maze task was devalued to equal the smaller reward. Following this devaluation, rats were immediately exposed to the CPP apparatus. We found that while hippocampus-inactivated rats did not adjust their behavior in the figure-8-maze task after the reward downshift, they increased their time spent in the side previously paired with cocaine similarly to control rats. These results suggest that animals with a dysfunctional dorsal hippocampus do not lack emotionality but rather experience cognitive

inflexibility. Our data could contribute to revealing the function of the dorsal hippocampus in goal-directed behavior and adaptation to loss.

Disclosures: E. Vogiatzoglou: None. **S. Chitale:** None. **G. Wallsinger:** None. **O. Aries:** None. **K. Miller:** None. **L. Anderson:** None. **H. Nawaid:** None. **N. Ahmed-Adedoja:** None. **A. White:** None. **M. Sabariego:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.01

Topic: H.08. Learning and Memory

Support: NIH/NINDS 1F32NS117732-01
NIH/NINDS R01NS115233
NIH/NIMH R01MH117964

Title: Combined Electrophysiology and Imaging to Investigate Hippocampal-Cortical Interactions During Memory Consolidation

Authors: *N. R. KINSKY[1], J. HADDAD[2], K. DIBA[1];
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Abstract: Systems consolidation theory posits that hippocampal-neocortical interactions following learning mediate plasticity in cortical circuits and allow for the creation of long-term episodic memories. One candidate mechanism for inducing cortical plasticity is the hippocampal sharp-wave ripple (SWR): a transient 150-250Hz oscillation which originates in the hippocampus during quiet periods and sleep and reverberates activity throughout the neocortex. However, testing the impact of this mechanism on cortical circuits has remained difficult due to technical limitations in tracking neural activity of the same neurons across days. Here, we perform simultaneous in vivo electrophysiology in the hippocampus and calcium imaging in the pre-limbic (PL) region of freely moving rats before, during, and after a trace fear conditioning task. This approach allows us to characterize how post-learning SWRs influence the development of memory-related neural activity in PL neurons (10-50 cells per session). We first performed pilot behavioral studies where rats learned that a 10 second tone (conditioned stimulus, CS) predicted a mild foot shock (unconditioned stimulus, US) following a 20 second trace interval. Rats were tested 1-7 days later to assess freezing responses to both the CS and the conditioning arena. These studies revealed variability in CS responses: some rats exhibited clear freezing to the tone while others exhibited generalized fear. Based on these studies, we next performed simultaneous neural recordings while male and female rats underwent a modified trace fear conditioning task with which incorporated a control tone (CS-) that was never paired with a shock. These rats developed a specific fear memory as exhibited by clear freezing responses to the CS, but not the CS-, 1-2 days following learning. Preliminary analyses revealed

that PL neurons were persistently active during training and developed CS responses during memory recall. Future analyses will characterize the development of CS responses in PL neurons, determine how this plasticity relates to PL neuron co-activity with SWRs, and examine contextual fear related neural responses to the conditioning arena.

Disclosures: **N.R. Kinsky:** None. **J. Haddad:** None. **K. Diba:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.02

Topic: H.08. Learning and Memory

Support: ONR N00014161253
ONR N000142012405
NSF ECCS-2024776
NSF ECCS-1752241
NIH R21 EY029466
NIH R21 EB026180
NIH DP2 EB030992

Title: Multimodal recordings with E-Cannula uncover spatiotemporally diverse hippocampal sharp-wave ripples associated with orthogonal cell assemblies

Authors: *J.-H. KIM[1], X. LIU[1], S. TERADA[3,4], M. RAMEZANI[1], A. D. GROSMARK[3,4], Y. LU[1], A. LOSONCZY[3,4,5], D. KUZUM[1,2];
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Abstract: A topographical interaction exists between spiking activity and prominent local field potentials in hippocampus. However, little is known how sharp-wave ripples (SWRs) are biased along the anatomical extent of hippocampus and whether this spatiotemporal diversity is associated with neuronal participations. Here, we developed E-Cannula, consisting of a fully transparent graphene microelectrode array and the imaging cannula, which enables simultaneous electrical recording and two-photon calcium imaging in ipsilateral hippocampal CA1 areas. We observed both global and local SWR events with different delays along the longitudinal and septotemporal axes. Moreover, the activities of CA1 pyramidal cells successfully decoded these spatiotemporal patterns. The majority of cells participated the distinctive assemblies showing selective activation in different SWR patterns. Therefore, in contrast with the prevailing view that SWRs are uniformly synchronized throughout hippocampus, we showed spatiotemporal diversity of SWRs recruiting different cell assemblies, suggesting that hippocampal activity could be topographically organized during SWRs. Our multimodal recording technology

provides a promising approach to comprehensively investigate the large-scale activity of hippocampus.

Disclosures: **J. Kim:** None. **X. Liu:** None. **S. Terada:** None. **M. Ramezani:** None. **A.D. Grosmark:** None. **Y. Lu:** None. **A. Losonczy:** None. **D. Kuzum:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.03

Topic: H.08. Learning and Memory

Support: NIMH R01MH117964

Title: Sleep inertia slows awake hippocampal theta frequency

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Abstract: Theta oscillations (5-9 Hz) are considered to be signatures of active processing in the hippocampus and are believed to be critical for learning and memory. Although the peak frequency of theta is generally robust, recent studies suggested that it can be affected by behavioral factors such as speed and acceleration. Manipulations of the theta frequency by optogenetics or temperature have further revealed the importance of theta frequency in cyclical integration of unit activity, which may be important for memory encoding. Given the detrimental impact of sleep loss on memory processing, we investigated the effects of sleep deprivation on theta frequencies in the rat hippocampus during extended awake states, or during wakings between sleep. We recorded 5 hours of extracellular data from the region CA1 (n=6, 3 males/females) during sleep deprivation (SD, 10 sessions) and regular sleep (NSD, 9 sessions). We compared spontaneous theta amplitude and peak frequency for awake states. Overall, theta amplitudes did not differ in SD and NSD. Peak frequencies remained high (>7 Hz) during SD, however a significant decrease was observed in the peak frequency (to ~6.5 Hz) in awake bouts between sleep. This effect was not specific to the beginnings or ends of the bouts or did not change by the duration of the bouts. Intriguingly, the frequency of slower awake theta was similar to the REM sleep theta in the same sessions, suggestive of sleep inertia. Surprisingly, theta frequencies in unit autocorrelograms did not differ between SD and NSD, suggesting a disconnect between inputs and outputs in this circuit. As hippocampal intracellular cAMP is also negatively affected by sleep loss, we administered rolipram to a second group of SD animals (n=6, 2 females; 5 control, 4 rolipram sessions) and observed a transient decrease in theta frequency, mimicking the effects of sleep. Together, these results suggest that slower theta oscillations can potentially be a signature of the sleep inertia and reflect the quality of sleep.

Disclosures: **U. Kaya:** None. **M. Alam:** None. **B.K. Giri:** None. **T. Abel:** None. **K. Diba:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.04

Topic: H.08. Learning and Memory

Support: Simons Foundation Grant 542981
HHMI

Title: Hippocampal replay outside of sharp wave ripples

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Abstract: Hippocampal replay is a phenomenon by which cells in the hippocampus reactivate spiking patterns related to previous experience. Replay events are often detected by first finding sharp wave ripples (SWRs) - a prominent electrophysiological signature in the hippocampal local field potential (LFP) - and then decoding the spatial trajectory represented by hippocampal neurons during the detected event. However, this two-stage procedure is indirect; it uses LFPs to identify times of interest rather than the hippocampal spiking activity itself. Furthermore, it relies on setting arbitrary thresholds to determine what constitutes a SWR and therefore a candidate replay event. Alternative approaches that use multi-unit activity (MUA) are similarly indirect and also involve arbitrary thresholds.
A more general way of detecting replay would use ensemble spiking information at all times to look for periods of coherent non-local representations expressed by the hippocampal population. Eden, Frank, and Tao (2018) developed a semi-latent state space model to detect replay directly from hippocampal spiking activity. Here we extend this model to use acausal clusterless decoding and our analysis shows that:
(1) This approach can reliably detect replay events within SWRs; (2) Replay, although strongly correlated with SWRs, can occur outside of SWR start and stop times and can occur at times where no SWR is detected. Additionally, not every detected SWR contains an identifiable replay event; (3) Results 1-3 hold true if using times of high multiunit activity instead of SWRs to detect replay events.
Our results suggest that methods using SWRs to identify replay events can miss some or all of the content of replay events, which can in turn impact scientific conclusions about the function of replay. Our approach takes full advantage of the recorded spiking activity and can also be generalized to detect non-local activity during movement. As a result, our state-space model

provides a broadly applicable, systematic, and mathematically precise definition of non-local activity that can be applied to hippocampal data across behavioral states.

Disclosures: **E.L. Denovellis:** None. **A. Joshi:** None. **U.T. Eden:** None. **L.M. Frank:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.05

Topic: H.08. Learning and Memory

Support: Simons Foundation 500639
NIH R01 MH105174
NIH K99 AG068425
HHMI

Title: Real-time feedback can promote task-relevant memory replay

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Abstract: Cognitive functions such as memory consolidation, retrieval, and planning involve the ability to mentally simulate past or potential future experiences. The neural mechanisms underlying such mental simulations are thought to include hippocampal sharp-wave ripples (SWRs), which are associated with the time-compressed "replay" of representations of past experience. Multiple lines of evidence implicate SWRs and replay in supporting learning and memory processes; for instance, SWR disruption impairs learning while SWR elongation can hasten learning. Further, rodent models of neurodegenerative disease have reported cognitive impairment coincident and correlated with SWR abnormalities, often including reduction of SWR occurrence rates. An intervention that would restore or increase SWR rate could thus prove therapeutically beneficial. We developed a neurofeedback paradigm for rats in which real-time detection of hippocampal SWRs triggers immediate positive feedback (food reward). This training protocol is embedded within a dynamic spatial memory task, and results in an approximately two-fold increase in SWR rate in a task-phase-specific manner. The neurofeedback paradigm preserved the replay coincident with SWRs and did not alter which experiences tended to be represented during replay events. In the spatial memory task used, the increase in SWR rate did not alter task performance on a trial-by-trial basis, consistent with a role for replay in stabilizing memory of past experience rather than guiding future choice. The efficacy of the neurofeedback training demonstrates that subjects can use SWR-triggered feedback to modulate physiologically relevant patterns of hippocampal network activity and opens doors for future positive manipulation studies of SWRs and replay.

Disclosures: **A.K. Gillespie:** None. **D.A. Astudillo Maya:** None. **E.L. Denovellis:** None. **S. Desse:** None. **U. Eden:** None. **L.M. Frank:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.06

Topic: H.08. Learning and Memory

Support: Howard Hughes Medical Institute
Life Sciences Research Foundation

Title: Dynamic Synchronization between Hippocampal Spatial Representations and the Stepping Rhythm

Authors: ***A. JOSHI**[1], E. L. DENOVELLIS[1], A. MANKILI[1], Y. MENEKSEDAG[2], T. J. DAVIDSON[1], A. K. GILLESPIE[3], J. A. GUIDERA[3], D. ROUMIS[3], L. M. FRANK[1]; [1]UCSF, HHMI, San Francisco, CA; [2]Hacettepe Univ., Ankara, Turkey; [3]UCSF, San Francisco, CA

Abstract: The hippocampus is a mammalian brain structure that expresses spatial representations and is critical for navigation. Navigation in turn intricately depends on locomotion; however, current accounts suggest a dissociation between hippocampal spatial representations and the details of locomotor processes. Specifically, the hippocampus is thought to primarily represent higher-order cognitive and locomotor variables like position, speed, and direction of movement, while the limb movements that propel the animal are thought to be computed and represented primarily in subcortical circuits, including the spinal cord, brainstem, and cerebellum. Whether hippocampal representations are actually decoupled from the detailed structure of locomotor processes remains unknown. To address this question, we simultaneously monitored hippocampal spatial representations and ongoing limb movements underlying locomotion at fast timescales. We found that the forelimb stepping cycle in freely behaving rats is rhythmic and peaks at ~8 Hz during movement, matching the ~8 Hz organization of information processing in the hippocampus during locomotion. We also discovered precisely timed coordination between the time at which the forelimbs touch the ground ('plant' times of the stepping cycle) and the hippocampal representation of space. Notably, plant times coincide with hippocampal representations closest to the actual position of the animal, while in-between these plant times, the hippocampal representation progresses towards possible future locations. This synchronization was specifically detectable when animals approached upcoming spatial decisions. Taken together, our results reveal profound and dynamic coordination on a timescale of tens of milliseconds between central cognitive representations and peripheral motor processes. This coordination engages and disengages rapidly in association with cognitive demands and is well suited to support rapid information exchange between cognitive and sensory-motor circuits.

Disclosures: **A. joshi:** None. **E.L. Denovellis:** None. **A. Mankili:** None. **Y. Meneksedag:** None. **T.J. Davidson:** None. **A.K. Gillespie:** None. **J.A. Guidera:** None. **D. Roumis:** None. **L.M. Frank:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.07

Topic: H.08. Learning and Memory

Title: Investigating the contribution of hippocampal replay to value-based decision-making

Authors: *H. B S ESMERALDO[1,2], A. GILLESPIE[3], T. J. SEJNOWSKI[2], M. G. MATTAR[1]; [1]Cognitive Sci., UCSD, La Jolla, CA; [2]Salk Inst., La Jolla, CA; [3]Physiol., UCSF, San Francisco, CA

Abstract: Good decisions often rely on the ability to evaluate current options in light of past experience. We compare the value of available actions by mentally simulating outcomes associated with them. The sequential reactivation of hippocampal place cells when an animal is at rest, a phenomenon known as memory replay (Foster, 2017), is a possible neural correlate for such memory simulation process. Replay has been shown to be critically involved in memory-guided behavioral tasks (Jadhav et al, 2012), and the fact that replay often precedes behavioral choices invites the hypothesis that the simulation process guides subsequent choice. However, recent studies have shown either a weak or a negative correlation between replay and subsequent choice (Gillespie et al, 2021; Pfeiffer & Foster, 2013; Widloski & Foster, 2022; Carey & van der Meer, 2019), posing a challenge to the interpretation that replay encodes subsequent choice directly. Here, we consider an alternative hypothesis for the role of replay in memory-guided behavior. We propose that replay mediates a value-update mechanism: when an action is replayed (in the hippocampus), reward outcomes of recent experiences are recalled and used to update the estimated value of the replayed action (possibly by coordinated activity in other brain regions). To test this hypothesis, we investigated the effect of replay on choice on a recent dataset consisting of an 8-armed bandit task (Gillespie et al, 2021). We fit a reinforcement learning (Q-learning) model whereby action values are updated by both real experience and replay. Importantly, our model considers that the direction of the effect (positive or negative) of replay on value, and consequently on choice, depends on the animals' last experience with that choice. In other words, if a reward was received last time a specific action was taken, replaying that action increases the probability of repeating it in future. Conversely, if the choice did not result in reward, its replay decreases the probability of choosing it again. Furthermore, the degree of influence of reward outcomes (experienced or replayed) in choice values is modulated in the model by learning rate parameters. We found that the learning rate of value updates associated with replay corresponds to approximately one fifth of the learning rate of real experience. This substantial effect size suggests that replay can have an important impact on internal representations of value. Our results reconcile conflicting interpretations of the role of replay in

behavior by providing evidence that it serves to update the value associated with actions - performing an essential, but indirect, role in shaping memory-guided choices.

Disclosures: H. B S Esmeraldo: None. **A. Gillespie:** None. **T.J. Sejnowski:** None. **M.G. Mattar:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.08

Topic: H.08. Learning and Memory

Support: NIMH R01NS115233
NIMH 5F32MH123003

Title: Real-time decoding with state space models of neural activity

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Abstract: Decoding algorithms provide a powerful tool for understanding the firing patterns that underlie cognitive processes such as motor control, learning, and recall. When implemented in the context of a real-time system, decoders also make it possible to deliver feedback based on the representational content of ongoing neural activity. That in turn allows experimenters to test hypotheses about the role of that content in driving downstream activity patterns and behaviors. While multiple real-time systems have been developed, they are typically implemented in C++ and are locked to a specific data acquisition system, making them difficult to adapt to new experiments. Here we introduce RealtimeDecoder, a software package that implements online clusterless decoding using state space models, in an effort to address those challenges. Our parallelized system processes neural data with temporal resolution of 6 ms and median computational latency <5 ms for medium- to large-scale (32+ tetrodes) rodent hippocampus recordings without the need for spike sorting. The code is written in pure Python for accessibility and packaged with a GUI for visualization and experimental control. Additionally its implementation as a client module encourages adoption, as in principle it may be interfaced with any data streaming application. For proof-of-concept, we demonstrate its use in a live rat behavior experiment in which the decoder allowed closed loop neurofeedback based on decoding hippocampal spatial content. Our system can enable new experiments that define the role of hippocampal spatial content in memory processes and assist the development of hippocampal neurofeedback approaches for treatment of learning and memory disorders.

Disclosures: **J. Chu:** None. **M.E. Coulter:** None. **D.F. Liu:** None. **E.L. Denovellis:** None. **L.M. Frank:** None. **C. Kemere:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.09

Topic: H.08. Learning and Memory

Support: NINDS R01NS115233
NIMH R01MH117964

Title: Is ephaptic coupling driving submillisecond synchrony between neuron pairs in the hippocampus of behaving rats?

Authors: *A. D. STANKOV[1], N. R. KINSKY[2], A. AMARASINGHAM[1], U. KAYA[2], K. DIBA[2];
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Abstract: Submillisecond synchrony has been observed and characterized between interneurons in the rat hippocampus (Diba et al. 2014). Our recent analysis, using new data, reveals that this synchrony has an intricate temporal structure featuring rapid periods of both precise excitation and precise inhibition. One possibility suggested by studies in other brain regions is that such pairwise features, especially submillisecond inhibition, may be due to neuron-to-neuron ephaptic coupling. Using high-density recordings in the rat CA1 and CA3 regions, we examined the cross-correlograms of spike times between pairs of neurons, yielding synchrony profiles between putative sources and receivers. When we aligned the resulting cross-correlograms with the action potential waveforms of the source units, we found a remarkable alignment between these features. This effect can be observed both locally and at distances up to 200 or 400 microns in CA1 and CA3, and can be observed both uni- and bidirectionally. In some instances, the pairwise interactions also show rapid modulation between different types of neurons (i.e. interneurons and pyramidal cells). In the literature these attributes are not characteristic of electrical synapses but may instead support an ephaptic coupling hypothesis.

Disclosures: **A.D. Stankov:** None. **N.R. Kinsky:** None. **A. Amarasingham:** None. **U. Kaya:** None. **K. Diba:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.10

Topic: H.08. Learning and Memory

Support: NIH Grant UF1NS107667
Howard Huges Medical Institute (HHMI)
Laboratory Directed Research and Development Program of Lawrence Berkeley National Laboratory under US DOE Contract No. DE-AC02-05CH11231

Title: Towards a 4096 channel modular neural recording system

Authors: *J. HERMIZ[1], B. BENEDICT[2], K. E. BOUCHARD[3], M. S. BRAINARD[5], E. A. BUFFALO[8], A. COMRIE[6], J. GLEICK[9], C. GRACE[2], E. GRAF[9], J. A. GUIDERA[6], R. HAQUE[9], M. JUTRAS[8], M. L. KARLSSON[10], M. P. KARLSSON[10], A. KISELEVA[6], K. LEE[6], T. L. MASSEY[9], W. H. MEHAFFEY[7], A. B. NELSON[7], A. PAPADOPOULOU[2], J. W. RUECKEMANN[8], A. M. YORITA[9], J. ZHOU[9], X. ZHUANG[7], L. M. FRANK[11], P. DENES[4]; [1]Biol. Systems and Engin. Div., [2]Engin. Div., [3]Scientific Data Division; Biol. Systems and Engin. Div., [4]Lawrence Berkeley Natl. Lab., Berkeley, CA; [5]Ctr. For Integrative Neurosci., [6]Dept. of Physiol. and Psychiatry; Howard Hughes Med. Inst., [7]Univ. of California, San Francisco, San Francisco, CA; [8]Dept. of Physiol. and Biophysics, Univ. of Washington, Seattle, WA; [9]Materials Engin. Div., Lawrence Livermore Natl. Lab., Livermore, CA; [10]SpikeGadgets, San Francisco, CA; [11]Dept. of Physiol. and Psychiatry; Howard Hughes Med. Inst., UC San Francisco, San Francisco, CA

Abstract: Brain functions including perception, cognition, and action are implemented by millisecond-timescale patterns of neural activity distributed across multiple brain areas. Understanding these functions therefore requires the ability to measure these patterns. Current systems are limited in the number of channels, the allocation of channels to distributed structures, the ability to support a wide variety of neural probes, and their compatibility with freely moving animals, limiting their ability to make the required measurements. To overcome these challenges, we have developed many of the components required for a modular, 4096 channel neural recording system that can be used with a variety of flexible probe designs. The system begins with flexible probes, with dimensions provided by UCSF, and design and fabrication of the probes done at LLNL. These probes have been shown to yield stable single units across several months [Chung 2019]. The flexible probes will be bump-bonded to one side of a compact print circuit board (PCB), eliminating the need for connectors. A custom integrated circuit designed at LBNL called EChip is bump-bonded on the other side of the PCB and amplifies and digitizes full bandwidth (30 kHz) neural activity from 512 electrodes. The system supports up to eight EChips and will be housed in a compact headstage that rats can easily carry, yielding 4096 total channels of recording that can be flexibly distributed to meet experimental needs. The front-end system will be integrated within the SpikeGadgets ecosystem enabling user-friendly signal processing, visualization and data saving. Once fully functional, the entire system will be made commercially available through SpikeGadgets, ensuring widespread access to these powerful tools. Our end-to-end neural recording system will enable neuroscientists to probe the brain with cutting edge spatial and temporal resolution paving the way for new discoveries.

Disclosures: **J. Hermiz:** None. **B. Benedict:** None. **K.E. Bouchard:** None. **M.S. Brainard:** None. **E.A. Buffalo:** None. **A. Comrie:** None. **J. Gleick:** None. **C. Grace:** None. **E. Graf:** None. **J.A. Guidera:** None. **R. Haque:** None. **M. Jutras:** None. **M.L. Karlsson:** 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.; SpikeGadgets. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SpikeGadgets, NeuralThread. **M.P. Karlsson:** A. Employment/Salary (full or part-time):; SpikeGadgets. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SpikeGadgets, NeuralThread. **A. Kiseleva:** None. **K. Lee:** None. **T.L. Massey:** None. **W.H. Mehaffey:** None. **A.B. Nelson:** None. **A. Papadopoulou:** None. **J.W. Rueckemann:** None. **A.M. Yorita:** None. **J. Zhou:** None. **X. Zhuang:** None. **L.M. Frank:** F. Consulting Fees (e.g., advisory boards); NeuralThread. **P. Denes:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.11

Topic: H.08. Learning and Memory

Support: NIH R01NS39600
NIH U01MH114829

Title: Hippocampome.org v2.0 - a knowledge base enabling neuron-type specific spiking neural network simulations of hippocampal circuits

Authors: *D. W. WHEELER[1], A. O. KOMENDANTOV[1], C. TECUATL[1], J. D. KOPSICK[2], N. SUTTON[1], G. A. ASCOLI[1];
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Abstract: Hippocampome.org is an open-access knowledge base of the circuitry of the rodent hippocampal formation at the mesoscopic level of neuron types. Peer-reviewed literature is utilized to define 170 neuron types by their main neurotransmitter, glutamate or GABA, and their patterns of axonal and dendritic presence across the parcels and subregions of the hippocampal formation: dentate gyrus, CA3, CA2, CA1, subiculum, and entorhinal cortex. For each neuron type, Hippocampome.org v2.0 integrates knowledge about molecular expression, intrinsic membrane biophysics, quantitative firing-patterns, parameters of single- and multi-compartmental Izhikevich models, estimated population size, and the *in-vivo* phase locking of neuronal firing to theta oscillations and sharp-wave ripples. Between pairs of neuron types, information is available concerning known and potential connectivity, statistical estimations of the connection probabilities, and the amplitude, kinetics, and short-term plasticity of synaptic signals. Also included at Hippocampome.org v2.0 is the Cognome, a literature review and

knowledge base of spiking neural circuit and network simulations of the hippocampal formation. All data contained herein are cross correlated with each other and linked to extracted publication excerpts and/or illustrations. We are pursuing the use of this collated knowledge in a real-scale spiking-neural-network computational simulation of the complete hippocampal formation, starting with subregion CA3. In addition, we endeavor to expand Hippocampome.org by continually data mining the literature for new neuron types and properties, while cross-linking and integrating new with existing knowledge.

Disclosures: D.W. Wheeler: None. **A.O. Komendantov:** None. **C. Tecuatl:** None. **J.D. Kopsick:** None. **N. Sutton:** None. **G.A. Ascoli:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.12

Topic: H.08. Learning and Memory

Support: LCF/PR/HR21/52410030
FPU17/03268

Title: Using convolutional neural networks to detect and interpret sharp-wave ripples

Authors: *A. NAVAS-OLIVE[1], R. AMADUCCI[2], T. JURADO-PARRAS[1], E. R. SEBASTIAN[1], L. MENENDEZ DE LA PRIDA[1];
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Abstract: Sharp-wave ripples (SWR) are high frequency events recorded in the local field potential (LFP) of the hippocampus of rodents and humans. During SWRs, ensembles of neurons fire sequencially to reactivate memory traces of previously encoded experience. SWR-related activity is crucial to understand memory, and real-time interventions can influence hippocampal-dependent cognitive function, enabling a better understanding of underlying mechanisms. However, existing SWR identification tools mostly rely on using spectral methods, which remain suboptimal.
Here, we introduce a deep 1D convolutional neural network (CNN) trained over high-density LFP recordings to detect hippocampal SWR. The adapted architecture included seven convolutional layers composed of different kernels in increasing hierarchical complexity and one output layer delivering the probability of an occurring SWR. During training, each kernel specializes in detecting the particular LFP features that maximizes detection performance. The trained CNN model was applied to several datasets and new types of recordings (including linear arrays, high-density probes, ultradense Neuropixels and performed similar to experts, as well as on open databases that were not used for training), species (mice and rats), and hippocampal regions (all CA1 layers from dorsal and ventral).
By saturating the operation of different kernels, we examine and interpret their optimal

behaviour associated to the ground truth versus a random selection. We also evaluate false positive events, finding less artifacts than spectral methods. Finally, we show how a custom plug-in for such Open Ephys, a widely used open system, significantly outperforms filters in real-time SWRs detection. We conclude with discussion on how this approach can be used as a discovery tool for better understanding the dynamics of SWRs.

Disclosures: **A. Navas-Olive:** None. **R. Amaducci:** None. **T. Jurado-Parras:** None. **E.R. Sebastian:** None. **L. Menendez de la Prida:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.13

Topic: H.08. Learning and Memory

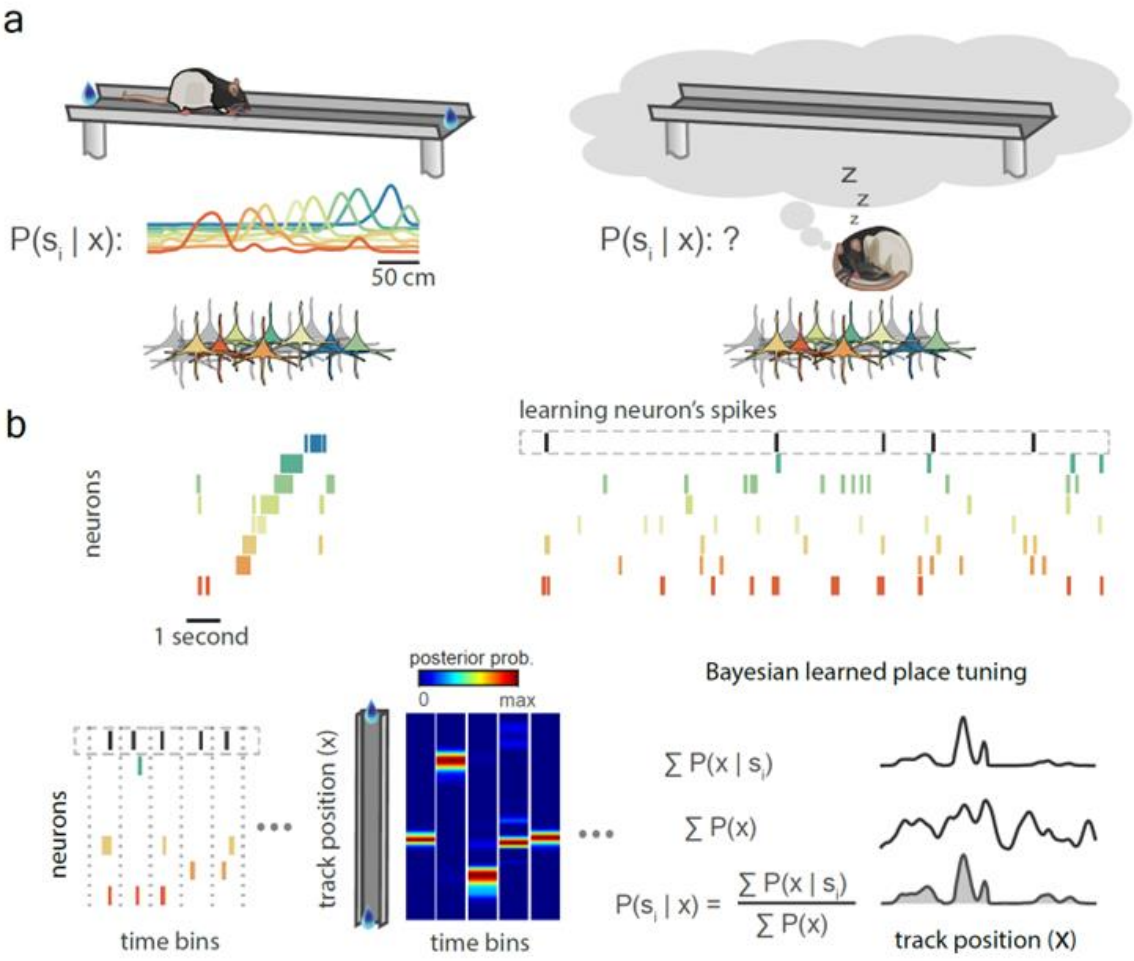
Support: NIMH R01MH117964
NINDS R01NS115233

Title: Bayesian learning of hippocampal place fields during sleep

Authors: *K. MABOUDI[1,2], B. K. GIRI[2], H. MIYAWAKI[3], C. KEMERE[4], K. DIBA[2]; [1]Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI; [2]Anesthesiol., Univ. of Michigan, Ann Arbor, MI; [3]Dept. of Physiol., Osaka City Univ., Osaka, Japan; [4]Electrical and Computer Engin., Rice Univ., Houston, TX

Abstract: Hippocampal neurons fire selectively when an animal enters specific locations (place-fields; PFs) within an environment and collectively constitute a map of this space (e.g., linear track in panel a). These neurons have been reported to replay trajectories through the environment during sleep following exposure, a phenomenon that has been proposed to play an important role in memory formation. To characterize replay trajectories, the spike patterns of neuronal populations are typically decoded using Bayesian methods based on each neuron's spatial tuning curve: P(s|x), the probability of spiking given position (panel a). However, it is unclear whether neurons can be assumed to encode the same locations when the animal is asleep. To examine this conjecture, we devised a method to calculate the spatial tuning of neurons using Bayesian learning—to learn each neuron's spatial tuning based on the posterior probability of position determined from the other neurons (panel b). We called these inferred place fields "learned tunings" (LTs) and found that they are stable during slow-wave sleep following track exposure and correlated strongly with the track PFs. In contrast, during sleep prior to the track most LTs were unstable and showed poor fidelity to their future PFs. We also examined whether LTs can be learned during rapid eye movement (REM) sleep, but these REM LTs showed poor correlations with the PFs, indicating that animals may not cognitively inhabit the track during REM sleep. Finally, we found that sleep LTs provided excellent predictors of the preferred locations of PFs upon re-exposure to the same track, indicating that sleep firing patterns are

consistent with PF stabilization. Overall, our novel approach supports the use of Bayesian decoding in post, but not pre-, slow-wave sleep and indicates that co-activations in sleep play an important role in determining the spatial map across exposures to an environment.



Disclosures: **K. Maboudi:** None. **B.K. Giri:** None. **H. Miyawaki:** None. **C. Kemere:** None. **K. Diba:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.14

Topic: H.08. Learning and Memory

Support: NIMH R01NS115233

Title: An Extension of Poisson Gaussian-Process Latent Variable Model for Unsupervised Neural Decoding of Hippocampal Spike Trains

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Abstract: Hippocampal neural activity exhibits both a precise temporal code reflecting an animal's position in an environment as well as a large-scale contextual code reflecting distinct maps for different environments. While contextual place codes can be extracted from correlated neural firing rates, to elucidate the more complex memory codes which the hippocampus supports, unsupervised methods for extracting context-dependent ensemble firing patterns are required. The Poisson Gaussian-process latent variable model (P-GPLVM) is a probabilistic, nonlinear, and dynamic dimensionality reduction approach that infers temporally smooth low-dimensional latent neural trajectories and smooth, non-parametric tuning curves from spike trains without referring to external variables [1]. However, the original model lacks an approach for projecting new input into the learned latent space, limiting its utility for decoding new neural data, especially during the time-compressed sequential reactivation of hippocampal neuronal ensembles during population burst events (PBEs) within sharp-wave ripples, which don't have behavioral variables as reference. Here, we extend the P-GPLVM framework to enable the projection of new neural data constrained by the learned smoothness parameters and tuning curves. We also describe a principled approach for projecting PBE data and providing metrics for assessing the projection. We apply our methods to hippocampal neural activity recorded from a rat running back and forth on a linear track. We simulate remapping in another context by randomly permuting the cell identities during the second half of the session. Trained from neural data during running, the model clusters data points from the two contexts into two separate manifolds in the latent space, each with a bifurcating shape representing the two running directions. The animal's position is encoded smoothly along each manifold. When projecting new neural data during behavior and PBEs into the learned latent space, neural trajectories lay accordingly and smoothly on the manifold, thereby allowing the external variables to be derived. Our results indicate that this extension of P-GPLVM is capable of revealing neural trajectory evolution, disentangling neural patterns between different contexts, and decoding external variables (i.e. animal position, running direction, context) from neural activity both during behavior and during PBEs in an unsupervised manner. [1] Anqi Wu, et. al. *NeurIPS*, 30, 2017.

Disclosures: **D. Luo:** None. **K. Diba:** None. **C. Kemere:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.15

Topic: H.08. Learning and Memory

Support: NINDS R01NS115233
NIMH R01MH117964

Title: Spike3d: a novel 3d visualization and processing pipeline for neural data

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Abstract: Technological breakthroughs have stimulated a boom in neural data recordings, allowing an unprecedented opportunity to decode neural activity. For example, within a given environment, the conjunction of hippocampal cells form "placemaps" that form and evolve over time. The activities of these hippocampal neurons can be used to decode an animal's physical location in space. In rodents, these placemaps are also rehearsed during sleep, suggesting a mechanism by which memories are refined for long-term storage, often referred to as "memory consolidation." However, many presumptive rehearsals prove elusive for decoding, limiting our understanding of this model system. To better understand the complexities of neuronal spike trains during rehearsal events, a tool for visualizing their activities and temporal evolution is essential. We recently developed Spike3D, a software platform that translates high-dimensional neural datasets to a three-dimensional visualization. Spike3D combines real-time processing via a visual programming language with on-the-fly 3D visualizations for data exploration. This enables expert-in-the-loop processing of neural data, allowing faster hypothesis testing in new and extant datasets. Specifically, Spike3D visualizes time-evolving placemaps by building-up and displaying occupancy (the proportion of time the animal spends in each portion of the environment), firing maps (the number of spikes per location bin that have accumulated), and placemaps (occupancy-weighted firing maps) in real or transformed time. This software runs on commodity off-the-shelf hardware and is accelerated by the presence of a discrete GPU. It is written in Python, an easily accessible language, without recompilation during runtime, making it extensible, and compatible across platforms and operating systems.

Available at: https://doi.org/10.5281/zenodo.6647482

Disclosures: P.J. Hale: None. **K. Diba:** None.

Poster

742. Hippocampus and Spatial Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 742.16

Topic: H.08. Learning and Memory

Title: Spyglass: a data analysis framework for reproducible and shareable neuroscience research

Authors: *K. LEE[1], E. L. DENOVELLIS[2], R. LY[3], J. MAGLAND[4], J. SOULES[4], A. COMRIE[1], J. A. GUIDERA[1], R. NEVERS[1], D. GRAMLING[1], P. ADENEKAN[1], J. BAK[1], E. MONROE[1], A. TRITT[3], O. RUEBEL[3], T. T. NGUYEN[5], D. YATSENKO[5], J. CHU[6], C. KEMERE[6], S. GARCIA[7], A. P. BUCCINO[8], E. AERY JONES[9], L. M. GIOCOMO[9], L. M. FRANK[2];
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Abstract: Although the technologies for recording and manipulating neural activity are advancing rapidly, the process of deriving scientific insights from neural data remains stagnant. In many labs, data storage and analysis are still done in an idiosyncratic fashion, with little regard for how data can be shared or analyses reproduced. As a result, it is difficult to reuse data for further insights or inspect the analysis process to validate scientific conclusions. To make progress toward solving these problems, we have built *spyglass*, a software framework for neural data analysis. By combining multiple open-source tools into a single coherent workflow, *spyglass* aims to be a full-fledged solution to storing raw data, analyzing it through reproducible pipelines, visualizing the results, and sharing them with collaborators. Analysis in *spyglass* begins with files containing both the raw data and the experimental metadata in the NWB 2.0 format. This ensures that *spyglass* pipelines can be applied to any NWB file, regardless of its origins. The metadata from these files, along with easily accessible pointers to the raw data, are then stored in a relational database managed by *DataJoint*. Subsequent analyses take advantage of domain-specific open source tools, such as *ghostipy* for spectral analysis and *SpikeInterface* for spike sorting. All parameters are stored in the associated *DataJoint* pipelines, ensuring transparency and reproducibility. As a result, we are able to share the entire analysis process rather than just the end product. In addition, we introduce novel software tools for sharing the results of the full set of intermediate analyses associated with a scientific result, including a web app to visualize and curate spike sorting. We describe the principles behind the design of the analysis pipelines and the integration of these tools. We also demonstrate the versatility of the spyglass framework by putting data from multiple labs through our pipeline to generate reproducible scientific results. We hope *spyglass* will be widely adopted by the community and promote data accessibility, reproducibility, and collaboration across research groups.

Disclosures: **K. Lee:** None. **E.L. Denovellis:** None. **R. Ly:** None. **J. Magland:** None. **J. Soules:** None. **A. Comrie:** None. **J.A. Guidera:** None. **R. Nevers:** None. **D. Gramling:** None. **P. Adenekan:** None. **J. Bak:** None. **E. Monroe:** None. **A. Tritt:** None. **O. Ruebel:** None. **T.T. Nguyen:** None. **D. Yatsenko:** None. **J. Chu:** None. **C. Kemere:** None. **S. Garcia:** None. **A.P. Buccino:** None. **E. Aery Jones:** None. **L.M. Giocomo:** None. **L.M. Frank:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.01

Topic: H.08. Learning and Memory

Support: NIH R01NS054281
NSF OAC 2018936

Title: Effects of excitability type on the synchronization properties of recurrent networks of inhibitory neurons

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Abstract: Previously (Brunel and Hansel 2006), the effect of noise on the synchronization properties of recurrent networks of inhibitory neurons was described in the parameter plane of noise versus connection strength with the average firing rate of individual neurons held constant at 30 Hz. Four firing modes were identified. At low noise levels and connection strength there is a regular synchronous mode. As the noise is increased at low connection strengths, asynchrony with neurons firing regularly emerges, then at even higher noise levels, asynchrony with neurons firing irregularly emerges. For high connection strengths, as the noise is increased there is a continuous transition from regular synchrony to a population oscillation in which neurons fire irregularly. Both regular (coupled oscillator) and irregular (stochastic population oscillator) synchronous modes arise from the asynchronous stationary state via Hopf bifurcation. Here we reproduce this analysis in generic (Izhikevich) models with Type 1 and Type 2 excitability. Networks composed of Type 2 neurons have not been previously characterized with respect to a stochastic population oscillation. We find that the parameter space and stability boundaries for Type 2 to be similar to that previously observed for Type 1. In coupled oscillator regime with low noise, each neuron participates in every cycle of the oscillation. In this regime, the average current is subthreshold at high connection strengths, but if you only consider the mean current during the active phase, you recover the definition of a suprathreshold, mean-driven regime for coupled oscillators. The coupled oscillator regime at high connection strength begins to exhibit cycle skipping as the noise is increased. As the noise is further increased, participation as quantified by the spike participation coefficient (SPC) gradually decreases, as neurons skip more and more cycles on average. The peaks in the ISI histogram corresponding to integer numbers of cycles skipped eventually coalesce into an approximately exponential distribution, with a refractory period. In addition, the tendency to emit doublets is strong in stochastic modes in which the trough of the AHP is near spike threshold, for every excitability type. Thus, the presence of spike doublets is an indicator of a highly stochastic regime, which could be synchronous or asynchronous.

Disclosures: R. Baravalle: None. **C.C. Canavier:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.02

Topic: H.08. Learning and Memory

Support: NINDS 1R01NS110501
DARPA grants N66001-17-C-4012 and N66001-19-C-4020

Title: Contrasting to visual landmarks, navigating a virtual reality with exclusively acoustic landmarks may not be sufficient to form place cell map

Authors: *S. GAO[1], C. KEMERE[1], M. J. MCGINLEY[2];
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Abstract: For decades, many neuroscientists have actively been uncovering how our brain recognizes the environment around us during spatial navigation. Traditionally, spatial navigation in animal models in virtual reality (VR) settings has been studied primarily using visual cues. There has recently been interest in exploring other sensory cues such as odor and sound. However, few studies have investigated VR navigation in environments promoting interactions between the auditory system and hippocampus. Here we present a novel virtual reality system defined by sound landmarks that are amplitude modulated based on the animal's position. Furthermore, we also developed a visual VR system that is synchronized with our previous sound VR.
Our sound VR environment track is 400 cm long and it consists of 4 sound stimulus zones separated by 4 no stimulus (background noise) zones with a constant tone cloud playing throughout the track, each zone covers 40 cm. Each sound is amplitude modulated directly with the animal's position using our VR system so that the amplitude is the lowest at the start and end of the sound zone and peaks at the middle of the zone. Animals are trained to lick for reward on each lap, and are rewarded with sucrose water in the reward zone. We report behavioral evidence that mice can learn to navigate in our sound VR task. Namely, we observed anticipatory licking and slowing preceding the reward region. Similarly, in the visual VR environment, we replaced the 4 sound stimuli with 4 different types of visual stimuli in the same location to preserve the spatial information for both types of VR environments. We used modified UCLA Miniscope to chronically image the CA1 area of head-fixed mice performing a navigation task collecting water reward using 3 different types of VR, namely, sound only VR; visual only VR; and combined sound and simple visual VR. We asked whether visual cues are necessary to engage a large population of stable place cells during navigation. We did not observe significant lap-by-lap stable place cells in the sound only VR, though we observed stable place cells in the visual only VR. With our combined visual and sound VR, and we are aiming to understand whether the inclusion of visual motion cues facilitate the formation of stable place cells defined by acoustic landmarks. We envision that combining our behavior paradigm with our novel

sound and visual VR system has the potential to provide new insight on how multiple neural systems interact with each other and respond to stimuli using spatial aspects of sound in an environment.

Disclosures: S. Gao: None. **C. Kemere:** None. **M.J. McGinley:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.03

Topic: H.08. Learning and Memory

Support: NRF 2017M3C7A1029661
NRF 2018R1A4A1025616
NRF 2019R1A2C2088799
the BK21 FOUR by the Ministry of Education and the NRF

Title: Adding visual noise to a familiar virtual environment divides the neural population into global- and rate-remapping subpopulations in CA1, but not in CA3

Authors: *J. SHIN[1], H.-W. LEE[2], S.-W. JIN[1], I. LEE[1];
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Abstract: It has been demonstrated that the CA3 of the hippocampus plays a crucial role in forming discrete representations of modified environments presumably through pattern separation and completion. In contrast, the neural population in the CA1 hardly shows such nonlinearity compared to the CA3, which is puzzling because the CA1 is the immediate downstream structure of the CA3. We tested whether adding visual noise to a familiar virtual environment would allow us to observe some CA3-like nonlinearity in the CA1 when representing the modified environment. In computational neuroscience, adding noise is a critical testing condition when simulating a network's capability of processing modified inputs, but it is almost impossible to test in a real environment. Thus, we used virtual reality (VR) apparatus to parametrically manipulate the environment by adding visual noise (i.e., virtual fog). We recorded single units with tetrodes simultaneously from the CA1 and CA3 in rats (n=8). The head-fixed rats on a cylindrical treadmill navigated the VR environment projected through three surrounding LCD monitors. Rats were required to move forward along a 3m-linear track to obtain water rewards at two randomized sites per trial (20 μL/site). After allowing the rat to experience the familiar environment, a fog block started. In the fog block, we introduced different levels of 'foggy' conditions (e.g., 0% as a control in the post-fog block; 15%; 30%) by adding virtual fog to the familiar environment. As a result, the place-cell population of the CA1 split into two classes, one showing global remapping and the other exhibiting fog density-dependent rate remapping. By contrast, in the CA3, most place cells showed rate remapping in the fog

conditions. Interestingly, those CA1 place cells that exhibited global remapping in the fog block maintained the changed firing patterns even when reexperiencing the original fog-free environment in the fog block, suggesting that the network was under the influence of a top-down or internal contextual shift. If one considers the rate-remapping class of place cells as pattern-completing cells and the global-remapping class as pattern-separating cells, our results suggest that the neural population in the CA1 can manifest both pattern-separating and pattern-completing classes of neurons in our virtual environment, and there is a possibility that the latter class is inherited from the dominant pattern-completion network in the CA3.

Disclosures: **J. Shin:** None. **H. Lee:** None. **S. Jin:** None. **I. Lee:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.04

Topic: H.08. Learning and Memory

Support: DFG SFB 779

Title: Preferential involvement of population spiking in proximal CA3 and distal CA1 and enhanced theta oscillation in non-spatial recognition memory

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Abstract: Evidence shows that neural firing and theta coherence are crucial for spatial navigation within either the hippocampal subfield CA1 or CA3. How the cross-regional coordination of population spiking and theta oscillations between CA1 and CA3 supports cognitive processes has however been very little investigated. Recent immediate early gene imaging studies indicate a proximodistal functional segregation of the hippocampal CA1 and CA3 subfields and suggest the existence of distinct spatial and non-spatial subnetworks segregated along this axis: the distal CA3-proximal CA1 (both close to CA2) subnetwork and the proximal CA3 (proxCA3, close to the dentate gyrus)-distal CA1 (distCA1, close to the subiculum) subnetwork, respectively (Nakamura et. al., *J. Neurosci*., 2013; Beer and Vavra et. al. *Plos Biol*., 2018). Some electrophysiology studies have suggested a preferential recruitment of distal CA3 or proximal CA1 in spatial navigation. However, *in-vivo* evidence for a preferential recruitment of the counterpart subnetwork, i.e proxCA3 and distCA1, in non-spatial memory is not yet available. Furthermore, whether proxCA3 and distCA1 interact with each other to form a functional coordinated network is still unclear. Here we performed *in-vivo* simultaneous electrophysiological recording of CA1 and CA3 along the whole proximodistal axis as animals performed a rat version of a standard high memory demand human task. In this task, the primary

sense of the rats was used and the memory for odors presented during a study phase was tested at retrieval after a delay by presenting the same odors ('repeated' odors) or other ('non-repeated') odors one at a time and memory performance evaluated. We found that only the population firing of neurons recorded in proxCA3 and distCA1 (the 'non-spatial' subnetwork), but not that of distCA3 and proxCA1 (the 'spatial' subnetwork), could account for memory performance and the support vector machine performance with all hippocampal neurons recorded. Moreover, neurons contributing most to this performance, termed 'effective neurons', were concentrated in proxCA3 and distCA1. In addition, we report that theta oscillations' amplitudes (i.e. theta power) are enhanced in distCA1 when compared to proxCA1, and only the phase information of CA3 neurons using distCA1 theta as reference can predict memory performance trial-by-trial. These results confirm *in-vivo* the hypothesis of a preferential recruitment of proxCA3 and distCA1 during non-spatial memory retrieval and suggest that the coordination of CA3 spikes and distCA1 theta might be one of the important underlying mechanisms supporting recognition memory.

Disclosures: S. Ku: None. **E. Atucha:** None. **N. Alavi:** None. **M. Yoshida:** None. **J.L. Csicsvari:** None. **M. Sauvage:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.05

Topic: H.08. Learning and Memory

Support: 1U19NS107616-01

Title: Oxytocin-modulated ion channel ensemble controls depolarization, integration and burst firing in CA2 pyramidal neurons

Authors: *J. LIU[1], K. EYRING[1], E. KOSTENIS[3], G. KÖNIG[3], R. TSIEN[2];
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Abstract: Oxytocin (OXT) and oxytocin receptor (OXTR)-mediated signaling control excitability, firing patterns, and plasticity of hippocampal CA2 pyramidal neurons, which are pivotal in generation of brain oscillations and social memory. Nonetheless, the ionic mechanisms underlying OXTR-induced effects in CA2 neurons are not fully understood. Using slice physiology in a reporter mouse line and interleaved current- and voltage-clamp experiments, we systematically identified the ion channels modulated by OXT signaling in CA2 pyramidal cells (PYRs) and explored how changes in channel conductance support altered electrical activity. Activation of OXTRs inhibits an outward potassium current mediated by inward rectifier potassium channels (I_{Kir}) and thus favoring membrane depolarization. Concomitantly, OXT signaling also diminishes inward current mediated by hyperpolarization-activated cyclic-

nucleotide-gated channels (I_h), providing a hyperpolarizing drive. The combined reduction in both I_{Kir} and I_h synergistically elevate the membrane resistance and favor dendritic integration while the membrane potential is restrained from quickly depolarizing from rest. As a result, the responsiveness of CA2 PYRs to synaptic inputs is highly sharpened during OXTR activation. Unexpectedly, OXTR signaling also strongly enhances a tetrodotoxin-resistant, voltage-gated sodium current that helps drive the membrane potential to spike threshold and thus promote rhythmic firing. This novel array of OXTR-stimulated ionic mechanisms operates in close coordination and underpins OXT-induced burst firing, a key step in CA2 PYRs' contribution to hippocampal information processing and broader influence on brain circuitry. Our study deepens our understanding of underpinnings of OXT-promoted social memory and general neuropeptidergic control of cognitive states.

Disclosures: J. liu: None. **K. Eyring:** None. **E. KostEnis:** None. **G. König:** None. **R. Tsien:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.06

Topic: H.08. Learning and Memory

Title: Fear memory engrams during reconsolidation and extinction

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Abstract: Memory storage processes and retrieval require specific populations of neurons that show increased neuronal activity during memory formation. The representation of a more stable memory in the brain has been referred to as memory engram or memory trace and discovering if a memory engram stays the same after reconsolidation or extinction of memories remains elusive.Recent studies have been able to manipulate engram cells of specific memories and examine the effect of their activation or inactivation. One of the recent technologies utilizes immediate early genes to drive gene expression in activated cells. One of the recent technologies utilizes immediate early genes to drive gene expression in activated cells. Two structures stand out in the mnemonic processes, the Basolateral amygdala (BLA) and dorsal Hippocampus (HPC). Thus, using Fos-LacZ transgenic rats, we aimed to characterize the fear memory engram and differentiate the extinction, reconsolidation, and consolidation engrams. With this technique, we can silence neurons that express the immediate early gene c-Fos at the moment of the infusion of the drug Daun02. Here, we tested the role of the BLA engram in the consolidation of an aversive memory and demonstrated that silencing the neurons active during consolidation caused an impairment of the memory. We then tested it during the reconsolidation and demonstrated that silencing the neurons active during retrieval caused an impairment of the memory trace. However, silencing BLA neurons active during an extinction memory recall did

not disrupt the original extinction memory. Then, we investigated HPC engrams during reconsolidation and extinction and observed that silencing the neurons active during both of the memory phases did not disrupt memory. With those findings, we can conclude that there is a difference between both structures and memory processes, meaning that only the engram of reconsolidation at BLA remains the same as what was first consolidated, while the extinction engram at BLA and from both memory processes at HPC are more dynamic.

Disclosures: J. Griebler Luft: None. **L. de Oliveira Alvares:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.07

Topic: H.08. Learning and Memory

Support: NIA 1RF1AG054654

Title: Impact of hippocampal Luteinizing hormone receptor knockdown on cognition and neuroplasticity

Authors: *H. HARDEGREE[1], L. LABRADOR[2], M. E. MEY[3], A. OWENS[2], L. WAGNER[2], G. CASADESUS SMITH[1,2];
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Abstract: The luteinizing hormone's receptor (LHR) has been identified within the central nervous system (CNS) in cognition associated areas such as the hippocampus. Previous studies have shown that activation of LHR modulates learning and memory, structural plasticity and hippocampal neurogenesis. However, how loss of LHR impacts hippocampal function and plasticity is not known. To address this question, we delivered CRISPR/Cas9 guides against Exon 11 of the LHR via AAV2/8, bilaterally to the hippocampus, to knockdown the extracellular domain of the receptor in this region. Cognition was assessed using the Morris Water Maze task. Hippocampal and SVZ neurogenesis were determined using BRDU and co-localization with CNS cell markers to address proliferation and differentiation changes. Our preliminary data show functional differences across groups that may be, at least partially, related to neurogenesis changes. This work further deepens our understanding of the role of gonadotropin hormones in CNS function and plasticity.

Disclosures: H. Hardegree: None. **L. Labrador:** None. **M.E. Mey:** None. **A. Owens:** None. **L. Wagner:** None. **G. Casadesus Smith:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.08

Topic: H.08. Learning and Memory

Support: JST ERATO (JPMJER1801)
the Institute for AI and Beyond of the University of Tokyo
JSPS Grants-in-Aid for Scientific Research (18H05525, 20K15926)

Title: Developmental changes in membrane potential responses of CA1 pyramidal neurons to sharp-wave ripples

Authors: *A. NOGUCHI[1], Y. IKEGAYA[1,2];
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Abstract: Hippocampal ripples are high frequency oscillations (100-250 Hz) associated with synchronous population activity in the CA1 subregion, playing a prominent role in memory consolidation and navigational planning (Buzsaki, 2015). During ripples, spatiotemporally organized spikes of CA1 pyramidal cells construct a variety of sequential activity that replay multineuronal spike series that are activated during behavior. The spike sequences during hippocampal ripples are regulated, at least in part, by the coordinated activity of inhibitory interneurons, which generate pre- and post-ripple hyperpolarizations in pyramidal cells (English et al., 2014; Hulse et al., 2016; Noguchi et al., 2022). Hippocampal ripples emerge during the third postnatal week (Buhl and Buzsaki, 2005), whereas interneurons mature anatomically and functionally throughout the first four postnatal weeks (Sauer and Bartos, 2011). To our knowledge, however, no study has described ripple-associated dynamics of the membrane potentials of CA1 pyramidal cells during postnatal development. Here, we conducted *in vivo* whole-cell patch-clamp recordings from pyramidal neurons simultaneously with local field potential recordings in the dorsal hippocampal CA1 area from postnatal day 16-to-40 mice under urethane anesthesia. CA1 pyramidal cells showed depolarizations during ripples, but not obvious pre- or post-ripple hyperpolarizations in the third postnatal week, and during the following week, both pre- and post-ripple hyperpolarizations became apparent. Consistently, the voltage-clamp recordings showed that inhibitory and excitatory postsynaptic conductances during the third postnatal week were significantly smaller and larger than those recorded from more adult mice, respectively. These results suggest that inhibitory controls of ripple-associated activity of pyramidal cells continue maturation with an increased need for precise controls of spike times in order to represent behavioral experiences as animals start to actively explore their environments after the end of the second postnatal week.

Disclosures: A. Noguchi: None. **Y. Ikegaya:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.09

Topic: H.08. Learning and Memory

Support: N00014-18-1-2114
N00014-21-1-2940

Title: Theta Initiated Self-Sustained Activity in Hippocampal Field CA3

Authors: *B. PRUESS[1], B. G. GUNN[1], G. LYNCH[2];
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Abstract: Episodic memory formation often involves the encoding of associated cues that are widely separated in time (tens of seconds to minutes). While it is well established how the hippocampus associates cues occurring closely together in time (milliseconds to seconds), the mechanisms for associating and ordering temporally distant cues in memory are poorly understood. Field CA3 generates an extremely dense recurrent collateral system that has been proposed to generate self-sustained, prolonged spiking – or reverberation – following brief activation. Theorists including Hebb have suggested that such networks could promote associations between temporally separate cues. It has been previously shown that such prolonged reverberating activity can be sustained for minutes in acute hippocampal slices; in the present work we demonstrate this result *in vivo*. Specifically, we tested if a two-second long train of theta frequency (5Hz) stimulation applied to stratum radiatum can elicit activity in CA3 that continues after termination of the input. In anesthetized 2-month-old male Sprague Dawley rats (n = 9), single pulses were delivered to the terminal field (stratum radiatum) in one hemisphere and after a 6ms delay were followed by a robust fEPSP dipole on the other side. We recorded unit activity in the pyramidal cell layer (positive end of the dipole) for 4 minutes and then applied a 2s theta train to the contralateral CA3 and recorded for 4 minutes. Locally developed software was used to analyze spike frequency and patterning after removal of 3-5Hz Sharp Waves. Action potentials accompanied the fEPSPs during the train and the cell firing remained >20% above the baseline rate for up to 4 minutes afterwards (n=6 out of 9, $p<0.001$, paired t-test). The within-train firing rate was a predictor of firing rate in the 4-minute period after stimulation ($R^2 = 0.93$). There was no evidence for epileptiform activity. CA3 receives a sizeable cholinergic input from the medial septum/ diagonal band complex. Multiple studies suggest that modulation of cholinergic transmission with the acetylcholinesterase (AChE) inhibitor donepezil (Aricept) has a positive effect on hippocampus and cognition in prodromal AD patients. To further investigate the properties of this network, a peripheral injection of the AChE inhibitor physostigmine was found to cause a pronounced increase in baseline firing in CA3. In summary, field CA3 has the capacity to generate self-sustained firing for a surprisingly long period after a brief input, an effect that is plausibly related to the role played by the hippocampus in forming associations across time.

Disclosures: B. Pruess: None. **B.G. Gunn:** None. **G. Lynch:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.10

Topic: H.08. Learning and Memory

Support: NSERC DG 315827

Title: Late postnatal juvenile stress and its impact on adult social memory and hippocampus CA2 function

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Abstract: Social memory involves social recognition: the ability to discriminate between two or more conspecifics. By discerning one conspecific from another, animals behave according to the social context that lead to favourable outcomes. The CA2 region of the hippocampus plays a crucial role in social memory as inhibition of the area results in social memory impairments. Early life stress (ELS) can lead to social memory impairments and is prevalent in conditions with symptoms of social memory deficits such as schizophrenia. In this study, we aimed to determine if impairments in social memory observed after juvenile stress were due to malfunction within the CA2 region of the hippocampus. Juvenile, Long-Evans rats were exposed to an adult male for 5 min, once per day from P19-21. These same animals (P60 or P61) were then tested for social memory, defined as increased interactions towards a novel juvenile rat in contrast to a previously-encountered juvenile. Brain tissue was collected 90 minutes post-test to observe c-Fos labeling within the CA2 using nickel-enhanced 3,3'-Diaminobenzidine (DAB) immunohistochemistry. Adult rats that experienced juvenile stress did not differ from control groups in sociability; however, they were unable to discriminate between the familiar and novel conspecifics. Within the female group, there was a wider disparity between controls and stressed rats with respect to social memory suggesting females not only possessed superior social memory but were also more sensitive to social memory deficits due to early life stress. These data indicate that the late post-natal period reflects a time of widespread neural connectivity changes underlying the later emergence of various cognitive functions.

Disclosures: T. Maletta: None. **M. Palummieri:** None. **M. Holahan:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.11

Topic: H.08. Learning and Memory

Support: MEXT Grant-in-Aid for Scientific Research 21H02585

Title: The effects of hibernation-like state on memory

Authors: *Y.-J. LIN[1], A. TAKAHASHI[1], B. M. HUMBEL[1], T. SAKURAI[2], K. Z. TANAKA[1]; [1]OIST, Okinawa Inst. of Sci. and Technol., Okinawa, Japan; [2]Univ. of Tsukuba, Univ. of Tsukuba, Tsukuba, Japan

Abstract: Hibernation is a physiological condition characterized by low body temperature and metabolism to conserve energy in harsh environments. In wild-hibernating animals, the hippocampus undergoes significant rewiring, including changes in dendritic branching and spine densities (Popov et al., 1992). Interestingly, behavioral studies showed cognitive enhancements despite the drastic changes in neuronal morphology during hibernation (Weltzin et al., 2006) and memories obtained before hibernation retained after arousal from hibernation (Clemens et al., 2009). However, the neural mechanism that supports the memory during hibernation remains unclear. To address this fundamental problem, we used a transgenic mouse line developed by Takahashi and colleagues to investigate the effects of a hibernation-like state. By chemogenetically activating the thermoregulating QRFP-producing neurons (Q neurons) in the hypothalamus, we induced a Q-neuron-induced hypothermia and hypometabolism (QIH) state (Takahashi et al., 2020), which captures features that simulate natural hibernation, such as decreased heart rate, respiratory rate, locomotor activity, and food intake. Using the Qrfp-iCre/c-Fos-tTA double transgenic mice bred in our lab, we can investigate the effects of the QIH on memories, cognitive abilities, and morphology in a well-controlled experimental setting as well as label memory engram neurons at desired time points with the c-Fos-tTA (TetTag) system. We first examined the retention of hippocampus-dependent contextual fear memory. Our preliminary data suggested that contextual fear memory encoded before the QIH was retained after mice fully recovered from the QIH state. Next, we labeled the c-Fos positive memory engram neurons during encoding to determine the functional contribution of the overlapping active neuronal ensembles during memory retrieval after QIH. Additionally, we compared the dendritic morphology in the hippocampus CA1 pre, during, and post QIH with electron microscopy. Our findings will provide insights into how memories can withstand global synaptic changes to support individual memories and pinpoint the necessary microstructures for memory engrams. Further, our results will help build the scientific basis for researching the potential medical applications in artificially induced hibernation.

Disclosures: **Y. Lin:** None. **A. Takahashi:** None. **B.M. Humbel:** None. **T. Sakurai:** None. **K.Z. Tanaka:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.12

Topic: H.08. Learning and Memory

Support: CIHR
UBC DMCBH

Title: The effects of silencing dorsal and ventral hippocampus in a probabilistic reversal learning task in rats

Authors: *M. COOKE, T. LIN, B. DUNGATE, 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 must therefore learn and adapt to these uncertainties and flexibly update their cognitive representations of where and how to procure rewards. The hippocampus has been shown to be involved in this uncertain probabilistic learning. In our animal model, rats are trained to determine a stimulus that rewards 80% of the time from one that rewards only 20% of the time. In order to evaluate behavioural flexibility, after 8 trials, our task switches which stimulus provides the greater reward. Although the hippocampus has been shown to be involved in these statistical learning scenarios, further research into how the hippocampus encodes this information is still unknown. Hippocampal function has often been divided into dorsal and ventral aspects. Although classically dichotomised, recent research has shown that both the dorsal and ventral hippocampus are involved in many aspects of memory. Our probabilistic reversal learning task is hypothesized to require both the learning of probabilistic stimulus-reward information as well as learning the emotional salience of the rewards. In order to test these hypotheses, we used a group of 8 male and 8 female Long-Evans rats. Rats were implanted with cannulae to prepare for the inactivation of the dorsal or ventral hippocampus and trained on our operant probabilistic reversal learning task. Operant chambers are equipped with two retractable levers, one of which is randomly selected to be “correct” and the other to be the “incorrect” lever. Once the animal responds correctly 8 times the contingencies switch. After training to criterion, rats were infused either with vehicle or a cocktail of GABA agonists muscimol and baclofen to silence either the dorsal or ventral hippocampus. We use a within-subject control where animals are infused with saline. The first cohort of animals has successfully been run through this paradigm and we are now adding another 8 male and 8 female rats to improve our sample size. Analysis of the data from the first cohort of animals reveals some interesting findings. There are significant sex differences in response rate between male and female animals; females, on average, responded significantly less. We also observe a trend in negative feedback sensitivity (lose-shift behaviour where the animal switches levers after failing to obtain a reward) after inactivation. Dorsal inactivation decreased lose-shift behaviours, while ventral inactivation increased them. It is hoped this work can provide some insights into the mechanisms by which the hippocampus mediates learning about probabilistic rewards.

Disclosures: M. Cooke: None. **T. Lin:** None. **B. Dungate:** None. **J. Schumacher:** None. **S. Floresco:** None. **J. Snyder:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.13

Topic: H.08. Learning and Memory

Support: NIH R01 GM118801

Title: The General Anesthetic Etomidate Suppresses Contextual Fear Conditioning Through a5-$GABA_A$Rs on both Pyramidal Neurons and Interneurons

Authors: *A. ABDULZAHIR[1], M. G. PERKINS[2], M. S. FANSELOW[3], R. A. PEARCE[4]; [1]Univ. of Wisconsin Madison, Madison, WI; [2]Dept. of Anesthesiol., Univ. of Wisconsin-Madison, Madison, WI; [3]Dept Psychol, UCLA Chapter, Los Angeles, CA; [4]Anesthesiol., Univ. of Wisconsin, Madison, WI

Abstract: Background: Etomidate (ETOM) is a general anesthetic that impairs contextual memory *in vivo* by modulating $GABA_A$ receptors that incorporate α5 subunits (α5-$GABA_A$Rs). In an earlier study we selectively eliminated α5-$GABA_A$Rs from interneurons (α5-i-KO) and found that memory suppression was attenuated, indicating that interneurons play a role in ETOM-induced amnesia. Here, we tested whether α5-$GABA_A$Rs on pyramidal neurons might also play a role. **Methods**: Mice lacking α5-$GABA_A$Rs in pyramidal neurons (α5-pyr-KO) were generated by crossing CaMKIIα-cre mice with floxed α5-$GABA_A$R mice. Experimental mice consisted of Cre-negative pseudo-wild type mice carrying floxed α5-$GABA_A$R alleles (pWt) and their Cre-positive α5-pyr-KO littermates. Prior to behavioral testing, mice were habituated to the experimental room 30 min per day for one week. Contextual memory was assessed using the Context Pre-exposure Enhancement of Fear Learning (CPEFL) paradigm. On day 1 (pre-exposure), mice were administered ETOM or saline (7 mg/kg IP) 30 min prior to being placed in the conditioning chamber for 10 minutes (pre-exposure). On day 2 (contextual fear conditioning), the mice were placed back into the same chamber, administered an aversive foot shock (1 mA x 2 sec) after 15 sec, and then removed after 30 sec. On day 3 (recall), mice were returned to the same chamber and allowed to freely explore. The fraction of time they spent freezing during the first 3 min was used as a measure of memory. **Results**: ETOM produced similar levels of sedation in p-WT and α5-pyr-KO mice (25.22% ± 2.6 vs. 25.21% ± 3.7; 2-way ANOVA, genotype x drug interaction factor, $F(1,61) = 0.194$, $p = 0.66$). Freezing was strongly suppressed in p-WT mice (Saline 58.57% ± 3.8 vs. ETOM 28.58% ± 2.4; $t(61) = 5.06$, $p < 0.0001$, Sidak's multiple comparison test) but not in α5-pyr-KO mice (Saline 53.65% ± 4.6 vs. ETOM 55.01% ± 5.3; $t(61)=0.233$, $p = 0.97$). Interestingly, etomidate again suppressed freezing differently between the two genotypes (p-WT 28.58% ± 2.4 vs. α5-pyr-KO 55.01% ± 5.3; 2-way ANOVA, genotype x drug interaction factor $F(1,61) = 14.2$, $p=0.0004$). **Conclusions**: These findings indicate that etomidate also engages pyramidal neuron α5-$GABA_A$Rs to block memory, consistent with previous experiments linking these receptors on CA1 pyramidal neurons specifically to control of spatial memory.

Disclosures: A. Abdulzahir: None. **M.G. Perkins:** None. **M.S. Fanselow:** None. **R.A. Pearce:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.14

Topic: H.08. Learning and Memory

Support: NIH ES100221

Title: Preferential expression of adeno-associated virus-packaged genetic cargo in hippocampal CA2 neurons

Authors: *G. M. ALEXANDER, N. P. MARTIN, S. M. DUDEK;
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Abstract: A common approach to studying hippocampal circuits is through viral delivery of genetic material that encodes effector molecules and fluorophores. This is often accomplished through injection of adeno-associated viral (AAV) particles into the hippocampus, or via the bloodstream for some serotypes. In previous studies and in our own experiments, we have observed preferential expression of AAV-delivered cargo in CA2 compared to CA1 and CA3, even when not targeted to CA2. This curious observation led us to ask why CA2 neurons are preferentially targeted by AAVs. We hypothesized that because different AAV serotypes can utilize different receptors, CA2 neurons may differentially express AAV-delivered cargo based on the AAV serotype. However, various serotypes of AAV-hSyn-eGFP injected into hippocampus of C57Bl/6J mice at a position equally adjacent to all CA fields revealed preferential eGFP expression in CA2. In addition, we found that eGFP was preferentially expressed in CA2 neurons after intravenous injection of the PHP.B serotype, which is known to cross the blood-brain barrier. We next hypothesized that the preferential targeting of AAVs to CA2 is mediated by the dense expression of a specialized extracellular matrix, perineuronal nets (PNNs), comprised of chondroitin sulfate proteoglycans (CSPGs) and uniquely surrounding excitatory CA2 pyramidal neurons in addition to specific populations of inhibitory neurons throughout the brain. To test this hypothesis, we used a conditional aggrecan gene (*Acan*) knock-out (KO) mouse that we generated. Aggrecan is a primary CSPG in PNNs detected around CA2 neurons as well as a class of interneurons that express parvalbumin (PV). By pairing this "floxed" *Acan* strain with our CA2-targeted *Amigo2* cre strain or parvalbumin (PV) neuron-targeted cre strain, we successfully deleted aggrecan expression and WFA-labeled PNNs from CA2 pyramidal neurons or from PV neurons, respectively. We found that, contrary to our hypothesis, CA2 *Acan* KO mice injected with PHP.B-hSyn-eGFP intravenously continued to express AAV-delivered eGFP, despite the absence of PNNs in CA2 neurons. We next asked whether preferential AAV targeting could be due to high expression of the recently-identified AAV receptor or other mediators of membrane binding in CA2. So far, we have found that expression of the AAV receptor, heparan sulfate proteoglycans, which initiate membrane binding, as well as an AAV co-receptor, FGFR1, are all highest in CA2 among the hippocampal subfields. These findings support the conclusion that CA2 neurons are endowed with multiple mediators of AAV binding and therefore expression of AAV-encapsulated genetic material.

Disclosures: **G.M. Alexander:** None. **N.P. Martin:** None. **S.M. Dudek:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.15

Topic: H.08. Learning and Memory

Support: NIH Early Independence Award (DP5 OD023106-01)
NIH Transformative R01 Award
NARSAD Young Investigator Award - Brain and Behavior Research Foundation
Ludwig Family Foundation Grant
McKnight Foundation Memory and Cognitive Disorders Award
Office of Naval Research
Center for Systems Neuroscience and Neurophotonics Center, Boston University

Title: Two-photon imaging of c-Fos tagged CA1 populations before and after learning

Authors: *A. MONASTERIO[1], G. K. OCKER[2], S. RAMIREZ[1], B. B. SCOTT[1];
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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 the expression of memory. Novel 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 these c-Fos tagged cells increase their coactivation after learning as a result of strengthened synaptic connectivity. Here we evaluated if c-Fos tagged cells increased their coupling of activity after learning. We utilized two-photon calcium imaging and the inducible c-Fos-driven Tet-Tag system to record spontaneous calcium activity in dorsal CA1 before and after c-Fos induction during learning. c-Fos tagged cells in dorsal CA1 were tagged either during fear conditioning or home cage exposure, and spontaneous calcium activity was recorded both before and after tagging. We found that while c-Fos tagged cells have higher calcium event rates, this increased activity rate was detectable in the spontaneous population activity, both two days before and after c-Fos tagging took place, in both learning and control mice (n=745 cells). However, we did not detect an increase in the pairwise correlations between c-Fos tagged cells in the learning group relative to the control group, indicating that spontaneous activity correlations are not significantly different in c-Fos tagged cells after learning. These findings demonstrate the feasibility of cellular resolution calcium imaging of c-Fos-tagged neurons in vivo and are consistent with previous studies that demonstrate highly active neurons are allocated to the engram population. Our future experiments will investigate if memory recall

differentially affects activity in c-Fos tagged compared to untagged cells by recording activity during recall with a conditioned stimulus after auditory fear conditioning.

Disclosures: **A. Monasterio:** None. **G.K. Ocker:** None. **S. Ramirez:** None. **B.B. Scott:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.16

Topic: H.08. Learning and Memory

Support: NINDS R01NS115233
NIMH R01MH117964

Title: Sleep deprivation impedes hippocampal replay following novel experience

Authors: *B. GIRI[1,4], U. KAYA[1], K. MABOUDI[5,2], T. ABEL[6], K. DIBA[3];
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Abstract: Memories are considered to improve or consolidate over the course of sleep, and studies using sleep deprivation indicate that the first 5 hours immediately following learning are critical for memory consolidation. One of the key mechanisms suggested for sleep-mediated memory consolidation is hippocampal replay during sleep, where neuronal patterns expressed during waking experience are reactivated during sharp-wave ripples (SWRs), brief periods of high frequency (125-250 Hz) oscillations. In support of this conjecture, our previous work demonstrated that hippocampal reactivation continues for several hours (~6h) in SWRs during sleep following novel experience. We next asked how hippocampal reactivations are affected when animals are subjected to prolonged wakefulness instead of sleep. To investigate this, we carried out long duration recordings (>14h) using high density silicon probes implanted in CA1 area of the rat hippocampus. After ~2.5 h of baseline activity, animals were put in a novel environment and then for 5 h were either sleep deprived by gentle handling or left undisturbed in their homecage. We observed that the rate of SWRs showed no decay during sleep deprivation as opposed to its gradual decay during regular and recovery sleep. Also, internal frequencies of SWRs during sleep deprivation were significantly higher compared to SWRs of regular sleep. Despite abundant SWR activity, standard methods using explained variance and Bayesian decoding revealed that reactivation and replay are significantly lower, and decay more quickly in sleep deprived animals compared to control animals. Additionally, even in recovery sleep following sleep deprivation we failed to observe reactivation, indicating that reactivations do not recover in “recovery sleep”. Combined, our results suggest that poor memory reactivation may underlie sleep deprivation-associated memory deficits.

Disclosures: **B. Giri:** None. **U. Kaya:** None. **K. Maboudi:** None. **T. Abel:** None. **K. Diba:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.17

Topic: H.08. Learning and Memory

Support: Packard Fellowship for Science and Engineering
McCamish Foundation
Lane Family
Friends and Alumni of Georgia Tech
NIH-NINDS R01 NS109226

Title: Learning-dependent reduction of inhibition underlies new learning

Authors: ***N. JEONG**, V. P. NGUYEN, S. R. THOMAS, C. E. GILPIN, M. C. GOODSON, A. C. SINGER;
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Abstract: Rapidly learning new places of importance is critical to goal-directed behavior. In the hippocampus, excitatory pyramidal cells have long been thought to store behaviorally relevant locations including locations associated with reward. While inhibitory interneurons have been reported to have varying degrees of spatial modulation, inhibitory contributions to learning about place of importance is unclear. Indeed, firing activity of excitatory neurons is under control of inhibitory interneurons, and therefore interneurons could gate increased excitatory activity that promotes memory processing. We posited that such gating would most likely occur in important locations such as reward locations during behavior. To test this hypothesis, we performed *in vivo* electrophysiology in the mouse hippocampal area CA3, a region known to be essential for developing new spatial memories. We recorded from head-fixed mice learning to navigate in familiar and novel virtual reality environments. We found a spatially selective reduction in firing rates of in task relevant locations. This inhibitory reduction could not be explained by position-related changes in speed or licking behavior. Furthermore, the timing or magnitude of this reduction was not consistent with simple balancing of increased excitation. We then optogenetically disrupted normal interneuron activity during learning to determine if perisomatic inhibition onto CA3 pyramidal cells impaired new learning. These results demonstrate that learning-dependent changes in interneuron activity gate new spatial information without disrupting old memories. Our findings highlight an important and understudied role for inhibitory neurons in the rapid formation of new important memories in goal-directed behavior.

Disclosures: **N. Jeong:** None. **V.P. Nguyen:** None. **S.R. Thomas:** None. **C.E. Gilpin:** None. **M.C. Goodson:** None. **A.C. Singer:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.18

Topic: H.08. Learning and Memory

Support: NSF GRFP Grant No. DGE-1444932
NIH T32 NS096050-22
NIH-NINDS R01 NS109226
Packard Fellowship for Science and Engineering
McCamish Foundation
Lane Family
Friends and Alumni of Georgia Tech

Title: Hippocampal and prefrontal activity during rapid updating of spatial trajectories in response to new information

Authors: *S. M. PRINCE[1,2], N. KATRAGADDA[2], T. C. ROBERTS[2], T. A. YASSINE[2], A. L. PAULSON[2], A. C. SINGER[2];
[1]Emory Univ., Atlanta, GA; [2]Georgia Inst. of Technol., Atlanta, GA

Abstract: Remembering our past and planning for our future are fundamental cognitive processes that guide our day-to-day lives. The ability to rapidly update our choices by integrating past experiences with new information is essential to navigating our world. In hippocampus and prefrontal cortex, regions that play key roles in memory and planning, neural representations of past experiences are reactivated on compressed timescales. This reactivation is theorized to support planning for upcoming choices. However, the role of prospective codes in updating versus maintaining decisions is challenging to study since planning is an internally driven process and it is often unclear when a choice is made. To address this question, we designed a novel decision-making navigation task in virtual reality in which we precisely controlled the introduction of new information that animals must integrate with existing plans. We found that mice learn this complex task and rapidly update their spatial trajectories when presented with new information. We then recorded electrophysiological activity from hippocampus and prefrontal cortex during behavior. We are determining how prospective codes in prefrontal cortex and hippocampus update when animals are presented with new information and how this activity predicts correct decisions. By precisely controlling the timing of when an animal must update their choices, these studies provide unique insights into how neural codes guide flexible decision making.

Disclosures: S.M. Prince: None. **N. Katragadda:** None. **T.C. Roberts:** None. **T.A. Yassine:** None. **A.L. Paulson:** None. **A.C. Singer:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.19

Topic: H.08. Learning and Memory

Support: NIA T32 (T32- AG020506/AG/NIA)
NIA R37 (R37-AG008796/AG/NIA)
NINDS R01 (R01 NS113804/NS/NINDS)

Title: Place cells are non-randomly clustered by field location in CA1 hippocampus

Authors: *H. S. WIRTSHAFTER[1], J. F. DISTERHOFT[2];
[1]Northwestern Univ., Northwestern Univ., CHICAGO, IL; [2]Northwestern Univ. - Chicago, Northwestern Univ. - Chicago, Chicago, IL

Abstract: A challenge in both modern and historic neuroscience has been achieving an understanding of neuron circuits, and determining the computational and organizational principles that underlie these circuits. Deeper understanding of the organization of brain circuits and cell types, including in the hippocampus, is required for advances in behavioral and cognitive neuroscience, as well as for understanding principles governing brain development and evolution. In this manuscript, we pioneer a new method to analyze the spatial clustering of active neurons in the hippocampus. We use calcium imaging and a rewarded navigation task to record from 100s of place cells in the CA1 of freely moving rats. We then use statistical techniques developed for and in widespread use in geographic mapping studies, global Moran's I and local Moran's I to demonstrate that cells that code for similar spatial locations tend to form small spatial clusters. We present evidence that this clustering is not the result of artifacts from calcium imaging, and show that these clusters are primarily formed by cells that have place field around previously rewarded locations. We go on to show that, although cells with similar place fields tend to form clusters, there is no obvious topographic mapping of environmental location onto the hippocampus, such as seen in the visual cortex. Insights into hippocampal organization, as in this study, can elucidate mechanisms underlying motivational behaviors, spatial navigation, and memory formation.

Disclosures: H.S. Wirtshafter: None. **J.F. Disterhoft:** None.

Poster

743. Hippocampus, Encoding, and Navigation

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 743.20

Topic: H.08. Learning and Memory

Support: FG23505

Title: Immunolabeling-compatible PEGASOS tissue clearing for high-resolution whole mouse brain imaging

Authors: *P. GAO[1], L. CHEN[2], X. XU[3];
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Abstract: Due to the inherent 3D structure of molecules, cells and tissues, improving high-throughput approaches for visualizing the intact biological samples is critical. Tissue clearing, by reducing the refractive index (RI) difference between different components of the tissue, enables opaque tissue to appear transparent. Combined with volumetric imaging by a Light-sheet microscope, new tissue technologies help to fully capture the spatial distribution and anatomical features of neural circuits in the intact samples. The Polyethylene glycol-associated solvent system (PEGASOS) described in 2018 is an organic solvent-based clearing method and renders superior transparency in nearly all types of tissue rapidly (Jing et al., 2021). Here, we report a whole-mount immunostaining compatible version of PEGASOS (iPEGASOS), which can restore and enhance endogenous fluorescent signals being quenched during clearing or immunolabeling processes. Our applications of iPEGASOS are extended from whole adult mouse brains with transgenic reporter expression, viral labels and Alzheimer's disease pathologies to large monkey brain samples with immunostaining. We further show large brain-wide neural circuit mapping can be achieved in the 3D, intact samples. We foresee that our new techniques have broad applications in large-scale neural circuit mapping.

Disclosures: P. Gao: None. **L. Chen:** None. **X. Xu:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.01

Topic: C.01. Brain Wellness and Aging

Title: Age-related white matter integrity & associated glucose metabolism changes in healthy subjects: a PET/MRI study

Authors: *L. KNUDSEN, M. S. VAFAEE, T. MICHEL;
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Abstract: Abstract Aging is a biological process associated with decreasing brain volume, function, and metabolism. The vast majority of studies investigating brain metabolism focuses on grey matter while neglecting the age-dependent trajectory of white matter. Therefore, the following study aims to investigate the relationship between white matter integrity and the metabolic rate of glucose, as well as their age-related trajectory, to explore the metabolic and

structural impact of aging on white matter. Ninety (36 reported, 21 female and 15 male) healthy subjects ranging from 20-80 years of age (mean age 43.29 SD 16.40) underwent simultaneous positron emission tomography (PET) and magnetic resonance imaging (MRI) scans. A 18F-fluorodeoxyglucose PET scan was used to quantify the cerebral metabolic rate of glucose (CMRglc), while a simultaneous diffusion tensor imaging (DTI) scan was acquired and utilized to evaluate white matter integrity using fractional anisotropy (FA) as the diffusion measure. Glucose metabolism and white matter integrity were estimated and subsequently investigated for age-dependent correlations and significance. Mean CMRglc of the corpus callosum was 10.76 ± 1.13 μmol/min/100g for the whole sample, while mean FA was 0.53 ± 0.04. A significant association between FA and CMRglc of the corpus callosum ($p = 0.0002$) was evident. Additionally, a clear age-dependent correlation between FA and CMRglc was demonstrated, i.e., FA and CMRglc decreased as a function of aging. However, the association between glucose metabolism and white matter integrity varied depending on the white matter tract. These results suggest that during the process of healthy aging, white matter displays an age-dependent metabolic and structural trajectory, albeit, in fluctuating degrees depending on the white matter tract in question. The tendency of decreasing white matter integrity and glucose metabolism resembles the propensity known from grey matter, where atrophy and decreased metabolism is associated with aging. Therefore, we hope that our continuous data collection will further expand our existing knowledge regarding this process in white matter, its similarity with the trajectory in grey matter and potential gender differences.

Disclosures: L. Knudsen: None. **M.S. Vafaee:** None. **T. Michel:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.02

Topic: C.01. Brain Wellness and Aging

Title: The role of base excision repair in major depressive disorder and bipolar disorder

Authors: M. KUCUKER[1], A. OZERDEM[1], D. CEYLAN[2], A. M. C. HO[1], B. JOSEPH[1], L. M. WEBB[1], P. E. CROARKIN[1], M. A. FRYE[1], A. CABELLO ARREOLA[1], ***M. VELDIC**[1]; [1]Mayo Clin., Rochester, MN; [2]Koc Univ., Instanbul, Turkey

Abstract: Introduction; In vivo and in vitro studies suggest that inflammation and oxidative damage may contribute to the pathogenesis of major depressive disorder (MDD) and bipolar disorder (BD). Imbalance between DNA damage and repair is an emerging research area examining pathophysiological mechanisms of these major mood disorders. This systematic review sought to examine current evidence on the association between mood disorders and deficits in base excision repair (BER), the primary repair mechanism for repair of oxidation-induced DNA lesions. Methods: We conducted a comprehensive literature search of Ovid MEDLINE® Epub Ahead of Print, Ovid MEDLINE® In-Process & Other Non-Indexed

Citations, Ovid MEDLINE® Daily, EMBASE (1947), and PsycINFO for studies investigating the alterations in base excision repair in patients with MDD or BD. Results: A total of 1,364 records were identified. 1,352 records remained after duplicates were removed. 24 records were selected for full-text screening and a remaining 12 articles were included in the qualitative synthesis. SNPs (Single Nucleotide Polymorphisms) of several BER genes have been shown to be associated with MDD and BD. However, it was difficult to draw conclusions from BER gene expression studies due to conflicting findings and the small number of studies. Conclusion: Future studies comparing DNA repair during the manic or depressive episode to remission will give us a better insight regarding the role of DNA repair in mood disorders. These alterations might be utilized as diagnostic and prognostic biomarkers as well as measuring treatment response.

Disclosures: M. Kucuker: None. **A. Ozerdem:** None. **D. Ceylan:** None. **A.M.C. Ho:** None. **B. Joseph:** None. **L.M. Webb:** None. **P.E. Croarkin:** 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.; Pfizer, Inc., Neosync, Inc., Neuronetics, Inc.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AssureX Health, Inc., Neuronetics, Inc., MagVenture, Inc.. F. Consulting Fees (e.g., advisory boards); Proctor & Gamble Company, Myriad Neuroscience, Sunovion, Engrail Therapeutics. **M.A. Frye:** 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.; AssureX Health, Inc., Mayo Foundation, Medibio. **A. Cabello Arreola:** None. **M. Veldic:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.03

Topic: C.01. Brain Wellness and Aging

Support: 5U54 MD007593
U54 CA163069
SCI CA182843
SC1 CA182843-07S1
33201-01622

Title: Mitochondrial calcium regulator Fus1/TUSC2 deficient mice exhibit short-term memoryimpariments

Authors: *T. FARRIS[1], T. KANAGASABAI[2], A. IVANOVA[2], A. SHIMAMOTO[2], A. SHANKER[2];

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Abstract: Mild cognitive impairment (MCI) occurs on a continuum from normal cognition to AD dementia. The hippocampus, which is responsible for memory formation and consolidation, is the first region to be affected by MCI/AD. The underlying mechanisms driving the development of this form of cognitive impairment remains elusive and yet to be precisely identified. Calcium cations (Ca^{2+}) regulate neuronal plasticity underlying learning and memory and neuronal survival. Dysregulation of Ca^{2+} is decisive for brain cell death and degeneration. Our group has found that mitochondrial protein TUSC2 (Tumor Suppressor Candidate 2), initially identified as Fus1, serves as regulator of mitochondrial Ca^{2+} fluxes in all cells. Fus1 protein resides on the inner membrane of the mitochondria and assists in Ca^{2+} uptake and extrusion via the Mitochondrial Calcium Uniporter (MCU) and mitochondrial sodium-calcium exchanger (mNCX), respectfully. The deficiency of Fus1 leads to increased oxidative stress and disturbed mitochondrial membrane potential and energy production in immune and cancer cells. However, it is not clear how Fus1 deficiency in the central nervous system (CNS) affects memory. Here we examined the role of Fus1 in memory by using a systemic Fus1 knockout mouse model. In this study we used 17 weeks old Fus1 knock-out (KO) and wild-type (WT) mice of both sexes. Both WT and KO mice underwent behavioral tests including, Y-maze and open-field (OF) tests, followed by measurement of MCU protein levels *via* Western blot (WB), and Ab_{1-42} of hippocampal tissue *via* ELISA. Fus1 deficiency impaired short-term spatial memory in males but not in females as assessed with Y- maze test ($p<0.05$). Fus1 KO females showed a trend for increase in locomotor activity as compared to KO males in OF test. Immunoblot analysis of hippocampal tissue revealed that Fus1 loss results in increased MCU protein levels. Levels of Ab1-42 were consistent amongst all groups. The loss of Fus1 increases expression of MCU, thereby yielding to the dysregulation of mitochondrial Ca^{2+} levels. Further research needs to be conducted to directly correlate the mechanism of these findings with memory impairments. Overall, Fus1 deficiency could play a pivotal role in the development of cognitive impairments early on in disease development.

Disclosures: T. Farris: None. **T. Kanagasabai:** None. **A. Ivanova:** None. **A. Shimamoto:** None. **A. Shanker:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.04

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant AG077253
NIH Grant AG054025
NIH Grant NS094557
NIH Grant AG072458

T32 AG067952
Mitchell Center for Neurodegenerative Diseases
Sealy Center for Vaccine Development

Title: Intranasal delivery of tau conformation-specific monoclonal antibody blunts oxidative stress and removes pathological tau in aged tauopathy mouse model

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Abstract: Accumulation of pathological tau aggregates is a hallmark of tauopathies, including Alzheimer's disease (AD), Progressive Supranuclear Palsy (PSP), and other neurodegenerative diseases. Evidence shows that oxidative stress is a key contributor in the development and progression of tauopathies and cognitive dysfunctions. Indeed, markers of oxidative damage are detected at very early stages in the brain of tauopathy patients. However, the link between toxic tau conformations and oxidative stress is unknown. Here, we generated a novel toxic tau conformation-specific monoclonal antibody (TTCM) and developed a strategy to efficiently remove the intracellular and extracellular pathologic tau through intranasal passive immunotherapy, bypassing blood brain barrier and reducing potential systemic side effects. We report that single dose of intranasal TTCM2 treatment effectively removes neurotoxic tau oligomers in 15-month-old hTau mice. We investigated the link between ROS metabolism and tauopathy, and possible amelioration of redox status in aged hTau mice, upon intranasal treatment with the TTCM2 or IgG control antibodies. To this aim, the levels of oxidative damage and antioxidant response markers were evaluated in the hippocampus and cortex, by immunofluorescence and immunoblotting analyses. We found moderate-to-significant decreased levels of 8-oxo-dG, as a marker of oxidative DNA/RNA modifications and 4-HNE, as a lipid peroxidation end product, in the hippocampus and cortex of TTCM2-treated mice compared with their IgG-treated counterparts. The levels of superoxide dismutase 1 and 2 (SOD1 and SOD2), peroxisome proliferator-activated receptor α (PPARα), PPARγ-coactivator 1 α (PGC1α), and catalase, as key factors in antioxidant response were also reduced upon TTCM2-treatment. Together, our study provides a novel pathomechanism by which toxic tau conformations mediate oxidative damage in the brain and cause cognitive deficits. Further, intranasal administration of TTCM2-antibody-loaded micelles could be useful to effectively reduce deposited toxic tau species and ameliorate the oxidative damage in the brain, thus opening the path for the development of new and effective therapeutic strategies.

Disclosures: R. Price: None. **S. Gaikwad:** None. **M. Montalbano:** None. **M. Kidd:** None. **S. Moreno:** None. **R. Kayed:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.05

Topic: C.01. Brain Wellness and Aging

Support: H2020-MSCA-COFUND-2017-801481

Title: Lack of neuronal Cd1d leads to lipid imbalances causing lysosomal storage disorder-like brain pathology

Authors: *J. LOMBARDIA GUTIERREZ[1], K. MÆDA[2], J. PEDERSEN[1], E. TRESSE-GOMMEAUX[1], S. ISSAZADEH-NAVIKAS[1];
[1]Biotech Res. and Innovation Ctr., Copenhagen N, Denmark; [2]Danish Cancer Society Res. Ctr., Copenhagen DK-2100, Denmark

Abstract: This project focuses on understanding the role of a well-characterized immune gene, Cd1d, in brain homeostasis.Cd1d is an MHC class I-like glycoprotein classically described in the context of the immune system.Its canonical function is to survey the intracellular space of antigen-presenting cells (APCs), looking for lipidic antigens to bind to and present to Natural Killer T cells (NKTs). However, Cd1d is also expressed in the brain, where no T cell receptor has been described. Furthermore, MHC class I, a very similar protein both in structure and function, has been related to neuronal development and plasticity (Elmer & McAllister, 2012). Therefore, we hypothesize that Cd1d plays an important role in brain homeostasis, mainly within neurons.
To investigate this hypothesis, we started by characterizing the phenotype of mice lacking Cd1d function. We discovered that these mice develop a wide array of spontaneous behavioral deficits. In addition, immunofluorescence analyses showed that these mice have a reduced number of neural cells at early time points. We discovered that both the behavioral and histological results were reproduced in mice lacking Cd1d signaling specifically in neurons but not in astrocytes, pointing towards neurons as the source of this novel role of Cd1d. Thus, we used primary neuronal cultures as our *in vitro* model to further elucidate the specific pathway dysregulated upon Cd1d absence. We found that neurons lacking Cd1d signaling have strong impaired organelle homeostasis, both in structure and function. Being Cd1d a molecule able to bind lipids, we hypothesized that an aberrant organellar lipidic profile could be the main cause of the phenotype, which would lead to a lack of functionality. Thus, we performed lipidomic analysis of cultured neurons lacking Cd1d pathway and found out they have a dysregulation of glycosphingolipid species affecting mainly the endo-lysosomal system. In summary, lack of neuronal Cd1d signaling leads to impaired neuronal and brain homeostasis, resembling the one observed in lysosomal storage disorders (LSDs).
Therefore, we propose a novel role for Cd1d within the brain, where lack of this protein in neurons leads to spontaneous glycosphingolipids dysregulation and impaired organellar homeostasis, giving rise to behavioral, histological, and cellular hallmarks of LSDs.

Disclosures: J. Lombardia Gutierrez: None. **K. Mæda:** None. **J. Pedersen:** None. **E. Tresse-Gommeaux:** None. **S. Issazadeh-Navikas:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.06

Topic: C.01. Brain Wellness and Aging

Title: Hormetic neuroprotection associated with the H63D HFE gene variant

Authors: *S. L. MARSHALL[1], J. R. CONNOR[2], E. B. NEELY[2];
[1]Penn State Col. of Med. Neurosci. Grad. Program, Hershey, PA; [2]Neurosurg., Penn State Col. of Med., Hershey, PA

Abstract: The goal of this project is to characterize neuroprotective pathways that are upregulated due to subclinical iron overload to progress exploration of therapeutics that prevent neurodegeneration. This project studies the role of the common H63D variant of the homeostatic iron regulator gene (HFE) in hormetic (adaptive) neuroprotection. H63D HFE can contribute to subclinical iron overload in the brain and has been implicated in neurodegeneration due to the proposed role of brain iron overload in exacerbating neurodegenerative pathologies. However, mouse and cell culture models containing the H67D HFE variant (the mouse homolog of H63D), which increases brain iron loading, have rigorously shown long term neuroprotection against toxin induced stress. The brain of H67D HFE mice has also shown upregulation of neuroprotective and mitochondrial quality control transcripts. H67D HFE-linked iron overload increases ROS which is a known mediator for upregulation of neuroprotective pathways. This subclinical toxin-induced upregulation of neuroprotective pathways is termed “neurohormesis.” It is known the transcription factor, Nrf2, is involved in the development of neurohormesis. Additionally, the known involvement of Nrf2 implicates significant metabolic alterations which likely support the upregulation of stress defenses. However, the developmental timeframe of neurohormesis, as well as whether neurohormesis is mainly driven intrinsically (by neurons themselves) or extrinsically (by astrocytes) is poorly understood. This project characterizes the age-dependent transcriptomic and proteomic alterations that occur in the brain of H67D HFE mice. Further, it elucidates the extent that neurons and astrocytes independently contribute to the development of neurohormesis and accompanying mitochondrial changes (mitohormesis).

Disclosures: S.L. Marshall: None. **J.R. Connor:** None. **E.B. Neely:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.07

Topic: C.01. Brain Wellness and Aging

Support: RF1NS121095
R01AA027097
R01NS115401
U24EB028941
R01NS091230

Title: Effects of voluntary exercise on cerebral microcirculation and oxygenation in aged mice

Authors: *P. SHIN[1], Q. PIAN[1], H. ISHIKAWA[1], G. HAMANAKA[1], E. T. MANDEVILLE[1], G. SHUZHEN[1], F. BUYIN[1], M. ALFADHEL[1], I. SENCAN[1], B. LI[2], C. RAN[1], S. A. VINOGRADOV[3], E. H. LO[1], K. ARAI[1], C. AYATA[1], A. DEVOR[4], S. SAKADZIC[1]; [1]Massachusetts Gen. Hosp., Charlestown, MA; [2]Shenzhen Inst. of Advanced Technology, Chinese Acad. of Sci., Shenzhen, China; [3]Univ. of Pennsylvania, Philadelphia, PA; [4]Biomed. Engin., Boston Univ., Boston, MA

Abstract: Despite the beneficial effects of aerobic exercise on the major neurological disorders associated with ageing and various neurodegenerative diseases, the mechanism of how exercise provides such benefits remains incompletely understood. Aerobic exercise interventions have been shown to improve neurocognitive function, reduce neuroinflammation, and enhance neurogenesis and synaptic plasticity in the hippocampus during aging and disease progression. These positive effects may be in part correlated with changes in cerebral microcirculation induced by exercise because the disruption in the microcirculation has been described as an early feature and a potential target for therapy in many neurological diseases. However, much uncertainty still surrounds the effects of exercise on the cerebrovascular physiology in both humans and animal models, with some studies showing increased cerebral blood flow (CBF) and microvascular density and others reporting no structural or functional cerebrovascular changes with exercise. Our recent works have shown spatial variation of capillary blood flow and oxygenation across cortical layers in the mouse brain and revealed that blood flow in the deep cortical layers and the subcortical white matter is more vulnerable to hypoperfusion than that in the superficial cortical layers. Here, we assessed exercise-induced changes in the microcirculation of the old awake mice at rest. All measurement were performed in 20-months-old C57BL/6N mice after four months of voluntary exercise. We employed two-photon microscopy using a far-red fluorophore Alexa680 to assess exercise-induced changes in the distributions of capillary red-blood-cell (RBC) flux from superficial cortical layers down to white matter regions. In addition, effects of exercise on capillary oxygen partial pressure (PO2) and microvascular density across cortical depth were investigated. Finally, we conducted behavioral assays to analyze the correlation between the cerebrovascular changes with cognitive performance. Our results suggest that exercise have a mitigating effect on the progression of age-related changes in cerebral microcirculation and oxygenation in the deep cortex and the white matter which may be correlated with attenuation of cognitive impairment.

Disclosures: P. Shin: None. **Q. Pian:** None. **H. Ishikawa:** None. **G. Hamanaka:** None. **E.T. Mandeville:** None. **G. Shuzhen:** None. **F. Buyin:** None. **M. Alfadhel:** None. **I. Sencan:** None. **B. Li:** None. **C. Ran:** None. **S.A. Vinogradov:** None. **E.H. Lo:** None. **K. Arai:** None. **C. Ayata:** None. **A. Devor:** None. **S. Sakadzic:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.08

Topic: C.01. Brain Wellness and Aging

Title: Sigma-1 receptor regulates energy metabolism by impacting the NAD/NADH ratio

Authors: *S. COULY[1], Y. YASUI[1], Y. KIMURA[1], G. PARITOSH[2], T.-P. SU[1];
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Abstract: Sigma-1 receptor (S1R) is a protein located at the junction of two organelles: endoplasmic reticulum (ER) and mitochondria. Upon activation by ER calcium depletion or ligand binding, S1R can increase calcium efflux from ER to mitochondria by chaperoning IP3 receptor type3. Thus, S1R ligands have been shown to be effective to treat numerous neurodegenerative disorder models where mitochondrial functions are impaired. Interestingly, it is known that affecting mitochondria impact glycolysis, the other source of energy for neurons. For example, compensatory glycolysis is observed when oxidative phosphorylation in the mitochondria is pharmacologically inhibited. However, despite the facts that the S1R regulates calcium entries into mitochondria, the consequences of S1R actions on glycolysis and on the overall cellular energy metabolism are not yet elucidated. This study utilizes Wild type (Wt) or S1R knockout (S1R-KO) Neuro2a (N2a) cells created by CRISPR-CAS9, and primary cortical neurons from Wt or S1R-KO mice to investigate the fundamental functions of S1R on the glycolysis, mitochondrial activity and on the NAD/NADH metabolism which is a key player on the homeostasis of cellular energy production. In S1R-KO N2a cells and cortical neurons we observed a reduced glycolytic activity, a decreased enolase and an increased mitochondria complex I protein. All three changes were successfully rescued by overexpression of S1R. To examine the underlying mechanisms behind those alterations, we first hypothesized that S1R could chaperone glycolytic proteins. Yet, we did not find any colocalization between those proteins and S1R. Interestingly, using extracellular flux analysis assay we observed that the compensatory glycolysis, induced by inhibitors of oxidative phosphorylation chain, is reduced in S1R-KO primary neurons, suggesting a lack of communication between mitochondria and the glycolysis system. Moreover, we measured the NAD+/NADH concentrations, key coenzyme essential for glycolysis and for mitochondrial complex I activity and found that the ratio is modified in S1R-KO conditions. Altogether, those data show for the first time that the S1R modulates the NAD metabolism. This new insight on the S1R function may lead to new therapeutic value of S1R ligands in diseases in which the cellular NAD+/NADH ratio is compromised such as aging.

Disclosures: S. Couly: None. **Y. Yasui:** None. **Y. Kimura:** None. **G. Paritosh:** None. **T. Su:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.09

Topic: C.01. Brain Wellness and Aging

Support: NIA R56 AG061051
NIA RF1 AG065301
P30AG013319-21
P30-AG044271-03 (AMP),

Title: Neuronal proteasome augmentation protects against age-related cognitive decline

Authors: *K. DAVIDSON, A. PICKERING;
Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Background: The proteasome is a critical driver of protein degradation and protein turnover in the cell. In the central nervous system, the proteasome also plays key roles in synaptic activity, plasticity, as well as learning, and memory. Proteasome function declines dramatically over the course of age, potentially contributing to age-related cognitive declines. **Methods:** In this study, we investigated whether neuronal targeted augmentation of proteasome function via overexpression of the rate-limiting proteasome subunit PSMB5 could alleviate age-related declines in cognitive function and astrocyte expression. Three cohorts were created and aged to 11-12 Mo (Young), 18-19 Mo (Middle aged) and 22-26 Mo (Old). Behavioral tests were performed to access spatial learning and memory and balance and coordination. Immunohistochemistry was performed to analyze markers of neuronal health. **Results:** Our preliminary data demonstrated an alleviation in age-related deficits in measures of coordination and balance (rotarod, $p<0.05$), along with reduced deficits in spatial learning and memory (Morris Water Maze, and closed arm Y-maze, $p<0.05$) in our middle and older overexpression PSMB5 male mouse model. Our investigation further demonstrated proteasome augmentation to drive changes in neuronal architecture an important driver of maintaining neuronal health ($p<0.05$). **Conclusion:** This study demonstrates neuronal proteasome overexpression to slow age-related cognitive decline in mice.

Disclosures: K. Davidson: None. **A. Pickering:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.10

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R35GM128823
CZI Grant 2020-222005

Title: Glycolytic metabolon assembly on mitochondria via O-GlcNAcylation

Authors: *H. WANG[1], J. VANT[5], L. MICOU[2], R. G. SANCHEZ[2], S. YU[2], A. ABUSHAWISH[2], M. JABBO[2], A. ZHANG[2], V. LUCZAK[2], M. GHASSEMIAN[3], E. GRIFFIS[4], A. SINGHAROY[5], G. PEKKURNAZ[2];
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Abstract: Glucose is the major fuel of cells, and its metabolism starts with the activity of the first rate-limiting enzyme Hexokinase (HK). HK1 is the dominant isoform in the brain, and it is mostly associated with the mitochondrial outer membrane. The positioning of HK1 on mitochondria is critical because it couples two energy generation pathways: Glycolysis and mitochondrial oxidative phosphorylation. Here, we report a new molecular mechanism which regulates HK1 activity and its localization on mitochondria via metabolic sensing enzyme O-GlcNAc transferase (OGT). OGT catalyzes a reversible post-translational modification by adding a GlcNAc sugar moiety to serine and threonine residues, this step is called O-GlcNAcylation. The catalytic activity of OGT is regulated by intracellular UDP-GlcNAc concentrations, which in response to glucose flux through the hexosamine biosynthetic pathway. In this study, we show that HK1 is dynamically modified with O-GlcNAcylation at its regulatory domain. O-GlcNAcylation of HK1 is elevated when OGT activity is genetically or pharmacologically upregulated. We further characterized that O-GlcNAc modification increases mitochondrial HK1, Aldolase A and Pyruvate kinase isozyme M. Increasing O-GlcNAcylation also enhances both glycolytic and mitochondrial ATP production rates. By mutating O-GlcNAcylation site of HK1, we see a decrease in both glycolytic and mitochondrial ATP production rates and dysfunction of presynaptic vesicle releasing in neuron. Our findings may reveal key molecular pathways that couple neuronal metabolism to mitochondrial function via OGT, and how their dysregulation leads to neurological disorders.

Disclosures: H. Wang: None. **J. Vant:** None. **L. Micou:** None. **R.G. Sanchez:** None. **S. Yu:** None. **A. Abushawish:** None. **M. Jabbo:** None. **A. Zhang:** None. **V. Luczak:** None. **M. Ghassemian:** None. **E. Griffis:** None. **A. SinghaRoy:** None. **G. Pekkurnaz:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.11

Topic: C.01. Brain Wellness and Aging

Support: NRF-2019R1A5A2026045
NRF-2020R1A2C1010399

Title: Identification of a TRIM protein as a core positive regulator of autophagy

Authors: *H. HEO[1], H. PARK[3], M. LEE[1], S. KIM[3], J. KIM[1], S.-Y. JUNG[1], S. LEE[3], J. CHANG[1,2];
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Abstract: Accumulation of various types of abnormal/unwanted intracellular substances is one of the main causes of the development of neurodegenerative diseases including Alzheimer's disease and Parkinson's disease. Autophagy is a fundamental intracellular process for clearance of unwanted or damaged materials accumulated in the cell. The autophagic process is initiated by the formation of phagophore mediated by sequential recruitment of specific protein complexes. The phagophore matures into the autophagosome which engulfs autophagic cargos such as cytoplasmic proteins and organelles. Autophagy is finally completed by the degradation of the materials at the autolysosome which is formed by the fusion of the autophagosome and the lysosome. Tripartite motif (TRIM) proteins are a subfamily of the RING-type E3 ubiquitin ligase family and various functional domains of TRIM proteins including the RING domain enable the proteins to play critical roles in a wide range of biological processes. Here, we investigated autophagic roles of TRIM22 especially focused on the regulation of autophagic initiation and the fusion of the autophagosome and the lysosome. Our findings also suggest that the roles of TRIM22 in autophagic clearance is linked to the onset or progression of neurodegenerative diseases.

Disclosures: H. Heo: None. **H. Park:** None. **M. Lee:** None. **S. Kim:** None. **J. Kim:** None. **S. Jung:** None. **S. Lee:** None. **J. Chang:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.12

Topic: C.01. Brain Wellness and Aging

Support: CIHR Grant PJT-159493 to MF
Ontario Graduate Scholarship to EK
Canada Graduate Scholarship to EK

Title: Retrograde axonal transport of proNGF is impaired in aged basal forebrain cholinergic neurons via nitrative stress-induced JNK activation

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Abstract: Rationale: Age-induced loss of basal forebrain cholinergic neurons (BFCNs) is associated with cognitive decline. BFCNs are highly vulnerable to neurodegeneration because of their reliance on proNGF axonal transport for survival. ProNGF transport is decreased in aging and contributes to loss of BFCN function. The mechanism of reduced proNGF transport with age is unclear. The biological activity of proNGF depends on its receptors. It exhibits neurotrophic activity via TrkA/ERK but apoptotic activity via $p75^{NTR}$/JNK when TrkA is reduced. Nitrative stress increases with age and activates JNK, but whether this alters transport of proNGF is unknown. **Objectives:** To determine whether nitrative stress-induced JNK activity contributes to age-induced proNGF transport deficits and if those deficits are receptor specific. **Methods:** Basal forebrains were dissected from embryonic rats. Neurons were cultured in microfluidic chambers, which fluidically isolate BFCN soma from axon terminals. Quantum dot-labelled proNGF was added to BFCN axon terminals, and its accumulation at the proximal axons was quantified using fluorescence microscopy in aged and young BFCNs. The aged phenotype was confirmed by staining for senescence-associated β-galactosidase. Receptor-specific effects were analyzed using proNGF mutants that bind selectively to TrkA (proNGF-KKE) or $p75^{NTR}$ (proNGF-Δ9-13). Downstream signaling was analyzed at the soma using immunocytochemistry following axonal treatment with either proNGF or proNGF-Δ9-13. Nitrative stress was quantified with DAF-FM staining. BFCNs were treated either with vehicle or with L-NAME to reduce nitric oxide, CC401 to inhibit JNK activity, or SIN-1 to generate peroxynitrite. All results were repeated in 3 independent experiments (n=30 images/group). **Results:** Nitrative stress increased and proNGF transport decreased in BFCNs aged *in vitro*. L-NAME and CC401 treatments increased proNGF transport in aged BFCNs, and CC401 partially rescued deficits induced by SIN-1. *In vitro* aging decreased transport of proNGF-KKE while increasing transport of proNGF-Δ9-13. ProNGF-Δ9-13 induced greater JNK activity and less ERK activity than proNGF. **Conclusions:** Nitrative stress contributes to age-induced proNGF transport deficits in BFCNs by inducing JNK activity. Aging increases transport of proNGF bound to $p75^{NTR}$ but decreases transport of proNGF bound to TrkA. Increased transport of proNGF-p75 increases apoptotic signaling while decreasing neurotrophic signaling. This study provides a better understanding of the neurodegeneration that occurs during aging, which is essential for rescuing age-induced cognitive decline.

Disclosures: E. Kropf: None. **C. Wu:** None. **M. Fahnestock:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.13

Topic: C.01. Brain Wellness and Aging

Support: CONACYT Ph.D. Fellowship No. 463895
CONACYT Grant No. 285184
PAPIIT Grant No. IN216422

Title: Txnip expression is induced by FOXO3 in response to reactive oxygen species production and promotes the death of cerebellar granule neurons

Authors: *B. GARCIA[1], J. MORAN[2];
[1]Inst. of Cell. Physiol., Natl. Univ. of Mexico, Mexico City, Mexico; [2]Natl. Univ. of Mexico, Natl. Univ. of Mexico, Ciudad de Mexico, Mexico

Abstract: Txnip has been recognized as a protein sensitive to oxidant conditions whose expression has been related to the progression of death in cancer, diabetes, ischemia, and neurodegenerative disease models. Due to this, many studies suggest Txnip as a therapeutic target to reduce cell death in several diseases. Exposure to staurosporine and low potassium are two models of neuronal death in cerebellar granule neurons in vitro. Both are characterized by an early production of reactive oxygen species (ROS) that induce the activation of the JNK pathway and the apoptotic machinery. In these models, it has been shown an increase in Txnip protein in response to ROS and oxidative conditions. In this study, we evaluated the signaling pathway involved in Txnip expression and its role in neuronal death. By using a low potassium model in cerebellar granule neurons and a genetically encoded intracellular hydrogen peroxide sensor Hyper, we observed an early increase in the oxidative conditions that correlated with the inactivation of Akt kinase and an increase of mRNA and protein levels of Txnip. When we evaluated the promoter of the Txnip gene we found JASPAR-reported FOXO1/3 transcription factor motifs close to the TSS. We then verified through the Chromatin Immunoprecipitation technique (ChIP) that FOXO 3 interacts with the Txnip promoter 1 hour after a low potassium stimulus. Finally, by using Txnip shRNA in the MSN cell line, we found that Txnip downregulation decreases the neuronal death induced by staurosporine stimulus. Together, these results suggest that ROS induce the expression of Txnip through the activation of the FOXO3 transcription factor by AKT inhibition and that Txnip expression is necessary to induce neuronal death in low potassium and staurosporine stimulus.

Disclosures: B. Garcia: None. **J. Moran:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.14

Topic: C.01. Brain Wellness and Aging

Title: Tocotrienols attenuate obesity-induced cognitive dysfunction by inhibition of brain oxidation

Authors: *Y. KATO, J. BEN, K. FUKUI;
Shibaura Inst. of Technol., Saitama, Japan

Abstract: Recently, it has been reported that obesity induces cognitive dysfunction, but the mechanisms how obesity leads cognitive dysfunction is remained unclear. It is well known that the neurons are degenerated and gradually die due to expose to oxidative stress. Previously, we reported that rats subjected to hyperoxia induced low cognitive function compared to the age-matched controls, and pre-treatment with tocotrienols (T3s) which are one part of vitamin E family inhibit decreasing cognitive function. From these evidence, we hypothesized that obesity may induce cognitive dysfunction via accumulation of brain oxidation. Additionally, treatment with T3s may be effective for inhibition of obesity-related cognitive dysfunction via its antioxidant function. The aims of this study were to elucidate the mechanism of obesity-induced cognitive dysfunction and to measure the improvement effect of cognitive function of T3s. C57BL/6 male mice were treated with high-fat diet (HFD) or high-fat high-sucrose diet (HFSD) with or without 0.05 % T3s. To measure cognitive function, Morris water maze, Rota rod and Open field test were performed. As the result, treatment with HFD did not alter the cognitive function. On the other hand, treatment with HFSD significantly decreased cognitive function, and treatment with T3s significantly attenuated cognitive decline. The lipid peroxide, oxidized-glutathione, protein oxidation levels were measured as the index of brain oxidation. The brain oxidation levels of HFSD-treated mice were significantly higher than those of the controls, and treatment with T3s significantly inhibited obesity-induced brain oxidation. The indexes (Neurotrophic factors and Histone modifications) related in the maintenance of cognitive function except brain oxidation were also measured, but there were no significant differences in all parameters regardless of obesity and T3s. As the conclusions, obesity-induced by HFSD (not HFD) leads to cognitive dysfunction via acceleration of brain oxidation. Treatment with T3s attenuates HFSD-induced brain oxidation and cognitive dysfunction. Now, we are performing proteome analysis to elucidate more detailed molecular mechanisms.
References1. Kato Y, et al., Molecules, 2022.2. Kato Y, et al., J Clin Biochem Nutr, 2021.3. Kato Y, et al., Int J Mol Sci, 2020.4. Fukui K, Kato Y, et al., Nutrients, 2019.

Disclosures: **Y. Kato:** None. **J. Ben:** None. **K. Fukui:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.15

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 NS086890
NIH DP1 DA041722
NIH R01 DA048882
NIH RF1 AG057409
NIH R35 AG071734

NIH R01 AG056259
NIH R01 AG061845

Title: S-nitrosylation of CRTC1 impairs CREB-dependent gene expression induced by neuronal activity

Authors: X. ZHANG[1], N. DOLATABADI[1], *J. C. PINA-CRESPO[1], H. SCOTT[1], M. BLANCO[1], O. PRIKHODKO[2], T. NAKAMURA[1], S. A. LIPTON[1,2];
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Abstract: CRTC1 regulation of CREB-dependent gene expression plays an important role in synaptic plasticity, learning, and memory. Moreover, dysregulated CRTC1 has been implicated in the pathogenesis of Alzheimer's disease (AD). Here, we report for the first time that CRTC1 is inhibited by protein S-nitrosylation, involving reaction of an NO group with a critical cysteine thiol (or more properly thiolate anion) on CRTC1 to form a SNO-protein. We found that aberrant S-nitrosylation of CRTC1, as observed in human AD brain as well as in models using hiPSC-derived cerebrocortical neurons and AD transgenic mice, disrupts CRTC1 binding to CREB, thus inhibiting activity-dependent gene expression. We identified a single Cys residue on CRTC1 as the primary target of NO. Using CRISPR/Cas9 techniques, we mutated this Cys residue to Ala in hiPSC-derived cerebrocortical neurons bearing one allele of the APPswe mutation (AD hiPSC-neurons). Introduction of non-S-nitrosylatable CRTC1 rescued AD-related defects in these neurons, including BDNF production, stunted neurite length, and subsequent neuronal cell death. Taken together, our results demonstrate that formation of SNO-CRTC1 contributes to the pathogenesis of AD by attenuating the neuronal activity-dependent CRTC1/CREB transcriptional pathway.

Disclosures: X. Zhang: None. **N. Dolatabadi:** None. **J.C. Pina-Crespo:** None. **H. Scott:** None. **M. Blanco:** None. **O. Prikhodko:** None. **T. Nakamura:** None. **S.A. Lipton:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.16

Title: WITHDRAWN

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.17

Topic: C.01. Brain Wellness and Aging

Support: RGC-ECS: 24107121
RGC-GRF: 16100219
RGC-GRF: 16100718
NSFC-EYSF: 32022087
Alzheimer's Association: AARF-17-531566

Title: Chronic alcohol metabolism results in DNA repair infidelity and cell cycle-induced senescence in neurons

Authors: *K. H. CHOW[1], J. SUN[1], R. P. HART[2];
[1]The Chinese Univ. of Hong Kong, Hong Kong, Hong Kong; [2]Rutgers Univ., Piscataway, NJ

Abstract: Binge drinking is a risk factor to age-related dementia, but the lasting and irreversible effect of alcohol to the brain remains elusive. Transcriptomic changes in brain cortices revealed pro-aging hallmarks upon chronic ethanol exposure and these changes predominantly occur in neurons. The changes are attributed to the prioritized ethyl alcohol oxidation in these cells through the NADPH-dependent cytochrome pathway, thereby hijacking the folate metabolism of the 1-carbon network which cross talks with the pathway choice of DNA repair through the non-cell cycle-dependent mismatch repair networks. The lost-in-function of such results in de-inactivation of the less preferred cell cycle-dependent homologous recombination repair, forcing these post-mitotic cells to re-engage in a cell cycle-like process. However, since mature neurons are fully differentiated, therefore instead of successfully completing a full round of cell cycle which is necessary for the repair by homologous recombination; these cells are arrested at checkpoints which halts the repair process. The resulting persistence of repair intermediates induces the expression as well as the nuclear-entrance of p21 and cyclin B—a trigger for permanent cell cycle exits and irreversible senescence response. Supplementation of the bioactive 5-methyl tetrahydrofolate simultaneously at times with ethyl alcohol exposure supports the fidelity of the 1-carbon network and hence the activity of mismatch repair. Therefore, this prevents aberrant cell cycle re-entry events as well as the irreversible cellular senescence of neurons. Together, our findings offer a direct connection between binge-drinking behaviour and its irreversible impact to the brain, which makes it a risk factor to dementia.

Disclosures: K.H. Chow: None. **J. Sun:** None. **R.P. Hart:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.18

Topic: C.01. Brain Wellness and Aging

Title: Deconvolution of proteomic signatures in healthy aging, mild cognitive impairment and early Alzheimer's disease in a paired CSF and plasma study

Authors: M. TOGNETTI[1], R. BRUDERER[1], C. MESSNER[1], D. KAMBER[1], A. LEWIS[2], J. DARROW[2], J. VOWINCKEL[1], A. MOGHEKAR[2], L. REITER[1], ***Y. FENG**[1];
[1]Biognosys AG, Schlieren, Switzerland; [2]Dept. of Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Aims:
While aging remains the most significant risk factor for neurogenerative diseases such as Alzheimer's disease (AD) or Parkinson's disease (PD), the biological pathways that are altered in healthy aging vs. pathologic aging leading to the disease onset remain to be elucidated. The lack of success of disease modifying drugs in late-stage clinical trials evidences the need for better biomarkers and biological understanding for age-related onset of neurodegenerative diseases. Here, we seek to address this unmet need by surveying fluid protein biomarkers through a novel mass spectrometry-based workflow. To unveil potential candidates, we analyzed matched CSF and plasma proteomes to investigate healthy aging and cognitive decline associated to the development of AD in its earliest phase.
Methods:
Matched CSF and plasma samples were obtained from individuals at the same visit. Samples were collected from young control subjects (n= 53), subjects with mild cognitive impairment (MCI) (n = 40), age-matched healthy control subjects (n = 40) and subjects with autopsy-proven AD (n = 21). The plasma and CSF samples were subsequently processed to tryptic peptides and analyzed using a Thermo Scientific Orbitrap Exploris 480 equipped with a FAIMS Pro device. Clinical biomarkers (abeta40/42, t-tau, ptau181) were assessed using the Lumipulse G1200 system.
Results:
Our analysis of the above-described cohort resulted in > 5700 proteins in CSF (> 60000 peptides) and > 3100 proteins (> 42000 peptides) in plasma. The depth and breadth of our approach covered numerous pathological mechanisms such as Abeta and Tau pathology, synaptic dysfunction, neuronal injury, endosomal/lysosomal trafficking and neuroinflammation. Using machine learning and classification methods, we identified sets of proteins and proteoforms as molecular discriminants of age and early cognitive decline. Based on published tissue- and cell-specific protein expression data, we classified Furthermore, the correlative analyses of paired CSF and plasma samples also allowed us to assess blood-brain barrier integrity in healthy and early pathological aging.
Conclusions:
Harnessing the power of the latest advancement in mass spectrometry-based technique, we generated a quantitative map of proteins and proteoforms linked to healthy and pathological aging, providing a rich resource for disease biomarker and therapeutic target discovery. Moreover, panels of protein signatures associated with aging and early cognitive decline could be identified. We envision that the monitoring of such panels may contribute to more sensitive disease subtyping and to improve stratification of patient populations.

Disclosures: **M. Tognetti:** A. Employment/Salary (full or part-time):; Biognosys AG. **R. Bruderer:** A. Employment/Salary (full or part-time):; Biognosys AG. **C. Messner:** A. Employment/Salary (full or part-time):; Biognosys AG. **D. Kamber:** A. Employment/Salary (full or part-time):; Biognosys AG. **A. Lewis:** None. **J. Darrow:** None. **J. Vowinckel:** A. Employment/Salary (full or part-time):; Biognosys AG. **A. Moghekar:** None. **L. Reiter:** A.

Employment/Salary (full or part-time):; Biognosys AG. **Y. Feng:** A. Employment/Salary (full or part-time):; Biognosys AG.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.19

Topic: C.01. Brain Wellness and Aging

Title: COVID and the dementias: Frameworks for comparing and mitigating outcomes across scales

Authors: *E. OHAYON[1,2], R. CONCHA[1], E. EDROSA[1];
[1]The Green Neurosci. Laboratory, Neurolinx Res. Inst., La Jolla, CA; [2]The Inst. for Green & Open Sci., Toronto, ON, Canada

Abstract: Early in the COVID-19 pandemic it became clear that outcomes in infection, spread and mortality, disproportionately impacted elderly populations. As the pandemic progressed, the neural impact also became increasingly apparent. In particular, neural symptoms and effects often overlapped those seen in Alzheimer's Disease and Related Dementias (ADRD). However, the relation between these conditions and potential long-term outcomes remain largely unknown. In this study, we performed a review and meta-analysis of the literature in order to construct a framework that might help elucidate the commonalities and differences in underlying mechanisms. First, we identified factors ranging from molecular pathways, system-level vulnerabilities, psychological stress, social and environmental level events. We then categorized and represented commonalities and differences in mechanisms and outcomes using a multi-scale collection of Venn diagrams. These representations help highlight important overlaps, differences and interactions between COVID and ADRD. To then model potential pathways, we drew on an Adverse Outcome Pathways (AOPs) framework but avoided molecular-centric tendencies which can obscure important factors in the causal cascade. In the case of ADRD, these include conflating psychological stress, disparities, and environmental conditions as outcomes rather than critical initiating factors and events. Here we illustrate how moving to a multi-scale framework together with incorporating temporality, recurrence, and other classical neural network modeling techniques can help provide new ways to represent and study COVID-related neurodegeneration. The framework also helps highlight potential overlapping causal pathways and their bi-directionality. Most importantly, understanding the multi-scale, recurrent nature and interrelatedness of these co-occurring conditions may help in implementing mitigating strategies that could impact individual and large-scale population health outcomes.

Disclosures: E. Ohayon: None. **R. Concha:** None. **E. Edrosa:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.20

Topic: C.01. Brain Wellness and Aging

Support: National Institute on Aging (AG067781, AG045571, AG073153)
National Institute on Aging Alzheimer Disease Center (AG072977)

Title: High Levels of the Dendritic Spine Protein Spinophilin in Cognitive SuperAgers

Authors: *R. TAEFI, K. HAYNES, I. A. AYALA, A. BAHRAMI, M. E. FLANAGAN, T. GEFEN, E. J. ROGALSKI, M.-M. MESULAM, C. GEULA;
Northwestern Univ., Mesulam Ctr. For Cognitive Neurol. and Alzheim, Chicago, IL

Abstract: Although memory decline is typically observed throughout the aging process, the Northwestern SuperAging Research Program has identified individuals who maintain superior memory performance in older age. “SuperAgers” (SA) are selected for having episodic memory at age 80 or older that is at least equivalent to those 20-30 years younger. Initial studies show SAs generally have larger cortical volumes, less ApoE4, more von Economo neurons, and less prevalence of Alzheimer’s disease (AD) pathology compared to their cognitively average peers. Loss of synapses is a common feature of cognitive decline associated with aging and AD. Spinophilin is a protein found in dendritic spines, dynamic structures that form the postsynaptic element of a majority of synapses in the CNS. Spinophilin displays distinct localization to the heads of dendritic spines in all brain regions, making it an excellent marker for quantitative assessment of spine integrity, and thus integrity of synapses. We had previously observed overall higher cortical levels of the pre-synaptic protein synaptophysin, and the post-synaptic density 95 (PSD-95) protein in SuperAgers. In the current study, we examined cortical levels of spinophilin using fresh frozen post-mortem human tissue from the middle frontal gyrus (MFG), hippocampus (HPC), middle temporal gyrus (MTG), and visual cortex (VIS) in SuperAgers (n=10), normal cognitive elderly (n=5), and AD patients (n=5). Western blot analysis was carried out using specific antibodies and results were expressed as percentage of the housekeeping protein GAPDH. In most regions, spinophilin levels were lower in the AD participants (5-46% less than control) and higher in all regions for the SA participants when compared with cognitively average elderly (12-41% more than control, $p<0.05$). These preliminary results indicate a potential relationship between the SuperAging phenotype and integrity of dendritic spines as indicated by spinophilin levels. These initial findings will be extended by determination of levels of spinophilin and other synaptic proteins in cortical tissue from additional participants to allow rigorous statistical analyses.

Disclosures: R. Taefi: None. **K. Haynes:** None. **I.A. Ayala:** None. **A. Bahrami:** None. **M.E. Flanagan:** None. **T. Gefen:** None. **E.J. Rogalski:** None. **M. Mesulam:** None. **C. Geula:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.21

Topic: C.01. Brain Wellness and Aging

Support: National Institute on Aging (AG067781, AG045571, AG073153)
National Institute on Aging Alzheimer Disease Center (AG072977)

Title: Cognitive SuperAgers are Protected from Phosphorylated Tau Accumulation in Basal Forebrain Cholinergic Neurons

Authors: *I. AYALA[1], T. GEFEN[2], M. E. FLANAGAN[1], E. J. ROGALSKI[3], M.-M. MESULAM[4], C. GEULA[5];
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Abstract: Cognitive SuperAgers are Protected from Phosphorylated Tau Accumulation in Basal Forebrain Cholinergic Neurons

Ivan Ayala, Tamar Gefen, Margaret E. Flanagan, Emily Rogalski, M.-Marsel Mesulam and Changiz Geula

Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Cognitive decline in memory has been well documented as a normal phenomenon of "typical" human aging. However, some elderly appear to avoid this age-related cognitive decline. We have coined the term 'SuperAger' to refer to individuals over the age of 80, whose performance on tests of episodic memory is at least equivalent to healthy 50-65 year-olds, and on tests of other cognitive domains at least equivalent to their cognitively normal aged peers. In a previous study, we described the presence of age-related alterations in the basal forebrain cholinergic system in the form of abnormalities in cortical cholinergic axons and accumulation of phosphorylated tau in basal forebrain cholinergic neurons (BFCN). Our preliminary findings indicated significantly lower abnormalities in cortical cholinergic axons in SuperAgers when compared with cognitively average elderly. In the present study, we investigated accumulation of phosphorylated tau in the BFCN in SuperAgers using the PHF1 antibody, which recognizes tau phosphorylated at Ser396/404 / Thr181. The number of magnocellular basal forebrain neurons containing PHF1 immunoreactivity were counted in sections spanning the basal forebrain using a counting box at 10X magnification and were expressed as average counts per section. BFCN containing PHF1 immunoreactivity were present in all SuperAger (N=6) and age-matched, cognitively average control (N=5) participants. However, significantly lower numbers of BFCN per section in SuperAgers contained PHF1 immunoreactivity when compared with cognitively average elderly ($p = 0.03$). Combined with our previous observations of lower numbers of abnormalities in cortical cholinergic axons, our findings indicate maintained integrity of the basal forebrain cholinergic system in SuperAgers. These observations are consistent with other reports indicating an overarching resistance of SuperAger brains to involutional processes that

characterize normal human brain aging. Given the known involvement of the basal forebrain cholinergic system in cognitive processing of memory, the preserved integrity of this system is a likely contributor to the greater memory capacity of SuperAgers.

Disclosures: I. Ayala: None. **T. Gefen:** None. **M.E. Flanagan:** None. **E.J. Rogalski:** None. **M. Mesulam:** None. **C. Geula:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.22

Topic: C.01. Brain Wellness and Aging

Support: Deakin University (PhD scholarship)
IMPACT Institute Seed Funding, Faculty of Health, Deakin University

Title: Asthma and mental health: transcriptome analysis within the hypothalamus of asthmatic mice reveals genes associated with mood disorders highlighting the lung-brain crosstalk

Authors: *E. M. B. AHMED[1,3], I. ERASLAN[1], L. VOGLSANGER[1], M. ZIEMANN[2], C. SUPHIOGLU[2], A. J. WALKER[1], O. M. DEAN[1,4], J. READ[5], C. M. SMITH[1];
[1]Fac. of Health, Sch. of Medicine, (IMPACT), [2]Fac. of Science, Engin. and Built Environment, Sch. of Life and Envrn. Sci., Deakin Univ., Geelong, Australia; [3]Fac. of Sci., Ain Shams Univ., Cairo, Egypt; [4]Florey Inst. of Neurosci. and Mental Hlth., The Univ. of Melbourne, Melbourne, Australia; [5]Murdoch Children's Res. Inst., Royal Children's Hosp., Melbourne, Australia

Abstract: Rationale Current literature suggests a strong correlation between different states of lung inflammation (e.g. as asthma) and mental illness including depression and anxiety. However, the molecular links underlying such lung-brain axis remain ambiguous. Dysfunction within the hypothalamus is a hallmark of many psychiatric diseases, particularly those with an inflammatory component due to many hypothalamic regions being unprotected by the blood brain barrier. In order to gain a better insight into such neuropsychological sequelae, this study aimed to interrogate gene expression differences in the hypothalamus by employing RNA transcriptome profiling after lung inflammation induction (i.e. asthma) in mice. **Methodology (a)** Two asthma models were utilised involving BALB/c mice to ensure consistency of results. The 1st mouse model was sensitized to the immunogen by IP injection with 100µg/kg lipopolysaccharide (LPS, *E. coli*, serotype 026:B6), once per week for 3 consecutive weeks. Mice were then challenged with nebulized LPS (0.05% (wt/vol%) in vapour chambers once/day/20min for 3 consecutive days, followed by once/week for 3 additional consecutive weeks. Likewise, the 2nd model, ovalbumin (OVA, 10µg, chicken egg) in alum adjuvant and 1% (wt/vol%) (OVA) were used for the sensitization and challenge phases, respectively. **(b)** The majority of the hypothalamus was micro-dissected from rostral to caudal by biopsy punch pens (cylindrically shaped, Bregma 0.50mm to -2.92) from serial 100 µm coronal brain sections. **(c)**

Total RNA was extracted then sequenced using standard protocols for Illumina NovaSeq6000. **(d)** Bioinformatics approaches were used, including DESeq2 and mitch Bioconductor package to assay differential expression between control and asthmatic groups. **Results** Asthma models were successfully validated (histopathologically) in post-mortem lungs, which showed typical signs of asthma including perivascular/peribronchial inflammation, mucus hypersecretion and airway remodelling. Moreover, this study identified differentially expressed gene candidates, including galanin (*GAL)* and interferon regulatory factor 7 (*IRF7*), which have previously been linked with mood disorders. Novel gene pathways associated with monoamine signalling and neuroplasticity were also altered in these models of asthma. **Conclusion**: These significant findings identify novel pathways altered in the hypothalamus due to lung inflammation. The importance of characterising these novel biological targets will contribute to the understanding of lung-brain crosstalk, improve mental illness outcomes and lead to the development of alternate therapies.

Disclosures: E.M.B. Ahmed: None. **I. Eraslan:** None. **L. Voglsanger:** None. **M. Ziemann:** None. **C. Suphioglu:** None. **A.J. Walker:** None. **O.M. Dean:** None. **J. Read:** None. **C.M. Smith:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.23

Topic: C.01. Brain Wellness and Aging

Support: NIA AG067781
NIA AG045571
NIA AG073153
NIA AG072977

Title: Von Economo neurons of the anterior cingulate cortex in the oldest-old with superior memory capacity

Authors: *K. SHEN[1], A. REZVANIAN[1], I. A. AYALA[1], T. GEFEN[1], M. M. MESULAM[1], E. J. ROGALSKI[1], M. CORRADA[2], C. KAWAS[2], C. GEULA[1];
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Abstract: Northwestern SuperAging studies show that elderly with exceptional memory have thicker anterior cingulate cortices. One potential contributor is increased density of von Economo neurons (VENs). Prior studies have found increased anterior cingulate VEN density in SuperAgers compared to both elderly and young controls. This does not appear to be a function of total neuronal density as total neuron counts were similar in the three groups. Prior

Northwestern SuperAging studies have also revealed lower Alzheimer tangle pathology within the anterior cingulate of elderly with high memory performance suggesting an association between tangle pathology and VEN density. The purpose of the current study was to replicate the past findings of higher VEN density in a different cohort of elderly with exceptional memory performance. Eight participants from the 90+ study, a community-based study of cognitive status, aged 95-100 years, were selected based on equal to or better performance than normative values for 50-65 year-olds on the California Verbal Learning Test-Short Form of episodic memory. Sections from the anterior cingulate cortex (Brodmann areas 24, 25 / 32) were stained for Nissl using Cresyl violet. Numbers of VENs per section were determined using a counting box at 10X magnification. As a group, these participants had high counts of VENs (31±2 per section), consistent with previous findings. However, there was variation between participants. Three participants displayed VEN counts that were exceptionally high (78±5 per section). Two showed VEN counts that were intermediate (35±2 per section), and the remaining three showed counts expected in cognitively average 90+ elderly (18±1 per section). We found a spectrum of overall Alzheimer's disease (AD) pathology in the eight cases, with two virtually free of such pathology and two satisfying pathologic criteria for AD. The variation in VEN counts did not show a relationship to overall AD pathology based on tangle and plaque counts in the middle frontal gyrus and hippocampus. The findings of high VEN counts in the anterior cingulate cortex are consistent with previous reports in elderly with exceptional memory function. Counts of plaques and tangles in the anterior cingulate cortex will be necessary to determine if VEN counts are related to local counts of AD pathology in this cohort.

Disclosures: K. Shen: None. **A. Rezvanian:** None. **I.A. Ayala:** None. **T. Gefen:** None. **M.M. Mesulam:** None. **E.J. Rogalski:** None. **M. Corrada:** None. **C. Kawas:** None. **C. Geula:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.24

Title: WITHDRAWN

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.25

Topic: A.09. Adolescent Development

Title: Aggression for boys, anxiety for girls: effects of mild traumatic brain injury on adolescents' affective symptoms

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Abstract: Mild traumatic brain injury (mTBI) leads to hundreds of thousands of pediatric/adolescent emergency room visits each year in the USA alone. Most patients' physical symptoms resolve within several weeks to months and medical care ends. But emerging findings reveal persistent cognitive, affective, and behavioral symptoms in adult mTBI populations. To test whether this pattern extends to adolescents, we used the Adolescent Brain Cognitive Development (ABCD) Study. The ABCD Study is a large, longitudinal study tracking adolescents from age 9/10 for a decade, collecting behavioral, biologically and neuroimaging data from enrolled individuals, and additional measures from parents. Data from ABCD Study Waves 1 and 2 were included in these analyses. Multivariable binary logistic regression models examined associations between a new mTBI (within the last year), a past mTBI (> 1 year), or recent and past mTBI, affective (aggression, depression, anxiety) and behavioral (somatic, thought, social, attention, ADHD, conduct) disorders while controlling for demographic factors and baseline affective symptoms. The results revealed different patterns of results as a function of sex. Boys who experienced a new mTBI were more likely to report significantly heightened aggression. Both boys and girls who had a past mTBI were more likely to experience anxiety. The most striking pattern was in girls who had a new and a past mTBI. In these adolescent girls, anxiety, aggression, social problems, thought disorder, and conduct disorder of clinically relevant levels were significantly more likely. Thus, boys and girls exhibit different short- and long- term outcomes after mTBI. One conclusion is that adolescents who have had an mTBI should be carefully screened for affective and behavioral symptoms well beyond physical recovery.

Disclosures: M.E. Berryhill: None. **P.T. Veliz:** None.

Poster

744. Molecular Mechanisms of Neurodegenerative Processes

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 744.26

Topic: C.01. Brain Wellness and Aging

Title: Transcallosal Fiber Reprofiling in High-grade Glioma: Complementarity between Whole-brain and Hemisphere-specific Features

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Abstract: Structural damage to cerebral integrity forms a significant subset of brain disorders; such damage can be caused by space-occupying lesions (SOL), such as tumors, hematoma, cerebral abscess, focal encephalitis, granuloma, tuberculoma, tumefactive multiple sclerosis, etc. Important space-occupying lesions are proliferative ones, where the causative agent replicates or grows, as in a tumour, tuberculoma, cysticercosis, granuloma or focal encephalitis. There are neuroplasticity changes about the space-occupying lesion as the cerebral hemispheres endevours to undergo compensatory architectural andconnectivity changes. The corpus callous, the main linkage between the hemispheres, may also undergo re-structuration due to such lesions. Generally, corpus callosum is thought of only from the mid-sagittal perspective as a C-shaped tissue bridge of about 0.5 cm thickness, between the two hemispheres. However,less investigated has been transverse fibres running through it (trans-callolar fibres). We have given attention to those glioma subjects withoutmalignant infiltration of corpus callosum, as we are interested to know the effect of glioma tumour mass onthe lengthy transcallosal fibres travelling across the two hemispheres per se, instead of the effect of gliomainvasion on the thin corpus callosum bridge. We have utilized several microstructural diffusioncharacteristics, as well as fiber tractography-based connectivity measures to examine the whole-brainarchitecture and hemisphere-specific alterations of integrity and structural connectivity of trans-callosalfibres. We have also elucidated Wallerian-like degeneration and Axonotmesis-Endoneuritis type neuralimpairment of transcallosal fibres observed glioma, so as to obtain an understanding and insight on thealteration on structural connectivity and diffusivity properties, as well as white matter reprofilingassociated with space occupying lesions in general, and cerebral malignant lesions in particular.

Disclosures: V. Pareek: None. **S. Paul:** None. **P.K. Roy:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.01

Topic: H.12. Aging and Development

Support: NIH R01AG072714
T32AG061892
Florida Department of Health Award 21A11
McKnight Brain Research Foundation

Title: Effects of chronic oral THC self administration on working memory in aging

Authors: *S. ZEQUEIRA[1], E. GAZAROV[3], A. GÜVENLI[1], E. BERTHOLD[1], A. SHARMA[1], C. R. MCCURDY[1], J. L. BIZON[4], B. SETLOW[2];
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Abstract: Individuals over age 65 have become the fastest-growing demographic of cannabis users. As the number of older adults in the US is expected to reach 90 million by 2050, it is imperative to understand the potential cognitive impacts of cannabis use in this population. Cannabis (as well as cannabinoids such as delta-9-tetrahydrocannabinol (THC), the major psychoactive component of cannabis) tend to impair cognitive performance, but almost all studies of cannabis and cannabinoids have been conducted in young adult subjects. Given that many aged individuals already exhibit cognitive deficits, it is important to determine how cannabis/cannabinoids affect cognition in this population. To address this issue, we evaluated the effects of chronic oral THC self-administration on performance in a working memory task in rats. Young adult (5 months) and aged (23 months) Fischer 344 x Brown Norway F1 hybrid rats of both sexes were trained in operant chambers on a delayed response working memory task, in which they had to remember the left/right position of a response lever over short delays (0-24 s) to earn food rewards. Upon reaching stable performance, rats were given 3 weeks of daily 1-hour access to either plain gelatin or gelatin containing 1.0 mg/kg THC in their home cage in the afternoons, while testing in the working memory task continued in the mornings. As expected, among rats that consumed plain (control) gelatin, aged rats performed worse than young, particularly at longer delays. In the young group, rats that consumed THC gelatin performed comparably to rats that consumed plain gelatin. In the aged group, however, rats that consumed THC gelatin performed more accurately than rats that consumed plain gelatin, particularly at long retention delays. These findings suggest that under some conditions (poor baseline performance and/or advanced age), cannabis may provide cognitive benefits, even when consumed chronically. A follow-up study evaluated the effects of chronic oral THC consumption on circulating inflammatory markers. A naïve cohort of aged rats (24 months) underwent 3 weeks of daily THC consumption (1.0 mg/kg), and blood samples were drawn at the completion of the regimen. Compared to control rats that consumed plain gelatin, rats that consumed THC gelatin had reduced levels of some pro-inflammatory cytokines (e.g., TNFα) and increased levels of some anti-inflammatory cytokines (e.g., IL-10), suggesting that reductions in peripheral inflammation could mediate the effects of chronic THC on cognitive performance.

Disclosures: S. Zequeira: None. **E. Gazarov:** None. **A. Güvenli:** None. **E. Berthold:** None. **A. Sharma:** None. **C.R. McCurdy:** None. **J.L. Bizon:** None. **B. Setlow:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.02

Topic: H.12. Aging and Development

Support: NIH Grant RF1AG060778
McKnight Brain Research Foundation

Title: Sex differences in the effects of age on prefrontal cortex-mediated cognition in Fischer 344 x Brown Norway F1 hybrid rats

Authors: *K. M. GONZALEZ[1], M. FARAJI[2], A. HAYMOV[3], V. S. KELLEY[1], J. L. BIZON[1], B. SETLOW[2];
[1]Neurosci., [2]Psychiatry, [3]Univ. of Florida, Gainesville, FL

Abstract: Aging is associated with alterations in multiple aspects of prefrontal cortex (PFC)-mediated executive functions. Such cognitive alterations can be modeled in rats, but the majority of such work has been conducted exclusively in males. With the recent availability of aged females, we began initial evaluations of young adult (6 mo.) and aged (22 mo.) Fischer 344 x Brown Norway F1 hybrid rats of both sexes in intertemporal choice, working memory, probabilistic reversal learning, and progressive ratio tasks, on all of which young adult and aged males have been shown previously to differ. In the intertemporal choice task, in which rats made choices between a small, immediate food reward vs. a large, delayed food reward delivered after a variable delay period (0-60s), there were neither age nor sex differences, which was inconsistent with previous findings. In the working memory task, in which rats had to remember the location of a lever over a delay period (0-24s), aged males were impaired relative to young males (particularly at long delays) whereas young and aged females performed comparably. In contrast, in the probabilistic reversal learning task, in which rats had to learn to discriminate between two levers that were reinforced at different probabilities and then switched multiple times per session, there was a significant sex difference, with females performing more reversals than males. Finally, in the progressive ratio task, in which the number of lever presses required to earn a food reward increased with each successive reward earned, there were significant age effects, with young rats pressing more and earning more food than aged. Data from this initial experiment suggest that aging may have both qualitatively and quantitatively different effects on executive functions in males and females, and highlight the importance of using both sexes in studies employing animal models of cognitive aging. Ongoing experiments are evaluating additional rats in a set-shifting task, to determine whether the age and sex differences described above extend to an additional measure of cognitive flexibility.

Disclosures: K.M. Gonzalez: None. **M. Faraji:** None. **A. Haymov:** None. **V.S. Kelley:** None. **J.L. Bizon:** None. **B. Setlow:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.03

Topic: H.12. Aging and Development

Support: The McKnight Brain Research Foundation
NIH/NIA 1R01AG049722
Thomas H. Maren Award Junior Investigator Fund

Title: Hippocampalca3 glucose levels in aged and young rats during rest and exploration: implications for ketogenic diet therapy

Authors: M. F. RAMIREZ[1], *C. N. LOGAN[1], R. C. FISHMAN[1], S. N. BURKE[2];
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Abstract: Cognitive decline is common in advanced age and interferes with independent living and quality of life. The hippocampus is among the brain regions that are vulnerable to age-related dysfunction and pathology. Within the CA3 subregion of the hippocampus, there is a disruption of the balance between inhibition and excitation that is associated with higher firing rats of excitatory pyramidal cells. One theory is that this hyperactivity is related to impaired glucose utilization and decline of neurometabolism, which can induce seizure-like activity in vulnerable circuits. In support of this idea, there is a reduction in the expression of transporters related to glucose and the major excitatory neurotransmitter glutamate in the aged compared to young hippocampus. Utilization of the high fat, low carb ketogenic diet improves cognition, by producing a metabolic shift from glucose utilization to ketone bodies. This metabolic shift to ketone bodies restores glutamate transporter expression and increases GABA transporter levels in the aged hippocampus. To assess how glucose levels are altered by age, we utilized *in vivo* microdialysis in the CA3 of young and aged rats. Rats were probed and 10-minute baseline samples were collected for an hour. Rats were then placed into a novel context, and 10-minute samples were collected for an hour. A recovery period was also assessed for an hour following exposure to the novel context. A separate group of rats were fed either a ketogenic diet or a calorie-matched control diet prior to undergoing microdialysis collections. High performance liquid chromatography was used to quantify glucose levels using a refractive index detector. We found that there was an increase in glucose levels in the CA3 of aged rats compared to young rats when they were exposed to a novel context. Samples are currently being processed to compare the effects of the ketogenic diet on glucose levels in aged and young rats. This work will help understand glucose modulation in the CA3 of the aged brain and how this relates to improvements in performance related to the ketogenic diet.

Disclosures: M.F. Ramirez: None. **C.N. Logan:** None. **R.C. Fishman:** None. **S.N. Burke:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.04

Topic: H.12. Aging and Development

Support: RF1AG060778
R01DA036534
K99DA041493
5T32AG061892-04

Title: Contributions of ventral tegmental area dopamine neurons to decision making under risk of punishment.

Authors: *W. PYON, S. BLAES, C. ORSINI, O. VIERA, K. GONZALEZ, S. JOSEPH, J. BARRETT, S. BETZHOLD, J. DIEDRICH, S. ATHAVALE, R. SAMANTA, B. BERRIOS, L. CAO, A. PETRISEK, S. SINGHAL, C. J. FRAZIER, J. L. BIZON, B. SETLOW;
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Abstract: Decision making necessitates numerous brain regions working in concert to obtain a desired outcome. At the root of this behavior lies dopamine signaling arising from the ventral tegmental area (VTA). The VTA plays a fundamental role in biasing decision-making processes, and dysfunction in this system accompanies maladaptive decision making in conditions such as substance use disorder. To elucidate the functional role of VTA dopamine neurons in decision making under the risk of punishment, male and female tyrosine hydroxylase-cre transgenic rats underwent calcium imaging during performance of a "risky decision-making task" in which rats made discrete choices between two levers: a small reward lever that dispensed one food pellet and a large reward lever that dispensed two food pellets accompanied by variable risks of mild footshock (0%, 25%, 75%). Preliminary recordings show an increase in neuronal activity in VTA dopamine neurons during anticipation and receipt of the large reward in the absence of punishment. Activity drops to baseline when that same reward was punished.
To further elucidate the role of VTA dopamine neuron activity during risky decision making, the inhibitory opsin, halorhodopsin, was expressed in VTA dopamine neurons to enable selective inhibition of activity during discrete timepoints of the decision-making process (during deliberation prior to lever selection, during receipt of the small reward, during receipt of the large reward with or without punishment, or during the intertrial interval). Preliminary findings show that inhibition of VTA dopamine neurons during receipt of the large reward in the absence of punishment (thus mimicking the decrease in activity induced by punishment itself) causes rats to become more likely to choose the small safe reward on subsequent trials. This shift toward risk-averse behavior is supported by our current understanding of reward prediction error signaling, with optogenetic inhibition of dopamine neuron activity potentially mimicking a reduction in tonic firing as found with a negative prediction error (i.e., a signal that the outcome of a choice was worse than expected).

Disclosures: W. Pyon: None. **S. Blaes:** None. **C. Orsini:** None. **O. Viera:** None. **K. Gonzalez:** None. **S. Joseph:** None. **J. Barrett:** None. **S. Betzhold:** None. **J. Diedrich:** None. **S. Athavale:** None. **R. Samanta:** None. **B. Berrios:** None. **L. Cao:** None. **A. Petrisek:** None. **S. Singhal:** None. **C.J. Frazier:** None. **J.L. Bizon:** None. **B. Setlow:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.05

Topic: H.12. Aging and Development

Support: Mckight Brain Research Foundation
NIH/NIA 2RF1AG049722

NIH/NIA K9AG058786
McNair Scholars Program

Title: Adaption and validation of the mnemonic similarity task to an operant touchscreen platform for rodent models of cognitive aging

Authors: *A. ROSS[1], C. N. LOGAN[2], T. GATTON[4], J. L. BIZON[5], A. P. MAURER[3], S. JOHNSON[6], S. N. BURKE[3];
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Abstract: The neurobiological basis of cognitive aging and brain resilience are currently unknown due to a limited understanding of the neural circuits responsible for cognitive decline. Previous work has demonstrated that older adults are impaired in their ability to distinguish between similar stimuli, referred to as mnemonic discrimination. In effort to translate behavioral assessments used in clinical settings, we have adapted the human mnemonic similarity task (MST) (e.g., Stark et al., 2013) for rodents. Using a variant of the object-cued spatial choice task developed by Ahn and Lee (2015), young (4 months) and adult (21 months) Fischer344 Hybrid x Brown Norway rats were tested on the rodent MST in a touchscreen operant chamber. This task requires rats to discriminate between morphed stimuli that share varying levels of overlapping visual features across trials. Results show that aged rats were less accurate at performing this task than young animals. To further understand the neurobiology of this impairment, we are currently manipulating neural activity via the utilization of Designer Receptor Exclusively Activated by Designer Drugs (DREADDs). Adeno-associated viral vectors will be used to selectively express an inhibitory DREADD to inhibit signaling between the prelimbic cortex (PrL) and the perirhinal cortex (PER), which are two brain regions that are vulnerable in old age and critical for MST performance. These experiments are ongoing, but we hypothesize that manipulating PrL-PER activity will alter MST performance. Together these experiments may provide insight into how coordinated neural activity supports behavior and is disrupted in advanced age.

Disclosures: A. Ross: None. **C.N. Logan:** None. **T. Gatton:** None. **J.L. Bizon:** None. **A.P. Maurer:** None. **S. Johnson:** None. **S.N. Burke:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.06

Topic: H.12. Aging and Development

Support: McKnight Brain Research Foundation
NIH Grant RF1AG060977
FLDOH Grant 20A16

Title: Cognitive effects of AAV-mediated human wild-type tau overexpression in the perirhinal cortex of rats

Authors: *J. SEEDANSINGH[1], C. N. LOGAN[3], A. BROTGANDEL[4], S. L. LOVETT[5], J. J. THOMPSON[4], J. FRANKLIN[4], M. F. RAMIREZ[4], T. J. GATTON[7], P. CHAKRABARTY[4], B. I. GIASSON[8], A. V. BUMANGLAG[9], J. L. BIZON[2], S. N. BURKE[6];
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Abstract: Intracellular inclusions comprised of tau proteins are among the earliest pathological features observed in Alzheimer's disease (AD). Although transgenic animal models have been useful in understanding AD-related tau pathology, it remains unclear how tau inclusions occurring with normal aging in the transentorhinal cortex affects cognition. We evaluated the behavioral effects of human wildtype tau overexpression in area 35 of the perirhinal cortex, which is homologous to the human transentorhinal cortex. Male (n=8) and female (n=8) F344/BN rats (aged 6-8 mo) received intercranial injections of adeno-associated viral vector containing either human wild-type tau (AAV-hWTtau) or eGFP alone (AAV-GFP) into 3 injection sites along the longitudinal extent of the perirhinal cortex area 35. After a 2-week recovery period, rats were behaviorally assessed on the paired associates learning (PAL) task in touchscreen operant chambers (Smith et al., 2021). After completion of PAL testing, spatial reference memory was assessed on the Morris watermaze. Two weeks following cognitive testing, animals were transcardially perfused and brains were processed for immunohistochemistry to assess Tau or eGFP expression within the perirhinal cortex and associated structures. PAL performance was not significantly different between the AAV-hWTtau and AAV-GFP groups, however, both groups were less accurate than rats that had previously been tested on PAL that had not received AAV injections. These data suggest that the surgical procedures or overexpression of Tau or eGFP in the transentorhinal cortex leads to behavioral impairments. Future experiments will include injections of an empty AAV vector to directly assess effects of protein overexpression.
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Disclosures: J. Seedansingh: None. **C.N. Logan:** None. **A. Brotgandel:** None. **S.L. Lovett:** None. **J.J. Thompson:** None. **J. Franklin:** None. **M.F. Ramirez:** None. **T.J. Gatton:** None. **P. Chakrabarty:** None. **B.I. Giasson:** None. **A.V. Bumanglag:** None. **J.L. Bizon:** None. **S.N. Burke:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.07

Topic: H.12. Aging and Development

Support: NIH/NIA 1R01AG049722
NIH/NIA T32-AG061892
Evelyn F. McKnight Brain Research Foundation
NIH/NIA R01AG055544

Title: Age-related alterations in theta-gamma interactions are evident in the ca3, but not ca1, of male rats

Authors: *N. DICOLA, A. LACY, K. KIMSEY, J. WHITNEY, S. LOVETT, P. TOH, A. SHEREMET, A. MAURER, S. BURKE;
Univ. of Florida, Gainesville, FL

Abstract: The theta oscillation (6-12 Hz) is a ubiquitous rhythm found throughout the brain that is observed during attentive behavior, locomotion, and REM sleep. During movement, the frequency of the theta rhythm is robustly modulated by running speed. Moreover, theta is correlated with the power of the gamma oscillation, which is a higher frequency rhythm (50-120 Hz) related to local inhibitory-excitatory circuits. In CA1 of the hippocampus, both rhythms have been reported to change with age. Specifically, while the frequency of the theta rhythm in young and aged rats increases with running speed, theta frequency for a given velocity is slower in aged rats (Shen et al., 1997; Crown et al., 2022). Moreover, it has recently been reported that gamma modulation by running speed is attenuated in aged compared to young rats (Crown et al., 2022). Interactions between theta and gamma have also been reported to change with age, with aged rats exhibiting less gamma amplitude modulation by theta phase than their young counterparts (Jacobson et al. 2013). However, all previous investigations have used either tetrodes, which do not allow for consistent anatomical localization between animals, or been relegated to the CA1 pyramidal layer, which is not among the hippocampal lamina in which aged-related differences in synaptic input have been observed. Moreover, the CA3 subregion of the hippocampus is known to show age-related disruptions in inhibition, and no studies to date have examined theta and gamma in this subregion with respect to age. We therefore implanted young (4- to 6-month-old) and aged (23- to 26-month-old) male, Fisher Brown-Norway hybrid rats with linear, 64 channel silicon probes that spanned 3.15 mm from the pyramidal oriens to the thalamus. Hippocampal sub-layers were then identified using current source density analysis to find areas of ionic sinks and sources known to occur in specific hippocampal lamina (Bragin et al. 1995, Ylinen et al. 1995), allowing for accurate and consistent probe localization. Across the hippocampus, theta frequency was lower in aged compared to young rats even when running speeds were equivalent; however, theta power and its non-linearity were only altered in CA3 but not the CA1 lacunosum moleculare or radiatum. Additionally, the modulation of gamma by theta as well as theta-gamma phase coupling was attenuated in aged relative to young rats in CA3, but not other subregions. This suggests that pyramidal cell-interneuron interactions in CA3 may become less influenced by afferent input, possibility due to reduced synaptic drive from the

entorhinal cortex. These observations highlight CA3 as being particularly vulnerable to functional alterations.

Disclosures: **N. DiCola:** None. **A. Lacy:** None. **K. Kimsey:** None. **J. Whitney:** None. **S. Lovett:** None. **P. Toh:** None. **A. Sheremet:** None. **A. Maurer:** None. **S. Burke:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.08

Topic: H.12. Aging and Development

Support: Florida Department of Health Ed and Ethel Moore Alzheimer's Disease Research Program Award 21A11
McKnight Brain Research Foundation

Title: Cannabinoid pharmacokinetics following exposure to cannabis smoke in mice

Authors: *E. GAZAROV[1], S. ZEQUEIRA[2], A. SENETRA[3], J. HOWARD[2], A. SHARMA[3], C. MCCURDY[4], J. LEWIS[2], J. L. BIZON[2], B. SETLOW[1];
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Abstract: With the rise in cannabis use among older adults, as well as increasing cases of Alzheimer's disease (AD), there is an urgent need to understand how cannabis impacts the aging brain and AD pathology. Mice offer a tractable preclinical model in which questions concerning such effects of cannabis can be addressed. As a first step in this process, we evaluated the pharmacokinetics of THC and several of its metabolites following acute exposure to smoke from burning cannabis cigarettes in mice of different ages and strains. To determine the time course of Δ9THC (the primary psychoactive component of cannabis) as well as two major metabolites of Δ9THC (11-nor-9-carboxy-Δ9THC and 11-hydroxy-Δ9THC), male and female C57BL/6J mice (n = 72, half female) were exposed to smoke generated from burning 5 cannabis cigarettes over one hour. Following smoke exposure, trunk blood and brain were collected at 6 time points (10, 20, 40, 60, 120 & 240 min following exposure). Plasma and brain homogenates were analyzed for Δ9THC and metabolites using a validated ultraperformance liquid chromatography-tandem mass spectrometry method. To assess the effects of age and strain on THC pharmacokinetics, male and female B6, FVB, SW, and 129 mice ranging from 4-24 months (n = 91) followed the same smoke regimen, with samples collected at two time points following exposure (10 and 40 min). Results from the time course study revealed that plasma Δ9THC concentrations peaked at 10 min for both males and females, while brain Δ9THC concentrations peaked at 20 and 40 min for females and males, respectively. Females also had significantly greater plasma 11-nor-9-carboxy-Δ9THC concentrations than males. There were no age or strain differences in plasma Δ9THC concentrations at 10 or 40 min; however, there was a significant main effect of strain on brain Δ9THC concentrations, with 129 mice having significantly higher levels than FVB mice.

Sex differences in plasma 11-nor-9-carboxy-Δ9THC concentrations were observed in this experiment as well, with females achieving higher levels than males. Ongoing studies are determining how chronic cannabis smoke exposure affects gene and protein expression in young adult and aged C57BL/6J mice.

Disclosures: **E. Gazarov:** None. **S. Zequeira:** None. **A. Senetra:** None. **J. Howard:** None. **A. Sharma:** None. **C. McCurdy:** None. **J. Lewis:** None. **J.L. Bizon:** None. **B. Setlow:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.09

Title: WITHDRAWN

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.10

Topic: H.12. Aging and Development

Support: McKnight Brain Research Foundation
NIH R01AG055544

Title: Investigating rodent dorsal striatum in age-related decline of hippocampal-associated behavior

Authors: *S. SMITH, S. LOVETT, N. DICOLA, E. GARCIA, A. MONTELONGO, S. MATHUR, C. DAVIDSON, S. BURKE;
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Abstract: For many older adults, the lifespan exceeds the span of cognitive health. Increasing cognitive longevity in our older adult population requires understanding the neurobiology of age-related cognitive decline as well as the mechanisms underlying preserved and adaptive cognition in old age. The hippocampus (HPC) is particularly vulnerable to age-related pathology, and most cognitive aging research has focused on its dysfunction. Conversely, the dorsal striatum (DS), may be resilient in certain aspects of cognition during normal aging (Gardner et al. 2020) and has been less widely studied. In spatial navigation contexts, a shift from HPC to DS-dependent learning with age has been extensively shown (Barnes 1980; Pereira et al. 2015). Furthermore, inactivation of the DS in aged rodents has recently been reported to rescue HPC-dependent

spatial learning (Gardner et al. 2020). Currently, it is unclear what role the DS has in other learning contexts in regard to age-related cognitive decline. To test the hypothesis that inactivation of the DS can rescue other age-related cognitive declines, the current study bilaterally inactivated the DS of young (n=8) and aged (n=7) rats during paired associates learning (PAL). PAL is an automated, touchscreen-based platform that assesses visuospatial associative learning, and we have shown that this task is sensitive to age-related cognitive decline in male rats (Smith, Zequeira, et al. 2022). This study found that inactivation of the dorsal striatum did not alter PAL performance in young or aged rats ($T_{(7)}$=1.258, p = 0.249; aged: $T_{(6)}$ = 0.098, p = 0.925), but did alter a control, DS-dependent spatial navigation task ($F_{(59,184)}$ = 11.67, p < 0.0001). To further investigate why inactivation of the DS may improve aged animals' performance on HPC-dependent navigation tasks, but not on other HPC-dependent tasks, current experiments using *in vivo* electrophysiology in the HPC and DS during spatial and associative learning are ongoing.

Disclosures: S. Smith: None. **S. Lovett:** None. **N. DiCola:** None. **E. Garcia:** None. **A. Montelongo:** None. **S. Mathur:** None. **C. Davidson:** None. **S. Burke:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.11

Topic: H.12. Aging and Development

Support: NIH/NIA 1RF1AG049722

Title: A deep learning-based pipeline for multimodal image analysis to interrogate the neurobiology of cognitive aging

Authors: *L. A. GJESTEBY[1], S. M. SMITH[2], M. SNYDER[1], D. CHAVEZ[1], M. FEBO[3], D. G. LAMB[3], L. J. BRATTAIN[1], S. N. BURKE[2];
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Abstract: Studying the neurobiological correlates of cognition and behavioral impairments in aging and disease necessitates bridging spatial and temporal scales of different data modalities to enhance the translational potential of discovery research using animal models. The temporal and spatial resolution of non-invasive imaging precludes an ability to determine specific cellular mechanisms in humans. Conversely, animal models have linked discrete cellular and synaptic changes to behavioral impairments, but the limited scope of brain regions investigated in previous animal studies restricts the ability to link cellular changes to the organization of distributed neural networks that support cognitive function. Thus, the development of therapeutic strategies for enhancing network dysfunction is impeded by a lack of understanding regarding how the constellation of different age-related neurobiological changes at the cellular level influences the organization of functional networks across the brain that support cognition. This

project details cross-disciplinary efforts to combat this problem through the use of light sheet microscopy and three-dimensional solvent-cleared brain tissue, structural magnetic resonance (MR) imaging, and machine learning algorithms tailored to these high-resolution data sets for analysis. The main features of this analysis pipeline include MR-light sheet co-registration, ROI segmentation, and deep learning segmentation algorithms for centroid detection and fiber tracing.
As a core component of this pipeline, a three-dimensional U-Net was developed to perform segmentation of c-Fos positive neuronal nuclei in light-sheet microscopy image volumes. The algorithm was trained and validated on two separate manually-labeled image stacks of the cortex region measuring 1920 x 1920 x 21 voxels and 951 x 1272 x 15 voxels, respectively, at a resolution of 0.227 um x 0.227 um x 1 um. Then, the algorithm was applied to light sheet image volumes of the hippocampus region at 4x and 12x magnification. Qualitative assessment confirmed high accuracy of segmentation and centroid localization of c-Fos positive neurons. Visual analysis is supported by quantitative metrics, including precision, recall, and F1-score. The segmented nuclei are then co-registered with MR by using key landmarks in the brain tissue to provide detailed information related to neurobiological changes. This is an ongoing effort to develop a feasible pipeline for multimodal imaging analysis to answer questions about the neurobiology of cognition.

Disclosures: **L.A. Gjesteby:** None. **S.M. Smith:** None. **M. Snyder:** None. **D. Chavez:** None. **M. Febo:** None. **D.G. Lamb:** None. **L.J. Brattain:** None. **S.N. Burke:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.12

Topic: H.12. Aging and Development

Support: 2RO1AG037868-06A1
University of Kentucky, Department of Pharmacology & Nutritional Sciences

Title: Glucocorticoid-driven Sgk1 signaling properties in young and aged dorsal and ventral hippocampus

Authors: *D. R. CRAIG[1], E. M. BLALOCK[1], Y. AL-SIRAJ[1], J. C. GANT[1], O. THIBAULT[1], C. M. NORRIS[2];
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Abstract: Objective & Rationale
Glucocorticoid (GC) signaling is thought to play a key role in stress' negative impact on brain aging (BA). Several lines of evidence indicate that stress and stress hormone exposure appear to accelerate BA, yet the mechanistic interaction between stress and aging remains unclear. The

GC-dependent downstream effector molecule, Sgk1, is increased with both stress and with BA. Sgk1's response to GC appears to be enriched in white matter, and may play a role in oligodendrocytic differentiation and morphological changes following stress exposure. Although, the organization of the HIP is conserved throughout its dorsal-ventral (D-V) axis, the DHIP is thought to play a more prominent role in spatial navigation and short-term memory, while the VHIP provides feedback inhibition of the stress response. However, little work has examined Sgk1 expression across the D-V axis in response to GCs with age. Here, an *ex vivo* HIP slice preparation is used to examine differential GC-driven Sgk1 signaling properties in DHIP and VHIP from young and aged male Fisher 344 rats to test the hypotheses that: Sgk1 levels are elevated by age and GC exposure, this elevation is stronger in VHIP, aged animals show higher baseline Sgk1 than young, and young will show a greater dynamic response to GC exposure than aged.

Methods

HIP slices (350 μm thick) are mapped according to their position in the D-V axis and maintained in oxygenated aCSF at 32°C in an interface chamber, and incubated in either 0.1% DMSO or 3.5 μM corticosterone for 2 hrs. RNA is then isolated, and concentration and integrity are assessed. cDNA is synthesized and then diluted (1:10). Real-time PCR is then performed with forward and reverse primers for Sgk1. Additional slices are examined for localization of Sgk1 mRNA expression using RNAscope.

Results & Conclusions

The well-established slice preparation, typically used for electrophysiology (EP), also is appropriate for investigating age-related, GC-driven Sgk1 signaling. In this preparation, GC exposure is sufficient to drive Sgk1 mRNA expression in DHIP and VHIP in young adult subjects. Further, adjustments to dose, duration, number of samples, as well as pre-vetting with EP may be appropriate. This model may also be appropriate to: Establish GC concentration-effect relationships, identify responding cell-types using IHC or *in situ* hybridization, and investigate pharmacologic interventions.

Disclosures: **D.R. Craig:** None. **E.M. Blalock:** None. **Y. Al-Siraj:** None. **J.C. Gant:** None. **O. Thibault:** None. **C.M. Norris:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.13

Topic: H.12. Aging and Development

Support: 5P20 GM103629-10
NIA Aged Rodent Colonies

Title: The Effect of Diet on Cognitive Function in Young and Aged Rats

Authors: *R. J. SOLCH-OTTAIANO[1], C. HARPER[1], E. B. ENGLER-CHIURAZZI[2], I. YU[1], H. WANG[2], K. MCDONALD[2], B. OUVRIER[2], I. J. BIOSE[2], G. J. BIX[2], D. M. MARAGANORE[1];
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Abstract: **Background:** Mild cognitive impairment affects millions of older adults each year. With no therapeutics for prevention, treatment, or conversion to dementia, preventative interventions are vital. One measure may be diet. The Western Diet, high in sugar and ultra-processed foods and low in fiber, is associated with risk factors for mild cognitive impairment such as obesity and cardiovascular disease. In contrast, adherence to a nutrient- and fiber-dense diet associated with reduced risk for cardiovascular disease, such as the Mediterranean diet (MeDi), may help to reduce the risk of mild cognitive development. We hypothesized that consumption of the MeDi would maintain cognitive function compared to the diet primarily consumed by Americans, the WD.
Methods: Two sequential studies were conducted: Study 1) 10-week-old Sprague Dawley male rats (n=10/group) and Study 2) 12-month-old Fischer 344 male rats (n=10/group). Cages (n=2/cage) were randomly assigned to a MeDi or WD. Energy intake (kcal) and weight was recorded biweekly and weekly, respectively. After three months, animals underwent cognitive assessments using the Morris water maze (MWM) and water radial arm maze (WRAM) to assess learning and memory. MWM and WRAM data were analyzed with Two-way RM ANOVA. To assess changes in energy intake during behavioral assessments, Week 8 was compared to the respective weeks of cognitive testing.
Results: There was no difference in energy consumption or weight between the MeDi and WD in either study after week 1. In young animals, energy intake was lower during the first week of cognitive assessments ($p=0.001$) compared to week 8 but did not differ for the remaining weeks. In contrast, energy intake was lower during all weeks of cognitive assessments ($p<0.0001$) in aged animals. MWM distance to the platform was not different between diets for young or aged animals. During the MWM reversal trial, used to assess cognitive flexibility, young animals consuming the MeDi swam a shorter distance to the reversal platform compared to the WD ($p=0.001$. However, there was no difference in distance swam between diets in aged animals ($p=0.52$). Compared to the WD, there were fewer WRAM total errors committed by the MeDi in young animals ($p=0.02$), but not in aged animals ($p=0.39$).
Conclusion: Compared to the WD, the MeDi maintained short- and long-term memory, as measured by the MWM and WRAM, in young but not aged animals. This is indicative that dietary interventions may need to be started earlier in the lifespan prior to normal cognitive aging in order to elicit detectable cognitive benefits.

Disclosures: **R.J. Solch-Ottaiano:** None. **C. Harper:** None. **E.B. Engler-Chiurazzi:** None. **I. Yu:** None. **H. Wang:** None. **K. McDonald:** None. **B. Ouvrier:** None. **I.J. Biose:** None. **G.J. Bix:** None. **D.M. Maraganore:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.14

Topic: H.12. Aging and Development

Support: AHA-Allen Initiative in Brain Health and Cognitive Impairment award made jointly through the American Heart Association and The Paul G. Allen Frontiers Group: 19PABH134610000AHA
NIH Grant 1R21AG068967-01
Larry L. Hillblom Foundation
Don and Lorraine Freeberg Foundation
Fiona and Sanjay Jha Chair in Neuroscience

Title: Aging common marmosets show domain-specific cognitive impairment

Authors: *C. R. VANDERLIP, C. GLAVIS-BLOOM, J. H. REYNOLDS;
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Abstract: Aging is the greatest risk factor for the development of neurodegenerative diseases, yet we still do not understand how aging processes make us vulnerable to these diseases. The common marmoset (*Callithrix jacchus*) is advantageous as a model in which to investigate the biological underpinnings of aging because marmosets: 1) share key, primate-specific neuroanatomical and behavioral features with humans, 2) develop age-related neuropathology similar to those in humans, and 3) have a short lifespan (10 years), facilitating longitudinal studies of aging. In humans, age-related impairment is evident across several cognitive domains, leaving others intact, and where impairment does occur, it varies in severity across the aging population. Here we evaluate the marmoset as a model of age-related cognitive impairment. We developed a marmoset-optimized automated touch screen testing system and a cognitive test battery to longitudinally characterize individual cognitive aging trajectories across multiple domains in a large cohort of marmosets varying in age from young adult to geriatric. To assess working memory capacity, we implemented the Delayed Recognition Span Task (DRST). We have analyzed individual learning curves over thousands of trials administered over several years and find that aged animals exhibit impaired learning and decreased working memory capacity. Embedded in the DRST is a Delayed Non-Match-to-Sample task on which performance revealed an age-dependent increase in the number of errors to criterion. We also administered two additional tasks: Simple Discrimination (SD) and Simple Discrimination Reversal (SDR), to assess, respectively, age-related decline in visual discrimination and cognitive flexibility. While aging was associated with slower initial learning of the SD task, there was no effect of aging on performance after acquisition of task rules. There was, however, a significant reduction in cognitive flexibility measured by errors to criterion on SDR. Finally, we implemented two non-cognitive control tasks. Performance on a Reaction Time Task revealed age-dependent motor slowing, while performance on a Progressive Ratio Task revealed decreased motivation with increasing age. Importantly, these non-cognitive changes do not account for the cognitive impairment observed on the other tasks. Together, these results show that, similar to humans, aging marmosets are selectively impaired on some domains and not others. To our knowledge, this represents the most thorough cognitive profiling of any marmoset aging study conducted to-date. This work firmly establishes the marmoset as a model of age-related cognitive impairment.

Disclosures: C.R. Vanderlip: None. **C. Glavis-Bloom:** None. **J.H. Reynolds:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.15

Topic: H.12. Aging and Development

Support: NIH Grant R01 AG063930
James S. McDonnell Foundation

Title: Cross-species homologies in patterns of large-scale functional brain network decline across aging mice and humans

Authors: *E. WINTER-NELSON[1], E. BERGMANN[2,3], M. Y. CHAN[1], L. HAN[1], A. KAVUSHANSKY[2], J. ASLEH[2,3], Y. LI[4], T. MURDY[4], S. ZHANG[4], J. A. HARRIS[5], M. FEBO[6], C. C. KACZOROWSKI[4], I. KAHN[2,3], G. S. WIG[1,7];
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Abstract: Examinations of resting-state functional connectivity (RSFC) brain networks are yielding important insights about heathy and pathological aging in human individuals. During adulthood, increasing age is associated with decreasing large-scale RSFC brain network segregation. Lower brain network segregation is linked to worse cognitive ability, alterations in brain function, socio-economic disparities, and age-related disease. In older individuals, longitudinal decline in brain network segregation is prognostic of dementia severity, independent of other markers of Alzheimer's Disease related pathology and genetic risk. Despite these advances in our understanding of the aging brain, the mechanisms underlying aging-related large-scale network reorganization remain largely unexplored, primarily due to challenges in lifespan human subjects research. Identification of the environmental and genetic factors that precipitate brain network changes and the functional sequala thereof can be advanced by establishing cross-species functional homologies in aging-associated brain network decline.
In a densely sampled dataset comprising 22 individual mice (6-months-old [mo]) scanned during resting-wakefulness using fMRI across multiple days, we first apply established methods developed in human brain network analysis to process and detect large-scale RSFC brain networks. Using a refined version of the Allen Mouse Brain Atlas, we first defined brain regions on which community detection was performed to identify groups of regions exhibiting functional coactivation during awake rest. Consistent with human RSFC networks, mouse networks exhibited a modular organization wherein the whole-brain network consists of segregated functional systems; measures of system segregation are reproducible within individuals scanned over multiple days. In an independent cross-sectional dataset (n=104), we found that RSFC brain system segregation is lower in 9mo mice when compared to 3mo mice ($t(101)=3.39$, $p=.001$),

paralleling previous observations in human brain aging across the lifespan. These results fortify examination of RSFC networks as a viable framework through which to investigate similarities and incongruencies between rodent and human models of large-scale brain network changes across the lifespan, and their impact on cognitive ability.

Disclosures: E. Winter-Nelson: None. **E. Bergmann:** None. **M.Y. Chan:** None. **L. Han:** None. **A. Kavushansky:** None. **J. Asleh:** None. **Y. Li:** None. **T. Murdy:** None. **S. Zhang:** None. **J.A. Harris:** None. **M. Febo:** None. **C.C. Kaczorowski:** None. **I. Kahn:** None. **G.S. Wig:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.16

Topic: H.12. Aging and Development

Support: NIH U34AG068482
NIH P51OD011133
NIH R01AG064091

Title: Biomarkers associated with age-related changes in olfactory discrimination in common marmosets (Callithrix bacchus)

Authors: *K. A. PHILLIPS[1,3], M. LOPEZ[1], E. E. BARTLING-JOHN[1], A. BUTEAU[1], A. SEIDL[2], L. ALVAREZ[4], C. ROSS[4];
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Abstract: While some loss of olfactory sensitivity and discrimination is typical in normal aging, pronounced olfactory deficits can be an early clinical marker of pathological brain aging, including such conditions as Parkinson's disease and Alzheimer's disease. Whether olfaction is associated with biomarkers of neuroinflammation is unclear. Common marmosets (Callithrix jacchus) are an advantageous nonhuman primate model for translational geroscience as they display a wide-spectrum of naturally-occurring age-related pathologies that compare similarly to humans. Due to their behavioral reliance on scent and social cues, marmosets offer a unique model for examining the association between olfactory impairment, aging, and risk of cognitive decline. We investigated olfactory discrimination and biomarkers of neuroinflammation in eight marmosets ranging in age from 5 to 19 years. Subjects were tested for odor discrimination using urine scents from familiar and unfamiliar male and female marmosets. Serum samples were analyzed via single molecule array (Simoa) for the biomarkers GFAP, Tau, NfL, and UCH-L1 to investigate relationships with olfactory performance. Our results indicated Tau, NfL, and UCH-L1 were not significant indicators of olfactory discrimination. However, lower olfactory discrimination indices were associated with higher serum levels of GFAP.

Disclosures: **K.A. Phillips:** None. **M. Lopez:** None. **E.E. Bartling-John:** None. **A. Buteau:** None. **A. Seidl:** None. **L. Alvarez:** None. **C. Ross:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.17

Topic: H.12. Aging and Development

Support: NSF BCS-1844144

Title: Intact cognitive flexibility and working memory in aged pigeons

Authors: *M. FLAIM[1], A. P. BLAISDELL[2];
[1]Ruhr Univ. Bochum, Bochum, Germany; [2]Psychology, UCLA, Los Angeles, CA

Abstract: It is well documented in humans and other mammals that even heathy aging results in deterioration of some cognitive abilities, specifically working memory (WM) and cognitive flexibility. It is commonly found that older subjects perform worse than younger subjects on tasks that rely on these abilities. Both abilities allow subjects to engage in the most appropriate behavior in the face of distracting stimuli, thus impairments can impact quality of life. Further, these cognitive abilities depend on the prefrontal cortex (PFC), indicating that it is sensitive to senescence. Mitigating age-related cognitive decline in the PFC would improve the quality of life for many people. Researching other long-lived species can reveal innate protective mechanisms against aging. Birds have been identified as such a species. In pigeons specifically, some age-related changes in cognitive performance and neuroanatomy have been found. Yet no studies so far have examined performance on tasks that rely on the avian equivalent to the PFC, the nidopallium caudolaterale (NCL). Despite differences in topography, topology, neurogenetics, and cytoarchitecture, many similarities have been found between the NCL and PFC, including which cognitive abilities they support. We investigated NCL function by administering a WM and cognitive flexibility task to young (n = 12; 0.5 - 3 years old) and old (n = 11, 11-17 years old) pigeons. To assess WM, we used a delayed match to sample task where subjects had to select the comparison stimulus that matched the sample stimulus after a delay period. To assess cognitive flexibility, we used a serial reversal learning task where, after reaching criterion, the contingency of the two stimuli reversed. Previous research has shown these tasks rely on the NCL and we predicted that older subjects would perform worse than younger subjects. Contrary to our predictions, there were no significant differences in performance based on age. Similar results were found when age was treated as a categorical variable and analyzed with an ANOVA and when age was treated as a continuous variable and analyzed with a correlation. These results indicate that pigeons may have a protective mechanism that prevents NCL senescence or compensatory mechanisms that maintain performance, even as NCL function declines. Additional research will be critical to understand how avian neural systems are maintained against aging and if these mechanisms could be translated to mammals.

Disclosures: **M. Flaim:** None. **A.P. Blaisdell:** None.

Poster

745. Neurobiology of Aging: Rodent

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 745.18

Topic: H.12. Aging and Development

Title: Cognitive dysfunction and increased phosphorylated tau in an aging mouse model of metabolic syndrome

Authors: *F. ALMASHHORI[1,4], S. GUPTA[2,4], S. JINKA[2], J. LALLO[2], A. MATHIAS[2], S. KHANAL[2,4], J. LEPP[3], Y. AL-RHAYYEL[3], D. HERMAN[3], J. G. HOLDEN[6], P. RAMAN[2,5], S. M. FLEMING[3,4];
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Abstract: Cognitive dysfunction and increased phosphorylated tau in an aging mouse model of metabolic syndrome
Fayez Almashhori[1], Shreya Gupta[1, 3], Sanjay Jinka[3], Jason Lallo[3], Amy Mathias[3], Saugat Khanal[1, 3], Josephine Lepp[2], Yasmine Al-Rhayyel[2], Danielle Herman[2], John G. Holden[4], Priya Raman[1, 3] and Sheila M. Fleming [1, 2]
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Metabolic syndrome (MetS) is characterized by hyperglycemia, obesity and hyperlipidemia and can increase the risk of developing late-onset dementia. However, how MetS contributes to the development of AD-related pathology and cognitive dysfunction is unclear. The goal of the current study was to investigate the link between cognitive function and tau pathology in an aging mouse model of MetS, the agouti KKAy$^{+/-}$ mouse. Male and female C57BL/6, non-agouti KKAy$^{-/-}$, and agouti KKAy$^{+/-}$ mice were fed a standard chow diet and aged to 12-18 months. Body weight, blood glucose, total cholesterol and triglyceride levels were measured to confirm MetS. Cognition, sensorimotor function, and emotional reactivity were assessed for each genotype. Plasma and brain tissues were collected from each genotype for biochemical and molecular analyses. The results show that body weight, blood glucose, total cholesterol and triglyceride levels are significantly elevated in the agouti KKAy$^{+/-}$ mice compared to C57BL/6 controls and non-agouti KKAy$^{-/-}$ mice, confirming the MetS phenotype. Behaviorally, agouti KKAy$^{+/-}$ mice show impairments in sensorimotor and cognitive function compared with age-matched C57BL/6 control and non-agouti KKAy$^{-/-}$ mice. Immunoblotting shows an increase in phosphorylated tau coupled with augmented unphosphorylated GSK3β expression in female KKAy$^{+/-}$ vs. C57Bl/6 control mice in hippocampal-associated tissues. The differences in

phosphorylated tau and GSK3β were observed only in female mutant mice. Together, these data demonstrate impairment in cognitive function and AD-related pathology in older female MetS KKAy$^{+/-}$ mice. Overall, this study suggests KKAy$^{+/-}$ mice are a useful model for studying the mechanisms that mediate AD-related pathology and cognitive dysfunction in MetS.

Disclosures: **F. Almashhori:** None. **S. Gupta:** None. **S. Jinka:** None. **J. Lallo:** None. **A. Mathias:** None. **S. Khanal:** None. **J. Lepp:** None. **Y. Al-Rhayyel:** None. **D. Herman:** None. **J.G. Holden:** None. **P. Raman:** None. **S.M. Fleming:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.01

Topic: I.04. Physiological Methods

Support: NIH BRAIN Initiative grants U01NS120822
NIH BRAIN Initiative grants UF1NS107610
NIH BRAIN Initiative grants U19NS104590
NSF NeuroNex DBI-1707261
NIH BRAIN Initiative grants U01NS103517
DARPA N6600117C4012 (NESD)
DARPA N6600119C4020 (N3)

Title: Optical technologies for tracking the concurrent membrane voltage dynamics of multiple cell classes in awake behaving mice.

Authors: ***S. HAZIZA**[1], M. KANNAN[4], G. VASAN[4], R. T. CHRAPKIEWICZ[1], Y. ZHANG[1], J. LI[1], M. Z. LIN[2], V. A. PIERIBONE[4], M. J. SCHNITZER[3];
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Abstract: Fluorescent genetically encoded voltage indicators (GEVIs) enable imaging studies of neuronal transmembrane voltage dynamics at the millisecond-scale in genetically identified or projection-targeted neuronal ensembles. To date, however, extant GEVIs and voltage-imaging methods have not yet enabled recordings of multiple, identified cell classes at once. To track the concurrent voltage dynamics and interactions of different neuron classes in behaving animals, we created two complementary technologies. First, we created an ultra-sensitive fiber-optic measurement technique called uSMAART (**u**ltra-**S**ensitive **M**easurement of **A**ggregated **A**ctivity in **R**estricted cell-**T**ypes) for tracking the aggregate membrane voltage dynamics (DC-200 Hz) of targeted neuronal populations in freely behaving mammals. uSMAART can monitor the concurrent voltage dynamics of two neuronal classes at the site of one fiber-optic probe. This approach has approximately 10-fold greater sensitivity than state-of-the-art fiber photometry methods, is immune to animal motion-induced noise, is more robust to hemodynamic artifacts

and allows continuous recordings for over an hour. uSMAART can accommodate for two fiber probes located at two different brain regions, with identical performances. Illustrating the utility and sensitivity of uSMAART, when we monitored the membrane voltage dynamics of sparse interneurons, we not only captured cell-type specific gamma frequency band activity (30-110 Hz) but also made the first measurements of cell-type specific theta-gamma cross-frequency coupling in freely behaving mice. We also monitored the simultaneous but distinct visually evoked oscillatory responses of excitatory and inhibitory neural populations in the primary visual cortex of awake mice. Second, we combined high-speed (~1 kHz) 1-photon epifluorescence microscopy and four mutually compatible FRET-opsin GEVIs based on the Ace opsin (Gong et al, Science 2015) to track the spiking and subthreshold dynamics of up to three different neuron classes simultaneously at single cell resolution in awake head-fixed mice. Using this approach, we uncovered behavioral-state-dependent interactions between different sub-classes of CA1 hippocampal neurons with anatomically distinct axonal projections. We also investigated the extent to which excitatory and inhibitory neuronal ensembles contribute to the local field potential in awake mice. Overall, our two new methodologies offer complementary ways to probe the interactions between different neuron-types, their contributions to local electric field potential dynamics and roles in brain function in awake behaving mammals.

Disclosures: **S. Haziza:** None. **M. Kannan:** None. **G. Vasan:** None. **R.T. Chrapkiewicz:** None. **Y. Zhang:** None. **J. Li:** None. **M.Z. Lin:** None. **V.A. Pieribone:** None. **M.J. Schnitzer:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.02

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH 1R01NS123681
Stanford Bio-X
Stanford Bioengineering

Title: In vivo voltage imaging of fast voltage transients with improved ASAP3 sensor

Authors: *Y. A. HAO[1,2], S. LEE[2], G. ZHANG[2], D. JIANG[2], T. R. CLANDININ[2], M. Z. LIN[1,2]; [1]Bioengineering, [2]Neurobio., Stanford Univ., Stanford, CA

Abstract: Voltage imaging has established a path for studying how neurons process information at subcellular and circuit levels in behaving animals. Genetically encoded voltage indicators (GEVIs) have enabled voltage imaging with a millisecond or sub-millisecond temporal precision in defined neuronal populations. However, current GEVIs suffer from various issues, including the low SNR under 2-photon imaging, or low membrane-trafficking quality, which limits the usage of GEVIs in various applications. Opsin-based FRET voltage indicators, such as Ace-

mNeon or Voltron, showed high SNR under 1-photon illumination due to high baseline brightness, but are much less responsive under 2-photon excitation, which limits their applications in deeper intact brain tissues. ASAP3, in contrast, demonstrated large responsivity under both 1-photon and 2-photon illuminations. However, it has slower onset kinetics than its precursors ASAP2f and ASAP1, and thus limits its usage in voltage imaging of fast voltage transients.Here we report an improved ASAP3 sensor. It is faster than both ASAP1 and ASAP2f, and has a larger steady-state response than ASAP3, resulting in 2X responsivity to action potentials (APs) in cultured HEK293A cells and cultured hippocampal neurons. The baseline brightness and the efficient membrane trafficking is maintained. Similarly, it has higher fidelity to report miniature EPSPs in vitro.In fruit flies, the improved ASAP3 sensor helped achieve higher fluorescence modulation than its precursors in lamina L2 neurons when the flies were stimulated with dark/bright full-field flashes. We also applied the improved ASAP3 sensor to record a few descending neurons and achieved robust single-trial recording of fast voltage transients at 1KHz. Currently, we are testing the improved ASAP3 sensor in various applications and conditions (both 1-photon and 2-photon) in behaving flies, fish, and mice.

Disclosures: **Y.A. Hao:** None. **S. Lee:** None. **G. Zhang:** None. **D. Jiang:** None. **T.R. Clandinin:** None. **M.Z. Lin:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.03

Topic: I.04. Physiological Methods

Support: NIH Brain Initiative Grant UF1NS107705
U01NS103517
U01NS090565
DARPA N6600117C4012
DARPA N660119C4020

Title: Genetically encoded voltage indicators optimized for in vivo imaging

Authors: *J. PLATISA[1], **J. E. GULCICEK**[1], M. KANNAN[1], G. VASAN[2], P. F. O'BRIEN[1], R. F. O'BRIEN[1], X. YE[3], A. AHRENS[4], J. L. CHEN[4], V. A. PIERIBONE[5];
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Abstract: Genetically encoded calcium indicators allow cellular resolution imaging of a large number of neurons simultaneously. However, recent studies have brought into question the correlation between calcium signals and neuronal spiking activity. Genetically encoded voltage indicators (GEVI) directly report action potential activity with high fidelity. However, GEVI imaging has not achieved significant adoption by the greater neuroscience community because

imaging needs to be performed at a much higher rate (500 Hz vs. 30 Hz for GECI) making it technically more challenging. The use of GEVIs requires different imaging setups than GECI imaging. For example, the high-performing opsin-based GEVIs allow for spike-resolution imaging under single-photon excitation but this approach is limited to superficial cortical layers. Two-photon imaging, necessary for imaging deeper brain structures, is incompatible with opsin-based GEVIs. The multi-photon voltage imaging has been demonstrated in a limited number of neurons using VSD-based GEVIs. The lack of rapid imaging systems and 2P-optimized voltage indicators limits large-scale voltage imaging using two-photon excitation. In vivo application of GEVIs asks for significant improvements in cellular expression and probe performance. We have used structure-guided protein evolution supported by a high throughput screening system to develop ultra-fast, sensitive, and photo-stable GEVIs optimized for prolonged 1P and 2P imaging.

Disclosures: **J. Platisa:** None. **J.E. Gulcicek:** None. **M. Kannan:** None. **G. Vasan:** None. **P.F. O'Brien:** None. **R.F. O'Brien:** None. **X. Ye:** None. **A. Ahrens:** None. **J.L. Chen:** None. **V.A. Pieribone:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.04

Title: WITHDRAWN

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.05

Topic: I.04. Physiological Methods

Support: NIH UF1 NS107705

Title: An ultra-fast two-photon microscope for sustained, low-light in vivo voltage imaging of neuronal populations in mouse cortex

Authors: *X. YE[1,2], A. M. AHRENS[3], N. MANJREKAR[3], J. PLATISA[5,6], V. A. PIERIBONE[5,6,7], C. LIU[1], L. TIAN[4,1], J. L. CHEN[3,1,2];
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Abstract: Understanding the complexity of neural networks *in vivo* requires simultaneous recordings of neuronal populations with action potential resolution. Genetically-encoded voltage indicators (GEVIs) that feature fast dynamics provide direct and reliable optical readouts of neural activity. The fast dynamic of spike-evoked GEVI responses necessitates the development of kilohertz-rate two-photon (2P) imaging systems. Existing high-speed 2P microscopes scan restricted field of views (FOVs), limiting the number of simultaneously imaged neurons. We developed an Ultra-Fast 2-Photon (UF2P) microscope which is capable of full-frame high-speed imaging of a 400x400μm^2 FOV of up to ~300μm deep in mouse cortex at a kilohertz scan rate. A combination of temporal and spatial multiplexing was applied in the system to generate eight parallel beams. A 920nm-wavelength, 31.25MHz repetition rate laser was used to deliver laser pulses that were temporally multiplexed into four interleaved beamlets. Emitted photons were de-multiplexed through digital temporal gating. Each beamlet was spatially multiplexed into beams that were spaced 200μm apart at sample to avoid crosstalk introduced by light scattering in deep tissue. Photons from spatially multiplexed beams were resolved by the multi-anode photomultiplier tube.We applied the UF2P microscope along with a novel positive-going voltage indicators with improved spike detection (SpikeyGi and SpikeyGi2) for *in vivo* voltage imaging in mouse cortex. A self-supervised denoising algorithm model (DeepVID) was trained for reducing shot noise in low photon-flux condition. Through combining all techniques above, we achieved simultaneous high-speed, deep-tissue imaging of more than one hundred densely-labeled neurons in awake behaving mice for over an hour with minimal effects on photobleaching, thermal effects, and photodamage during this period of time. The system demonstrates the capability for sustained voltage imaging across large neuronal populations.

Disclosures: X. Ye: None. **A.M. Ahrens:** None. **N. Manjrekar:** None. **J. Platisa:** None. **V.A. Pieribone:** None. **C. Liu:** None. **L. Tian:** None. **J.L. Chen:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.06

Topic: I.04. Physiological Methods

Support: 1F31MH123111-01A1

Title: Development of open-source, high performance miniature multiphoton microscopy systems for freely behaving animals

Authors: *B. MADRUGA[1], M. SHTRAHMAN[2], D. AHARONI[1], P. GOLSHANI[1]; [1]Dept. of Neurol., UCLA David Geffen Sch. of Med., Los Angeles, CA; [2]Dept. of Neurosciences, UCSD Sch. of Med., La Jolla, CA

Abstract: Miniaturized microscopy is an extremely valuable research tool due to its ability to optically capture dynamics from large neuronal populations in freely behaving animals. The vast

majority of miniature microscopes used to date have been single-photon systems which hold inherent optical limitations due to the rapid scattering of short wavelength light through brain tissue. As a result, 1P miniature microscopes are only able to resolve cell bodies very close to an implanted lens or cranial window, and are thus unsuitable for addressing many key scientific questions. Recently, several groups have designed and developed transformative multiphoton miniaturized microscopes which surmount many of the optical limitations facing 1P systems, and are able to image high resolution fields of view deep into tissue. We expand on these advances by developing the largest FOV multiphoton miniature microscope to date, capable of resolving 750um x 750um FOVs in freely behaving mice. The system weighs ~3.6g and records an imaging area more than twice that of top-of-the-line systems reported in the literature. An electrotunable lens is used to adjust the WD of the custom-made 0.3/0.6NA (excitation/emission) objective assembly from 300um-950um, enabling optical access to deep brain regions. Because effectively sharing this multiphoton miniature microscope with others is a large goal for us, all hardware is designed to be as straightforward to assemble and deploy as possible, and all custom optical assemblies have been designed to be affordable to most labs. The miniature microscope itself and all supporting equipment are completely open source and all files needed for reproduction by anyone can be accessed through the UCLA miniscope project's GitHub repository following publication.

Disclosures: **B. Madruga:** None. **M. Shtrahman:** None. **D. Aharoni:** None. **P. Golshani:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.07

Topic: I.04. Physiological Methods

Support: NIH Grant R01NS091230
NIH Grant U24EB028941
NIH Grant R01NS115401
NIH Grant RF1NS121095
NIH Grant U01HL133362
NIH Grant 1U19NS123717-01

Title: Background signal rejection for cerebral pO_2 measurements using optical vortex in two-photon phosphorescence lifetime imaging microscopy

Authors: *Q. PIAN[1], B. LI[1,2], I. SENCAN-EGILMEZ[1,3], X. CHENG[4], J. DUBB[1,4], X. HUANG[1], B. FU[1], S. A. VINOGRADOV[5,6], D. A. BOAS[4], S. SAKADZIC[1];
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Abstract: Partial pressure of oxygen (pO_2) measurements in cerebral vasculature and tissue can provide insights to the evaluation of brain function under normal and diseased conditions with critical oxygen transport and consumption information. Two-photon phosphorescence lifetime imaging microscopy (PLIM) has been a key tool for the preclinical investigation of cerebral oxygenation by retrieving pO_2 from cortical vasculature and tissue in mice with the help of oxygen-sensitive phosphorescent probes. Although the high two-photon absorption cross-section, quantum yield, and red-shifted emission peak wavelength of those probes allow for absolute pO_2 measurements in cortical layers I-IV and up to ~600 μm depth, the accumulation of out-of-focus phosphorescence signal from both ballistic and scattered light with the increase of imaging depth and excitation laser power at deep cortical layers has been a known factor that compromises the accuracy of pO_2 measurements in two-photon PLIM. In this work, we aim at tackling the background phosphorescence signal in two-photon PLIM with an optical vortex beam generated by adaptive optics and quantitatively evaluating its performance in rejecting background signal and improving pO_2 measuring accuracy. The platform employs a liquid crystal-based spatial light modulator (SLM) to impose phase masks on the wavefront for the creation of both unaberrated and aberrated (optical vortex) focuses for two-photon excitation. Background signal rejection is achieved by subtracting the measurement with aberrated focus from that of unaberrated focus. Numerical simulation has shown ~5% relative error in estimating the background signal with proper optical vortex beam size. The performance of the proposed technique is further validated with *in vivo* intravascular cerebral pO_2 imaging on six awake C57BL6 mice with a cranial window prepared over the barrel cortex region. A ~5 mmHg average pO_2 correction has been observed for the arterial pO_2 measurements using the proposed method. As predicted, the pO_2 corrections are larger for vessels with both high initial pO_2 and large imaging depth since the out-of-focus signal is dominated by the phosphorescence from the capillaries and venules. We have proved the feasibility to use optical vortex for improving the quantitative accuracy of pO_2 measurements in deep cortical layers in mice.

Disclosures: Q. Pian: None. **B. Li:** None. **I. Sencan-Egilmez:** None. **X. Cheng:** None. **J. Dubb:** None. **X. Huang:** None. **B. Fu:** None. **S.A. Vinogradov:** None. **D.A. Boas:** None. **S. Sakadzic:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.08

Topic: I.04. Physiological Methods

Support: NIH Eureka
HHMI

Title: Simultaneous Ca^{2+} imaging of neural dynamics in multiple anatomically separated brain areas using a robotic, multi-arm two-photon microscope

Authors: *T. H. KIM[1,2], Y. SHIKANO[2], O. JAIDAR[2], Y. ZHANG[1,2], T. ROGERSON[2], J. B. DING[2], M. J. SCHNITZER[1,2];
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Abstract: Advances in fluorescence Ca^{2+} neural activity imaging have allowed neuroscientists to track the Ca^{2+} activity of genetically targeted or projection-defined neural populations at single-cell resolution in behaving animals. However, nearly all microscopes used for neural Ca^{2+} imaging are limited to a single contiguous field-of-view, which severely limits the sets of brain areas that can be monitored concurrently. This limitation has precluded Ca^{2+} imaging studies of brain area interactions involving distally located brain regions, as well as studies of superficial and deep areas. To enable optical investigations of arbitrary pairs of brain areas, we previously developed a dual-axis two-photon microscope that permits two conventional microscope objectives to be flexibly positioned around the cranium of a head-fixed behaving mouse. Using this system, we investigated how neural dynamics in the cortex and cerebellum are transformed as mice learn a forelimb movement task, and we are currently using this dual-axis microscope to examine cortico-striatal dynamics during a full-body motor learning task.
Here, we present the 'Octopus', a multi-arm robotic imaging system that enables simultaneous two-photon Ca^{2+} imaging in 4 or more brain areas of a head-fixed mouse, including combinations of superficial and deep brain regions. Each arm of the Octopus is mechanically articulated, functions as an independent two-photon microscope, and has a custom-designed micro-optic objective providing a 400-µm-wide field-of-view. Mechanical control of the imaging arms is based on principles from surgical robotics and facilitates the alignment of the micro-objectives to arbitrarily located and oriented imaging targets throughout the brain. Using a 4-armed version of the Octopus microscope, we have performed two-photon Ca^{2+} imaging in the rodent cortex, striatum, hippocampus, and cerebellum, with each imaging field-of-view containing hundreds of functionally active neurons. With its capacity to monitor neurons in many arbitrarily-located brain regions simultaneously, the Octopus microscope unlocks a new class of imaging studies that aim to understand how global circuit dynamics underlie neural information processing and shape animal behavior.

Disclosures: T.H. Kim: None. **Y. Shikano:** None. **O. Jaidar:** None. **Y. Zhang:** None. **T. Rogerson:** None. **J.B. Ding:** None. **M.J. Schnitzer:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.09

Topic: I.04. Physiological Methods

Support: NIH 1R01MH120162-01A1
NIH 1DP2MH122399-01
One Mind
McKnight Foundation
Klingenstein-Simons Fellowship
Klingenstein-Simons Fellowship
Brain Research Foundation

Title: Simultaneous dual-color calcium imaging in freely-behaving mice

Authors: *Z. DONG[1], F. SANGIULIANO JIMKA[2], Y. ZAKI[1], A. BAGGETTA[1], D. M. MORALES-RODRIGUEZ[1], B. M. SWEIS[3], Y. FENG[1], D. M. KIRCHER[1], P. A. SLESINGER[1], T. SHUMAN[1], D. AHARONI[2], D. J. CAI[1];
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Abstract: Miniaturized fluorescence microscopes (miniscopes) enable imaging of calcium events from a large population of neurons. Traditionally, miniscopes have only been able to record from a single fluorescence wavelength. However, recording from multiple wavelengths simultaneously would provide much more flexibility and function. For example, simultaneous imaging of calcium signals along with a static signal can be beneficial, as the static signal can be used as a landmark for registration of neurons across recording sessions, which remains a major challenge in long-term calcium imaging. Another use case is to image two dynamic signals simultaneously. For example, imaging from two different populations of neurons can provide insight of how different cell-types interact to underlie behavioral function. Imaging FRET (Fluorescence Resonance Energy Transfer)-based signals can uncover the molecular mechanism underlying signal transmission in neural circuits. Here, we present a new open-source dual-color miniscope. To enable simultaneous acquisition of two fluorescent wavelengths, we incorporated two CMOS sensors with two independent sets of emission filters into a single miniscope. This enables us to acquire images at the full frame rate that the CMOS sensor supports. An additional benefit of using two sets of emission filters is that the crosstalk between channels can be eliminated, which enables imaging fluorophores that heavily overlap in the emission spectrums (for example, GFP and tdTomato). To correct for the axial difference of focal plane between the two channels caused by chromatic aberration of the GRIN lens, we adopted a design that enables adjusting the position of one imaging sensor along the light path to match the focal plane of the other sensor, providing additional flexibility for calibrations. We have validated our dual-channel miniscope ex vivo, imaging two wavelengths on a test slide to ensure that we can overlay the two images and record from the same focal plane. We have also validated our dual-channel miniscope in vivo. We have imaged mouse hippocampus that expressed dynamic GCaMP and constitutively active tdTomato signals during behavior. We also imaged FRET responses from cell-based neurotransmitter fluorescent engineered reporters (CNiFERs) to measure the release of dopamine in real-time. Our results suggest that our miniscope can image two fluorescence wavelengths in the same focal plane and that there is minimal crosstalk between the two channels.

Disclosures: **Z. Dong:** None. **F. Sangiuliano Jimka:** None. **Y. Zaki:** None. **A. Baggetta:** None. **D.M. Morales-Rodriguez:** None. **B.M. Sweis:** None. **Y. Feng:** None. **D.M. Kircher:** None. **P.A. Slesinger:** None. **T. Shuman:** None. **D. Aharoni:** None. **D.J. Cai:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.10

Topic: I.04. Physiological Methods

Support: NIH RF1NS113287

Title: Micro-camera arrays for ultra-widefield, multi-site cellular resolution Calcium imaging across the dorsal cortex of behaving mice.

Authors: ***J. HU**[1], S. FAUSNER[1], A. CHERKKIL[1], V. PATHAK[2], R. F. HOSSAIN[1], Z. VIAVATTINE[1], I. OLADEPO[1], D. SURINACH[1], L. GHANBARI[1], R. HORTMEYER[2], S. B. KODANDARAMAIAH[1];
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Abstract: Recording the activity of individual neurons distributed across multiple brain regions can provide new insights into the brain's functions and animal behavior. Over the last few years, a number of miniaturized devices have been developed to image the activities of neurons in small fields of view in freely behaving animals. Scaling the devices to image large fields of view results in large imaging objectives and correspondingly large cameras that are difficult to be miniaturized for studying freely locomoting and behaving animals. Furthermore, such imaging devices need to contend with the complex three-dimensional surface of the brain. Here, we introduced two innovations to enable calcium imaging at cellular resolution across the dorsal cortical surface. First, we engineered a multi-planar transparent skull implant with 4 glass coverslides stacks to open up 42 mm^2 of the dorsal cortical surface for imaging. This area encompasses most of the bilateral primary and secondary motor cortices, much of the somatosensory cortex areas, the Retrosplenial, association, higher visual, and part of the primary visual cortex. We next built an array of fluorescent micro-cameras to image each of the four planes defined by the coverslides. The fluorescent micro-camera consists of a 1:1.4 relay objective lens, a fluorescent imaging filter, and a miniaturized CMOS sensor. Each micro-camera can image 8-12 mm^2 FOV at resolutions ranging from 12 to 17.5 µm. A laser-coupled fiber-based illumination system is used to deliver 450-470 nm excitation light with a light intensity power of 4.2-6.7 mW to each targeted brain region. We imaged neuronal activity using the micro-camera in head-fixed Ai163 x Cux2-creERT2 transgenic mice that sparsely expressed GCaMP6s in layers 2-3 pyramidal neurons in the cortex. Further, we realized a low-cost sub-miniaturized version of the camera arrays supported by a simple low-friction passive gantry

system that can be used to perform multi-site cellular resolution imaging across the cortex in mice navigating and exploring two-dimensional behavioral arenas.

Disclosures: **J. Hu:** None. **S. Fausner:** None. **A. Cherkkil:** None. **V. Pathak:** None. **R.F. Hossain:** None. **Z. Viavattine:** None. **I. Oladepo:** None. **D. Surinach:** None. **L. Ghanbari:** None. **R. Hortmeyer:** None. **S.B. Kodandaramaiah:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.11

Topic: I.04. Physiological Methods

Support: NSF NeuroNex 1704708 (HTB, PG, DA, JC)
1UF1NS107668 (DA)
MH122800 (AI, HTB)

Title: Decalcion: a hardware system for real-time decoding of in-vivo calcium imaging data

Authors: Z. CHEN[1], G. J. BLAIR[6], C. GUO[1], J. ZHOU[2], A. IZQUIERDO[3], P. GOLSHANI[7], J. CONG[2], D. AHARONI[4], ***H. BLAIR**[5];
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Abstract: Epifluorescence miniature microscopes (“miniscopes”) are widely used for in vivo calcium imaging of neural population activity. Imaging data is usually collected while subjects are engaged in a task and stored for later offline analysis, but emerging techniques for online imaging offer potential for novel real-time experiments in which closed-loop interventions (such as neurostimulation or sensory feedback) are triggered at short latencies in response to neural population activity. Here we introduce DeCalciOn, a plug-and-play hardware device for online population decoding of in vivo calcium signals that can trigger closed-loop feedback at millisecond latencies, and is compatible with any existing miniscope that uses the UCLA Data Acquisition (DAQ) interface. The DeCalciOn system is implemented on an AvnetTM Ultra96 development board (featuring a XilinxTM Zynq Ultrascale+ MPSoC with embedded FPGA and ARM core) mated to a custom interface board that receives real-time image data directly from the UCLA Miniscope’s Data Acquisition (DAQ) interface. Online processing of each image frame (up to 512x512 pixels at 30 Hz) is performed in four sequential steps: 1) motion stabilization, 2) background removal, 3) calcium trace extraction, and 4) population vector decoding. Steps 1-3 are performed by firmware running in the fabric of the FPGA, whereas Step 4 is performed on the ARM core. In performance tests conducted with a Large Field-of-View (MiniLFOV) of the UCLA Miniscope, the position of rats (n=13) on a linear track was decoded in real time from hippocampal CA1 population activity by 24 linear classifiers. DeCalciOn

required <2.5 ms after each end-of-frame to decode up to 1,024 calcium traces and trigger TTL control outputs. DeCalciOn does not perform online crosstalk correction (demixing) of real-time calcium traces, but we found that position decoding from offline traces (demixed using CNMF) was no more accurate than decoding from DeCalciOn's online (non-demixed) traces, so there was no evidence that decoding accuracy was compromised by crosstalk between sources during online trace extraction. We also found that decoding was most accurate and efficient using a 'contour-free' method of extracting traces from a tiled mosaic of ROIs that were unaligned with neurons in the image. However, traditional 'contour-based' extraction from neuronal ROIs (identified by offline analysis) is also supported. In summary, DeCalciOn is an easy-to-use system for real-time decoding of calcium fluorescence that enables closed-loop feedback experiments in behaving animals. DeCalciOn hardware, software, and firmware are openly available through miniscope.org.

Disclosures: **Z. Chen:** None. **G.J. Blair:** None. **C. Guo:** None. **J. Zhou:** None. **A. Izquierdo:** None. **P. Golshani:** None. **J. Cong:** None. **D. Aharoni:** None. **H. Blair:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.12

Topic: I.04. Physiological Methods

Title: Deciphering Brain Function by In vivo multicolor imaging and multi-opsin stimulation in four brain regions of freely behaving animals with Chromatone

Authors: *R. CHRISTO[1], A. PAPANICOLAOU[2], J. KANEM[2], Y. SOUDAGAR[3];
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Neurescence Inc, Toronto, ON, Canada; [3]Neurescence US Inc., Toronto, ON, Canada

Abstract: Miniscopes are used to study brain activity at cellular and network levels of behaving animals. Ability to simultaneously record neural activity of multiple cell-types within a field of view, across multiple brain regions, while concurrently performing optogenetics in any region will offer unprecedented power for testing hypotheses about coordinated circuit mechanisms underlying naturalistic behavior. Miniscopes are unable to simultaneously image and stimulate multiple neuronal subpopulations from > 2 regions. To address this, we developed multiscope: an integrated approach to observe, manipulate and perturb neuronal subtypes in upto 4 brain regions, with single cell resolution. To use the system in experiments, it should adhere to size constraint, enforcing 3 challenges to be resolved: a. 3 high power LEDs should fit within 6cm X 6cm X 8cm illumination cube, requiring a non-trivial method of LED temp control. b. Limited size of optics limits coupling efficiency. Sophisticated optical design required to enable light power at the tissue (blue ≤ 5mW, green ≤ 1.2mW, red ≤ 3mW). c. System should simultaneously focus on 2 colors and after imaging, separate green neurons from red. To address size constraints, we chose a modular design, where 4 illumination cubes connect to imaging unit,

each through a multimode fiber. Light is coupled into coherent imaging fiber bundle**,** carrying excitation and emission light to and from implanted GRIN lens and to the tissue. There are 4 such imaging fiber bundles. For temp control, we implemented active temp control using Peltier coolers, with passive heat sink. Multiple optical designs were simulated and characterized for light coupling efficiency and implemented. Optical design using achromatic optics was used to ensure same focus for red and green neurons. Color camera with optical filter allowing green and red light, ensure simultaneous imaging of 2-color neuronal populations. Algorithm is implemented in software that separates the colors. We validated baseline effectiveness of multiscope by imaging GFP and RFP simultaneously in mouse brain slices.

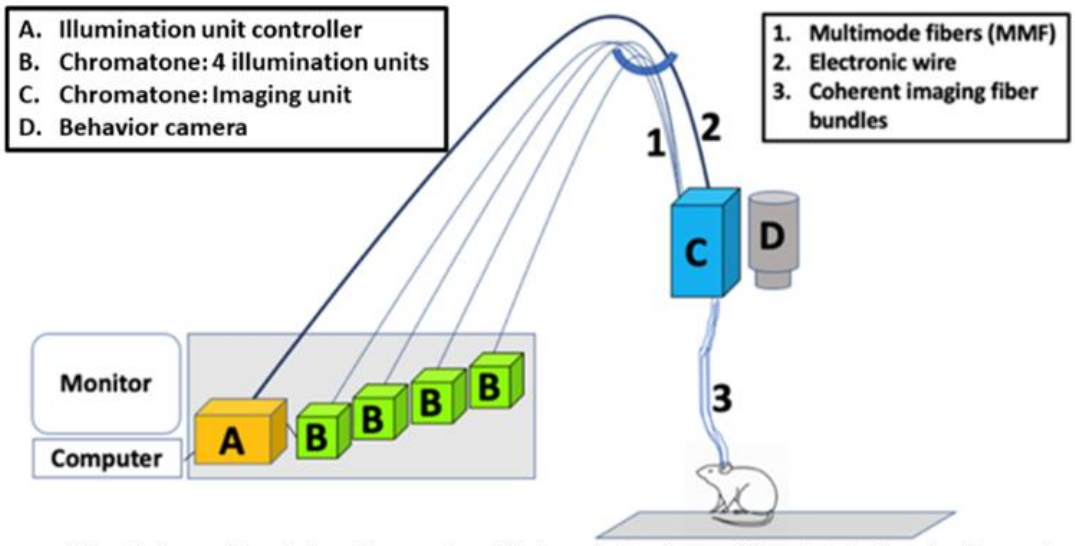


Fig. ***Schematic of the Chromatone™ in a behavior setting:*** Each illumination unit **(B)** connects to the imaging unit **(C)** through a multimode fiber **(1)**. The light is then coupled into coherent imaging fiber bundle **(3),** which carries the excitation and emission light to and from the implanted GRIN lens and to the tissue. There are four such imaging fiber bundles.

Disclosures: R. Christo: None. **A. Papanicolaou:** A. Employment/Salary (full or part-time):; Neurescence Inc. **J. Kanem:** A. Employment/Salary (full or part-time):; Neurescence Inc. **Y. Soudagar:** A. Employment/Salary (full or part-time):; Neurescence Inc.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.13

Title: WITHDRAWN

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.14

Topic: I.04. Physiological Methods

Support: 1DP2MH129986
1UF1NS122124

Title: Open-source UCLA Miniscope Project: Updates and new developments

Authors: *F. SANGIULIANO JIMKA[1], G. CHANGLIANG[1], P. ZHAO[2], M. SEHGAL[6], G. J. BLAIR[7], K. KLEUS[2], H. T. BLAIR, IV[3], M. A. BASSO[4], A. J. SILVA[5], P. GOLSHANI[8], D. AHARONI[2];
[2]Dept. of Neurol., [3]Dept Psychology, [1]UCLA, Los Angeles, CA; [4]WaNPRC, UCLA, Seattle, WA; [5]Dept Neurobiol, UCLA, Los Angeles, CA; [6]Neurobio., Univ. of California Los Angeles, Los Angeles, CA; [7]Ctr. for Neural Sci., NYU, New York, NY; [8]UCLA Dept. of Neurol., Los Angeles, CA

Abstract: There has been a growing concerted effort in recent years to develop new tools to expand researchers' ability to investigate and understand how neural circuits in the brain encode, store, modify, and retrieve information in behavioral contexts where animals are allowed to freely behave. These devices are used to study a large range of topics, from learning and memory to neurological disorders. Miniaturized fluorescent microscopes (miniscopes) provide one such avenue of advancement. When paired with genetically encoded calcium indicators (GECIs), these head-mounted lightweight imaging devices enable researchers to study the dynamics of neural populations with single-cell resolution in freely behaving animals. Much of the work surrounding the development of miniscopes, including our own, is based on open-source principles aimed at democratizing access to transformative tools while also advancing, integrating, and streamlining neuro-behavioral research.
Here we present our continued efforts to advance and disseminate this technology through the open-source UCLA Miniscope project and highlight our most recent developments, including 1) a dual-color Miniscope for color-sequential imaging of two fluorophores or for GECI imaging plus optogenetic actuation, 2) a new generation wire-free Miniscope with expanded field-of-view, smaller size/weight, and on-board changing, 3) a wire-optional large field-of-view (3.2x2.5 mm2) Miniscope for rats and larger animals, and 4) supporting tools and pipelines for streamlining neuro-behavioral research. All of our work has been developed under open-source licensing, with over 700 labs across 18 countries using and modifying these tools for their specific research needs. Through open-source development and engagement with the scientific community, we hope to continue addressing economic and technical hurdles and to broaden access to these transformative technologies.

Disclosures: **F. Sangiuliano Jimka:** None. **G. Changliang:** None. **P. Zhao:** None. **M. Sehgal:** None. **G.J. Blair:** None. **K. Kleus:** None. **H.T. Blair:** None. **M.A. Basso:** None. **A.J. Silva:** None. **P. Golshani:** None. **D. Aharoni:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.15

Topic: I.04. Physiological Methods

Title: Combined single-cell calcium imaging and functional MRI in awake animals

Authors: *R. L. E. M. UBAGHS[1,2], R. BÖHRINGER[1], V. ZERBI[2], M. F. YANIK[1], B. F. GREWE[1];
[1]Inst. of Neuroinformatics, ETH Zurich and Univ. of Zurich, Zurich, Switzerland; [2]Ctr. for Biomed. Imaging, Swiss Federal Inst. of Technol. Lausanne, Lausanne, Switzerland

Abstract: Functional Magnetic Resonance Imaging (fMRI) is a powerful tool that allows us to measure neural activity without the need for invasive surgery. Since the inception of fMRI, the neural underpinnings of the Blood-Oxygen Level Dependent (BOLD) response have been investigated intensively. However, the relationship between the BOLD response and the activity of the underlying neural circuitry has not been fully resolved. To investigate how cortical activity at the cellular level shapes the BOLD response, we designed a novel MRI-compatible fluorescence microscope and behavioral setup to measure the activity of genetically predefined neuronal populations in awake behaving mice. To visualize the neural activity during fMRI acquisition, we implanted a custom headbar and cortical window over the barrel fields in mice expressing GCaMP6m in excitatory neurons. All materials used were determined to be MR safe and did not induce any artifacts during acquisition. To avoid well-known non-linear effects of anesthesia on neurovascular coupling, we performed all experiments in awake mice. However, conducting in vivo experiments in an MR environment with high noise levels (~95 dB) while the animals are being head restraint leads to undesirable neuromodulatory effects, as well as excessive movement related artifacts. To minimize these artifacts, we used a rigorous habituation protocol before starting experiments. During habituation, we gradually increased the intensity of the whisker stimulation and the sound produced by the MR over the course of two weeks. Once mice did not show any visual signs of stress inside the MR, and the framewise displacement was below 0.06 mm for 2 consecutive days, experiments were initiated.Using the newly designed habituation protocol allowed us to record BOLD activity without the confounding influence of anesthesia. We were able to simultaneously record between 50-100 cells in each animal without any visible artifacts or signal degradation in the BOLD signal due to the presence of the microscope and implant. Our preliminary data shows a strong modulation in the barrel field of both the BOLD response and the underlying neural activity in response to whisker stimulation.Our novel combined awake imaging approach will allow a deeper investigation into the nature of neurovascular coupling. Lastly, while previous studies mainly focused on the

correlation between excitatory pyramidal neurons and the BOLD signal, our approach could also be used to further investigate other genetically defined neuronal types at single cell resolution.

Disclosures: R.L.E.M. Ubaghs: None. **R. Böhringer:** None. **V. Zerbi:** None. **M.F. Yanik:** None. **B.F. Grewe:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.16

Topic: I.04. Physiological Methods

Support: NIH Grant 1R03AG061645-01A1R
Georgetown University Dean's Toulmin Pilot Award FY18

Title: Non-contact, optical recording of hippocampal sharp waves using GCaMP6f

Authors: *C. O. MARTIN[1], J.-Y. WU[2];
[1]Integrative Neurosci. MS Program, [2]Neurosci., Georgetown Univ., Washington, DC

Abstract: Hippocampal sharp waves and associated ripple oscillations (SWRs) are spontaneous population events that are essential for memory consolidation and are impacted by aging and neurodegenerative disease. In hippocampal slices, SWRs occur at a rate of 30-200 events per minute, similar to the SWR rate observed *in vivo*. Thus, *in vitro* recording of SWRs can serve as a valuable method for studying age-related neuropathology. In slices, SWRs are traditionally recorded via local field potential (LFP) recordings. Electrode insertion, however, causes local tissue damage, resulting in a one-half to two-thirds amplitude reduction during the initial 10-30 minutes of recording. To avoid this tissue damage and signal attenuation, we used the genetically encoded calcium indicator, GCaMP6f, to record hippocampal sharp waves optically. Fluorescent GCaMP6f signals are typically used as an indicator for action potential-related calcium dynamics. During SWRs, the majority of CA1 neurons do not fire action potentials, and sharp waves have much lower amplitudes than action potential signals (approximately 0.1% of resting fluorescent intensity, dF/F). This 0.1% dF/F amplitude can still exhibit high signal-to-noise ratio (S/N) under single photon, brightfield fluorescent illumination. In our photodiode-based detector, the S/N can reach 10. Conveniently, similar S/N can also be achieved using inexpensive, 8-bit complementary metal oxide semiconductor (CMOS) cameras when multiple pixels within the area of interest are averaged together. As we recorded sharp waves from Thy1-GCaMP6f mouse hippocampal slices, we examined GCaMP6f bleaching and phototoxicity. While bleaching caused a half reduction in dF/F after 30 minutes of light exposure, we found phototoxicity to be undetectable during intermittently recorded trials (30-second trials interspaced by one- and five-minute dark intervals). Prolonged continuous light exposure, by contrast, resulted in reduced SWR rate, suggesting the presence of phototoxicity. Overall, optical recording using GCaMP6f is an effective and practical method for recording sharp waves. Without electrode manipulation

and related damage, optical recording can be used as a drug screening platform for quickly analyzing large numbers of tissue slices.

Disclosures: C.O. Martin: None. **J. Wu:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.17

Topic: I.04. Physiological Methods

Support: NIH 1R01NS089688
NIH R01NS110564-01

Title: Integration of microprism and micro-electrode array to enable chronic two-photon imaging and electrophysiology across all cortical layers

Authors: *Q. YANG, B. WU, E. CASTAGNOLA, M. Y. PWINT, A. L. VAZQUEZ, T. X. CUI;
Univ. of Pittsburgh, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Intracortical neural recording and stimulation microelectrode arrays (MEAs) have been widely used in basic neuroscience research and in translational neuroprosthetics. However, exactly how neural electrodes interact with brain cells is not well understood due to limitations in existing electrophysiological and optical imaging techniques, especially with chronic implants in deeper brain regions. In this work, we integrate a microprism with a transparent MEA to build a multi-functional platform for chronic studies of the neuroelectronic interface. We take advantage of microprism implantations for long-term in vivo imaging across all cortical layers (up to ~1mm). The custom-fabricated flexible and mostly transparent MEA is glued to the vertical face of the microprism for imaging and electrophysiological recording as well as electrical stimulation. The MEA features narrow (5 μm wide) ring-shaped platinum electrode sites to improve the visibility of regions behind the electrode while maintaining the same surface area as a standard 30 μm diameter round electrode site. Here, we demonstrate the capabilities of chronic in vivo two-photon microscopy (TPM) of the brain-electrode interface through the microprism, as well as electrophysiological recordings and electrical stimulations from the MEA on awake Thy1-GCaMP6 mice for over 16 weeks. For the first time, we visualized the cortical laminar neuronal activation pattern in response to electrical stimulation, elucidating the influence of amplitude, frequency, and location on neuronal activity using in vivo TPM. This novel MEA-on-microprism design provides a powerful multimodal method to investigate the brain-electrode interface with a new viewing perspective that provides easier access to deeper brain regions than previously accomplished.

Disclosures: Q. Yang: None. **B. Wu:** None. **E. Castagnola:** None. **M.Y. Pwint:** None. **A.L. Vazquez:** None. **T.X. Cui:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.18

Topic: I.04. Physiological Methods

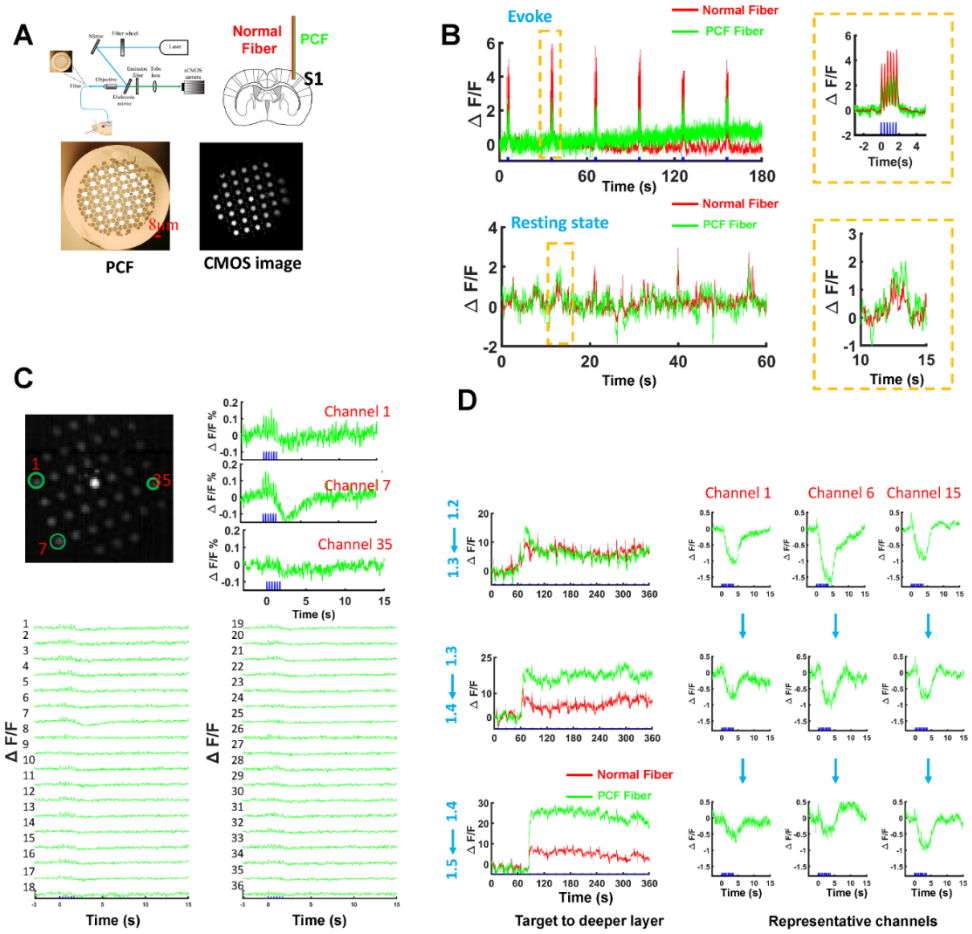
Support: NIH RF1NS113278
NSF 2123971
NIH R01NS122904
NIH R01NS120594
NIH R01MH111438
NIH S10MH124733
NIH R21NS121642

Title: Identify cellular spatiotemporal dynamics based on photonic crystal fiber(PCF)-based multi-channel fiber photometry

Authors: *Y. JIANG[1], S. MOHAMMED[1], M. H. FROSZ[3], X. YU[2];
[1]Massachusetts Gen. Hosp., Massachusetts Gen. Hosp., Charlestown, MA; [2]Radiology, Massachusetts Gen. Hosp., Malden, MA; [3]Max Planck Inst. for the Sci. of Light, Erlangen, Germany

Abstract: The conventional fiber photometry records a assemble fluorescence signal from a volume of a few hundred micrometers beneath the fiber tip, there is a lack of spatial resolution to detect the cellular-specific neuronal signal with simultaneously fMRI measurement. Also, there is a lack of sensitivity in a focal volume to differentiate the temporal dynamics of from different cell types labeled with different genetically encoded biosensors, such as the neuronal or astrocytic Ca^{2+} (Ca^{2+} sensor: GCaMP6f) dynamics and glutamate (Glu sensor: iGluSnFR) transients in animal brains. We designed the photonic crystal fiber (PCF) array with interleaved solid and hollow cores to transmit optical signals through the solid cores located at different cell dimension (**Fig 1A**). Each solid core has a diameter of 8-10 microns, matching the size of the neuronal soma. The cellular specific neuronal signal can be directly recorded from multi-channels using an sCMOS camera. We have implemented the PCF array-based multi-core recording of the glutamate signals. As shown in **Fig 1B**, compared with conventional fiber photometry, it is feasible to detect the fluorescent signals from individual cores in parallel to specify Glu signals in the FP-S1 of rats under the resting state and forepaw electrical stimulation. In particular, we are detecting the different temporal dynamics of the evoked Glu signals from individual cores (e.g. Fig 1B, core 1, 7, 35), indicating a the cellular-specific cellular recording capability of the PCF-based imaging device **(Fig 1C)**. Moreover, individual channels revealed different evoked dynamic patterns at different cortical layers while the fiber was targeted to different somatosensory depths (1.2 to 1.5 mm), (**Fig 1D).** In summary, different from conventional fiber bundles, the PCF array enables multi-channel ultrafast cellular recording with

significantly reduces crosstalk, providing a unique recording device to measure distinct signaling events in the local NGV circuit.



Disclosures: **Y. Jiang:** None. **S. Mohammed:** None. **M.H. Frosz:** None. **X. Yu:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.19

Topic: I.04. Physiological Methods

Title: Visualizing somatodendritic dopamine release using a near-infrared fluorescent nanosensor.

Authors: C. BULUMULLA[1], A. KRASLEY[3], ***A. BEYENE**[2,4];
[2]Janelia Res. Campus, [1]Janelia Res. Campus, Ashburn, VA; [3]HHMI Janelia Res. Campus, Ashburn, VA; [4]Howard Hughes Med. Inst., Ashburn, VA

Abstract: Neurons communicate through chemical signaling molecules that may diffuse beyond their point of release in axon terminals and modulate the activity of larger neuronal networks. Molecules such as dopamine belong to this class of diffusive neurotransmitters. In addition to canonical release from axonal arbors, somatodendritic dopamine release constitutes an important signaling mechanism for dopamine neurons. However, the spatiotemporal dynamics as well as regulatory mechanisms of somatodendritic release have not been adequately explored, and it is not clear if release arises from soma or dendrites. These gaps in our understanding of somatodendritic dopamine release are driven in large part by the inability of current assays to measure dopamine release with subcellular spatial resolution. To address this, we developed DopaFilm, a 2-dimensional chemi-sensitive surface on which rat primary dopamine neuron cultures are grown. DopaFilm is a composite nanofilm generated by drop-casting a solution of intensiometric, near-infrared fluorescent dopamine nanosensors onto glass coverslips and passivating the surface with polylysine. Optogenetic stimulation of dopamine neurons cultured on DopaFilm elicited fluorescence transients driven by putative dopamine release. When imaging in axonal arbors, evoked release of dopamine generated DopaFilm fluorescence hotspots that colocalized with boutons. DopaFilm enabled visualization of release and diffusion simultaneously from hundreds of boutons in axonal arbors, with quantal sensitivity. Taking advantage of the synaptic spatial resolution and quantal sensitivity, we subsequently imaged from dopamine neuron cell bodies and dendrites. DopaFilm revealed that somatodendritic effluxes of dopamine primarily arise from dendrites and not from the soma. We found that dopamine release is broadcast from a subset of dendritic processes as hotspots that have a mean spatial spread of ≈ 3.2 μm (full width at half maximum) and are observed with a mean spatial frequency of 1 hotspot per ≈ 7.5 μm of dendritic length. Intriguingly, release was detected only from a subset of dendrites, suggesting dendritic molecular specializations may be required for release competency. We used retrospective immunofluorescence and super-resolution imaging to explore molecular correlates of release in dendrites and found that release hotspots are colocalized with enriched clusters of Bassoon puncta, suggesting that Bassoon may contribute to organizing release sites in dendrites. Our work sheds light on the spatiotemporal dynamics of dopamine release from dendrites and offers explorations of molecular mechanisms that govern release.

Disclosures: C. Bulumulla: None. **A. Krasley:** None. **A. Beyene:** None.

Poster

746. Imaging Approaches for Monitoring Neuronal Activity

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 746.20

Topic: I.04. Physiological Methods

Support: NIH R21EY032382
NIH NS118302
NIH U01NS107689

Title: Clear optically matched panoramic access channel technique (compact) for large volume deep imaging of mammalian brain

Authors: *M. CUI;
Purdue Univ., Purdue Univ., West Lafayette, IN

Abstract: Clear optically matched panoramic access channel technique (compact) for large volume deep imaging of mammalian brain
Abstract:Genetic optical indicators and sensors have been widely employed in neuroscience research, which enables cell type-specific observation and control of neuronal activity at high spatiotemporal resolutions. However, a major challenge is that the optical access in the mammalian brain is limited to the superficial depth by the random scattering of light in tissue. Currently, the widely adopted method to gain optical access to the deep brain regions is to deliver light through miniature optical components such as the GRIN lenses. Despite its wide adoption, the imaging through these miniature optical components is restricted to a small imaging field of view, which limits the measurement throughput and success rate. Recently, we have developed a method for large volume imaging of deep mammalian brain regions[1]. Compared to the common GRIN lenses of similar insertion dimensions, COMPACT can achieve near three orders of magnitude larger tissue access volume. The idea of COMPACT is very simple. Through the insertion of ultrathin wall fused silica capillaries into the brain, COMPACT converts deep brain imaging into endoscopic imaging, which allows the imaging probes to spin and translate inside the brain to form a large-volume panoramic view of the brain tissue. We have combined COMPACT with two-photon microscopy for in vivo calcium imaging. Recently, we have upgraded the optical design and reduced the diameter of COMPACT from 1 mm to 0.5 mm, which is well suited for mouse brain studies. In this work, we will discuss the design and the performance of 0.5 mm COMPACT for in vivo calcium imaging.
Reference:1.Wei, B., Wang, C., Cheng, Z., Lai, B., Gan, W.-B. & Cui, M. Clear optically matched panoramic access channel technique (COMPACT) for large-volume deep brain imaging. *Nature Methods* 18, 959-964 (2021).

Disclosures: M. Cui: None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.01

Topic: I.04. Physiological Methods

Support: NIH R44OD024879
NSF 2036439

Title: Wide-field, Multi-point Zebrafish Motion Tracking Throughout an Open Swim Arena using a Gigapixel Microscope

Authors: T. J. J. DOMAN[1], J. P. EFROMSON[1], K. ZHOU[2], M. ZHENG[1], A. BÈGUE[1], J. P. BECHTEL[1], P. BOKADIA[1], V. SALIU[1], C. COOK[2], ***G. HORSTMEYER**[1], M. HARFOUCHE[1], R. HOSRTMEYER[2];
[1]Ramona Optics, Durham, NC; [2]Duke Univ., Durham, NC

Abstract: Zebrafish (Danio rerio) are scrutinized by microscopy to study neural development and pathology. Using conventional microscopes, each fish is observed one at a time within a narrow field of view. Behavior can be monitored over time using video acquisitions, but again, scope, efficiency and thus utility is limited due to the low throughput and small observable area of traditional techniques. With these methods an increase in the field of view decreases resulting resolution. Huge improvements can be made by using an sensor array to increase visible area while maintaining maximal resolution, however, this introduces new challenges and complexity for monitoring behavior such as calibration and constancy between sensors and image stitching between adjacent sensors when a fish is in between. In this work, we demonstrate accurate keypoint detection and motion tracking over time throughout an entire 8 x 12 cm arena. A novel micro-camera-array-microscope (MCAM™) Falcon was utilized to acquire time series images of one zebrafish freely swimming in the arena. Fifty-four overlapping camera sensors form the imaging array and together enable acquisition of ~700 megapixels over the full microscope stage. Our algorithm initially determines a centroid location of the zebrafish by finding the area of maximal difference between the current frame and a background image created from a subset of the frames. A region of interest is cropped from this frame around the fish and then these smaller images are passed through a convolutional machine learning key-point detection algorithm to precisely locate eight key-points of interest on the fish. This outputs cartesian coordinates for each point of interest on the zebrafish for each frame. Finally, the tracked frame is then mapped back into the overall frame array and the frames from each sensor are stitched together throughout the dataset time course yielding a 16k by 25k pixel (400 MP) video. Using this technique, high spatio-temporal resolution data can be acquired over a huge area unlocking many possibilities for further observation and research.

Disclosures: **T.J.J. Doman:** None. **J.P. Efromson:** None. **K. Zhou:** A. Employment/Salary (full or part-time):; Ramona Optics. **M. Zheng:** None. **A. Bègue:** None. **J.P. Bechtel:** None. **P. Bokadia:** None. **V. Saliu:** None. **C. Cook:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ramona Optics. **G. Horstmeyer:** None. **M. Harfouche:** None. **R. Hosrtmeyer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ramona Optics.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.02

Topic: I.04. Physiological Methods

Support: NRF Grant 2022R1A2C3007818

Title: Label-free phase microscopy for morphogenetic screening of zebrafish brain

Authors: *Y. KIM[1], U. SHIN[2], I. PARK[1], N. AIMAKOV[1], M. CHOI[1], Y. LEE[3], W. JUNG[1]; [1]Dept. of Biomed. Engin., [2]Ctr. for Genomic Integrity Inst. for Basic Sci., UNIST, Ulsan, Korea, Republic of; [3]Sch. of Med., Kyung Hee Univ., Seoul, Korea, Republic of

Abstract: Zebrafish are emerging specimens in morphogenesis studies, due to their genetic similarity to humans, fast development, embryonic transparency, and the availability of rapid phenotypic screening. Monitoring the phenotype in zebrafish conventionally involves a visual assessment and scoring of morphological features. As advanced microscopic imaging techniques are introduced for high resolution and volumetric anatomy, these techniques have been initially applied to neuroscience and developmental studies. However, existing methods are time-consuming and methodologically limited to provide fast and morphogenetic information of whole-mount zebrafish due to shallow imaging depth and the availability of transgenic reagents. In this study, we propose a novel label-free phase microscope for morphogenetic screening of the brain of zebrafish embryos in several development stages. Our system is based on quantitative phase imaging (QPI) which recovers phase delays after light passes through the specimen. Among the various QPI methods, we used four asymmetric NIR illumination patterns providing improved contrast and penetration depth. Using clear embryo samples within 1% agarose gel, prepared by 1-phenyl 2-thiourea (PTU) treatment, we acquired the dorsal and lateral views at 3, 4, and 5 days post fertilization (dpf). As a result, we confirmed that QPI had sufficient contrast and imaging depth to identify brain regions in dorsal and lateral QPIs than bright-field images. Lateral QPIs clearly showed detailed brain structures of normal zebrafish embryos, such as epiphysis, optic tectum, and cerebellum. To further evaluate our imaging system, we compared wile-type (WT) zebrafish embryos to the atad5a mutants at 3 and 5dpf. We segmented specific parts within the brain and found that there is significant differences in size and morphology between WT and mutant animals. The midbrain of atad5a mutants became smaller and flatter than WT controls from 3 dpf and the morphological appearance of the optic tectum showed visible alteration in the mutants at 5 dpf. In conclusion, we demonstrated that our phase microscope has sufficiently high contrast and depth penetration to visualize the developmental morphology of the zebrafish brain without any labeling or contrast agents. These results showed the possibility of applying our imaging system to the screening of brain morphological alterations by genetic modification or drug treatment. Finally, the imaging capability of our system can be enhanced when it is combined with the 360-degree rotation of the specimen, which provides a quantitative, volumetric, and comprehensive brain of zebrafish developmental studies.

Disclosures: Y. Kim: None. **U. Shin:** None. **I. Park:** None. **N. Aimakov:** None. **M. Choi:** None. **Y. Lee:** None. **W. Jung:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.03

Topic: I.04. Physiological Methods

Support: National Institutes of Health Director's New Innovator Award DP2DK128800
National Institute of Diabetes and Digestive and Kidney K01DK114165
Dana Foundation
Baxter Foundation
Dorris Scholars Fellowship

Title: Visualize peripheral innervation through HYBRiD body clearing

Authors: *V. LEUNG, Y. WANG, V. NUDELL, Z. PANG, N. K. LAL, M. HUANG, W. KANIM, A. PATAPOUTIAN, A. MAXIMOV, L. YE;
The Scripps Res. Inst., San Diego, CA

Abstract: The Peripheral Nervous System (PNS) plays a crucial role in transmitting information between the external environment, the body, and the Central Nervous System (CNS). Despite recent advances in brain clearing and optical imaging techniques, visualizing the PNS *en bloc* remains extremely difficult due to the unique heterogeneity and complex interfaces between PNS and peripheral tissues. Recently, we developed HYBRiD (hydrogel-based reinforcement of three-dimensional imaging solvent-cleared organs (DISCO)) by recombining components of organic-and polymer-based clearing pipelines. We achieved high transparency and protein retention as well as compatibility with direct fluorescent imaging and immunostaining in cleared mammalian bodies. Previously, using parvalbumin- and somatostatin-Cre models, we demonstrated the utility of HYBRiD for imaging of genetically encoded fluorescent reporters without antibody enhancement of signals in whole juvenile mice. Now, we coupled *en bloc* HYBRiD with AAV-based tracing from the Dorsal Root Ganglia (DRG) to characterize sensory innervation of the adipose tissues. HYBRiD and lightsheet imaging resolved the entire axonal projection from DRG soma to individual adipocytes across 1.2 cm, providing unequivocal anatomical evidence for this previously-underappreciated somatosensory branch. The imaging data also allowed characterization of the structural and molecular features of the adipose innervation at unprecedented resolution and scale, paving the way to probe the communicative function of sensory neurons in maintaining adipose-brain crosstalk.

Disclosures: V. Leung: None. **Y. Wang:** None. **V. Nudell:** None. **Z. Pang:** None. **N.K. Lal:** None. **M. Huang:** None. **W. Kanim:** None. **A. Patapoutian:** None. **A. Maximov:** None. **L. Ye:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.04

Topic: I.04. Physiological Methods

Support: NIH R35 NS105067
NIH DP2DK128800
NIDDK K01DK114165
Whitehall Foundation
Baxter Foundation
Dorris Scholars fellowship
Damon Runyon 243 Cancer Research Foundation, DRG-2405-20

Title: Dissecting the interoception circuit of the adipose tissues

Authors: *Y. WANG, V. LEUNG, Y. ZHANG, V. S. NUDELL, M. LOUD, M. R. SERVIN-VENCES, D. YANG, K. WANG, A. PATAPOUTIAN, L. YE;
Scripps Res., Scripps Res., La Jolla, CA

Abstract: Interoception includes the conscious and unconscious process of detecting sensory signals from the internal organs for maintaining whole-body homeostasis. While vagal innervation has been extensively studied for this role, the functions of somatosensory dorsal root ganglia (DRG) neurons innervating internal organs are less understood. For example, adipose tissue, which plays a key role in energy metabolism and receives strong sympathetic efferent, does not possess significant vagal innervation. Despite early literature describing DRG innervation in fat, its anatomical existence and physiological relevance remain controversial due to a lack of specific manipulation tools. Here, we developed viral, genetic, and imaging strategies to manipulate sensory nerves in an organ-specific manner. The combination of these strategies enabled us to (1) visualize the entire axonal projection from DRG soma to subcutaneous adipocytes; (2) manipulate the fat-innervating DRG neurons selectively; (3) characterize the structural and molecular diversity of spinal sensory innervation of fat. Together, we demonstrated that adipose tissues have robust sensory innervation and that it serves as a counteractive mechanism for suppressing sympathetic functions. This discovery suggests that adipose signals can be transmitted to the brain through hard-wired somatosensory circuits, challenging the canonical view that such feedback is primarily mediated by secreted hormones. These results reveal an important role of DRG innervation of adipose tissues and provide a general platform to study the role of sensory innervation of disparate interoceptive systems.

Disclosures: Y. Wang: None. **V. Leung:** None. **Y. Zhang:** None. **V.S. Nudell:** None. **M. Loud:** None. **M.R. Servin-Vences:** None. **D. Yang:** None. **K. Wang:** None. **A. Patapoutian:** None. **L. Ye:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.05

Topic: I.04. Physiological Methods

Support: DWG: AA016852, AA026117, W81XWH-13-2-0095, NS116519, Neuroscience Clinical Trials and Innovation Center, the WFU Clinical and Translational Science Institute, and UL1TR001420.
JBD : AA028007, AA021099-S1, AA026117, UL1TR001420, OD010965 and internal CTSI Ignition funds.
CC: MH097695.
DCK:AA016852, NS105005, NS116519.
GEA: F30 AA 23708 and NS073553.
JSK: VA/DoD W81XWH-13-2-0095, NIH grant NIAAA R21 AA028007, and internal CTSI Ignition funds.

Title: Combined Optogenetics and Magnetoencephalography in an Awake, Non-Human Primate

Authors: E. E. ROGERS[1], J. R. STAPLETON-KOTLOSKI[2], D. C. KLORIG[2], G. ALBERTO[2], C. CONSTANTINIDIS[4], J. B. DAUNAIS[3], *D. W. GODWIN[2];
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Abstract: Nonhuman primates (NHPs)provide versatile and robust models of human brain function and dysfunction.While NHPs are employed in electrophysiological and functional imaging studiesusing fMRI, they are not commonly employed in magnetoencephalography (MEG), asensitive imaging technique used to directly measure neuromagnetic activitywith both high temporal and spatial resolution. We have previously reported theuse of NHPs for functional brain mapping using a novel experimental platformcombining MEG-compatible optogenetic techniques (optoMEG) in anesthetized NHPs(*Nat Comm 12, 5259 (2021)*). Anesthesia may alter cortical function andconnectivity, thus in our current study we extend and implement this method inan awake, behaving African Green Monkey (vervet; *Chlorocebus aethiopssabaeus*). Intracerebral injections of AAV-ChR2 targeted deep brainstructures. A combined depth electrode and optical fiber (optrode) composed ofMEG-compatible materials was implanted at the site of injection.Optogenetically-evoked activity was used to functionally track the expressionof ChR2 over the course of the experiment, which lasted over 4 years. After 5weeks, responses were stable for ~2 years before diminishing in years 3 and 4to approximately 30% of maximum. The monkey was trained to sit quietly in aplexiglass recording chair for MEG scans, and the head was stabilized using animplant and head bolt assembly composed of MEG-compatible materials. We usedsynthetic aperture magnetometry to localize optogenetically-evoked signals todeep brain structures of the awake NHP under multiple stimulation conditions ata resolution of 750 μm^3, and we tracked the activation or inhibitionof downstream structures, including thalamic nuclei, contralateral hippocampus,and extended temporal networks. These findings demonstrate: 1) the first awakeNHP MEG recordings that are stable enough for long term behavioral experiments;2) the long-term stability of functional ChR2 expression lasting for severalyears in a NHP model; 3) the utility of combining optogenetics and MEG as anovel

platform for experimenter-controlled stimulation, ground-truthdetermination, high-resolution source localization, and downstream networkmapping across a wide range of spatiotemporal scales.

Disclosures: **E.E. Rogers:** None. **J.R. Stapleton-Kotloski:** None. **D.C. Klorig:** None. **G. Alberto:** None. **C. Constantinidis:** None. **J.B. Daunais:** None. **D.W. Godwin:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.06

Topic: G.04. Emotion

Support: RF1NS118287
R61DA051049

Title: Wireless devices for in vivo optogenetics, pharmacology, microdialysis, and two-photon imaging

Authors: *C. M. PIZZANO[1], S. C. PIANTADOSI[1], J. CHEN[1], D. C. CASTRO[2], M.-K. LEE[3], Y. WU[3], V. ABDULLA[4], R. M. DRENAN[5], Y. ZHANG[4], J. A. ROGERS[3], M. R. BRUCHAS[1]; [1]Univ. of Washington, Seattle, WA; [2]Washington Univ., St. Louis, MO; [3]Northwestern Univ., Chicago, IL; [4]Univ. of Connecticut, Mansfield, CT; [5]Wake Forest Univ., Winston-Salem, NC

Abstract: Technological advances in neuroscience have broadened our understanding of the molecular, cellular, and circuit basis of behavior. Optogenetics and pharmacological techniques allow for precise neural circuit manipulation and targeting during behavioral assays, providing unique insight to drug interactions in the brain and their impact on behavior. Microdialysis enables us to assess the types of neurotransmitters, peptides, or hormones in the brain during specific behaviors. Two-photon imaging allows us to visualize live neuron activity and activate specific neuron populations in real time. Harnessing multiple of these methods at once could uncover mechanisms to better inform therapeutics for brain-related diseases. However, simultaneous use of these techniques *in vivo* presents a challenge due to the physical limitations of multiple probes needed to target delicate brain regions. This can result in variable behaviors, tissue damage, and challenges for experiments that require freely moving animals. Here, we present several types of wireless devices that utilize many of these approaches in a single platform. The optofluidic device includes a probe with a microfluidic channel and micro-LED implanted into the brain, enabling temporally specific microinfusions and optostimulation. We implanted these devices into the Nucleus Accumbens (NAc) as well as the preBötzinger Complex (preBötC) and infused fentanyl and photoactivable (PA) fentanyl to observe pharmacological effects. We found that post infusion, locomotion and grooming were increased in NAc implanted animals. Additionally, we observed a decrease in the respiratory rate following fentanyl infusion into the preBötC. We also report that when optically activated, PA fentanyl

produced similar results to regular fentanyl in our assays. Membrane-free neurochemical sampling devices use a push-pull microsystem that collects brain fluids *in vivo* through microfluidic probes. These microdialysis devices were implanted in the NAc combined with optogenetic stimulation for neurochemical content analysis in the brain fluid collected. Finally, the GRIN lens fluidic device has an implantable GRIN lens with a microfluidic channel which can be used for single-cell endoscopic imaging along with microinfusions. We implanted this GRIN lens fluidic device into the striatum to record neuronal activity while locally delivering pharmacological agents into the imaging field of view. These new devices have the potential to combine many crucial neuro-technologies to better address the circuit, cell type, and molecular mechanisms that contribute to behavior and ultimately neuropsychiatric diseases.

Disclosures: C.M. Pizzano: None. **S.C. Piantadosi:** None. **J. Chen:** None. **D.C. Castro:** None. **M. Lee:** None. **Y. Wu:** None. **V. Abdulla:** None. **R.M. Drenan:** None. **Y. Zhang:** None. **J.A. Rogers:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); COI with Neurolux. **M.R. Bruchas:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); COI with Neurolux.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.07

Topic: I.02. Systems Biology and Bioinformatics

Title: Ion Sensitive Field Effect Transistor Coupled To Resonating Antenna For Wireless Neural Monitoring

Authors: *S. BHATT, E. MASTERSON, A. VAREBERG, A. HAI;
Univ. of Wisconsin, Madison, Madison, WI

Abstract: Wireless brain technologies are empowering basic neuroscience and clinical neurology by offering new platforms that minimize invasiveness and refine possibilities during electrophysiological recording and stimulation. However, most systems require bulky accessory circuits for efficient operation. Here we present a minimalistic circuit for wireless sensing of ionic fluctuations in the brain by an ion-sensitive field effect transistor (ISFET). We validate this new architecture *in vivo* in brains of anesthetized rats during hindpaw stimulation. Male Sprague-Dawley rats were purchased from Envigo and used in all experiments. The animals were housed and maintained on a 12h light/dark cycle and permitted ad libitum access to food and water. Rodents were anesthetized with isoflurane and mounted on a stereotactic device. A stimulation electrode was inserted through the right contralateral hindpaw. The scalp was retracted and a cranial window opened to expose the hindpaw region of the somatosensory cortex (2.2mm posterior and 2.0mm lateral to bregma). The active site of the MSFET 3351 ISFET was then fixed and secured to the cranial window. The drain and source of the ISFET were coupled to an

LC wireless resonator which itself was fixed underneath a single spiral antenna connected to a VNA. The same area was also recorded with a Neuronexus microelectrode array as a conventional recording baseline. Response to contralateral stimulation at 2Hz, 5Hz, and 10Hz was then recorded. Wireless ISFET and conventional electrode recordings correlated closely under stimulation at all frequencies relative to their baselines. Consistent with previous findings, electrode recordings reported an average increase of 10dB relative to baseline for 2Hz stimulation, particularly in the 0-5Hz band, otherwise known as the Beta wave band. The experiment reported a threshold-like effect for frequencies of stimulation greater than 2Hz. At 5 and 10Hz, corresponding increase relative to baseline was about 3dB on average. The wireless ISFET response showed a similar effect, with a reduction from an average increase of 3dB to 1dB and lower from 2Hz to higher frequencies of stimulation. This data was gathered from a sample of n=5 subjects. As shown by the results before, we show that wireless ISFET data can successfully record neural data consistent with LFPs. Further work will be done to miniaturize the ISFET and resonator to be injectable by needle.

Disclosures: S. Bhatt: None. **E. Masterson:** None. **A. Vareberg:** None. **A. Hai:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.08

Topic: I.04. Physiological Methods

Support: McKnight Technological Innovations in Neuroscience Award
Chan Zuckerberg Biohub

Title: Micromirror-based spatial light modulators for high-speed optical neural interfaces

Authors: *C. YALCIN[1], N. ERSARO[1], L. MURRAY[1], A. PANDEY[1], M. GHANBARI[1], D. LOPEZ[2], N. C. PEGARD[3], L. WALLER[1], R. MULLER[1];
[1]Electrical Engin. and Computer Sci., Univ. of California, Berkeley, Berkeley, CA;
[2]Pennsylvania State Univ., State College, PA; [3]Applied physical Sci., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: Optical neural interfaces are a promising class of tools for neuroscience research that enable simultaneous monitoring and manipulation of neuronal activity with light. The most capable all-optical systems incorporate computer-generated holography (CGH) through the use of spatial light modulator (SLM) devices to sculpt light. State-of-the-art SLMs operate at <300 Hz, limiting the temporal resolution and overall throughput of holographic stimulation and imaging systems. We seek to develop high-speed SLMs for holographic optogenetics and fluorescence imaging using fast-settling micromirrors, an endeavor that mandates concurrent innovations in microelectromechanical system (MEMS) mirror arrays, CMOS driver systems, and hybridized packaging.We have developed a varifocal micromirror array comprised of

>24,000 MEMS micromirrors in 32 independently addressable channels. Together with a custom application specific integrated circuit (ASIC) driver the system enabled random-access single-point light focusing, dwelling-capable focus tuning at low voltages (<30 V), across wavelengths of up to 1,100 nm, and at a refresh rate >15 kHz. This speed represents an approximately 100-fold improvement over comparable commercial varifocal tools such as optofluidic lenses and liquid crystal SLMs. Our functional testing of this varifocal tool demonstrated a wide focus tuning range which could illuminate 10 µm-thick depth planes across a total thickness of 300 µm under a standard 20x objective. We are now developing a complete SLM system that can actuate each individual mirror in a >4,000 MEMS micromirror array. The micromirror structure was updated for improved stability, planarity, efficiency, and robustness to process variations based on the measured performance of the varifocal lens. Coupled with an ASIC co-designed with these arrays, our approach allows for >10 kHz drive of up to 64x64 micromirrors, enabling simultaneous random-access targeting of multiple neurons at speeds faster than action potential durations, with dwelling capability and no hysteresis.

Disclosures: **C. Yalcin:** None. **N. Ersaro:** None. **L. Murray:** None. **A. Pandey:** None. **M. Ghanbari:** None. **D. Lopez:** None. **N.C. Pegard:** None. **L. Waller:** None. **R. Muller:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.09

Topic: I.04. Physiological Methods

Support: NIH Grant R01NS111749

Title: Neuronal imaging using incoherent color holographic lattice light sheet

Authors: M. POTCOAVA[1], *S. ALFORD[2];
[1]Anat. and Cell Biol., Univ. of Illinois at Chicago, Chicago, IL; [2]Anat. and Cell Biol., Univ. of Illinois At Chicago, Chicago, IL

Abstract: Lattice light sheet imaging improves imaging speed with reduced excitation intensity. Sheet scanning allows capture of individual frames at rates limited only by the camera frame rate, and the lattice structure allows both high z-plane resolution (close to diffraction limited; ~400 nm) and good tissue penetration (up to 100 µm) in brain slices. However, neurons are 3 dimensional and although z plane scanning of the lattice sheet to visualize in 3D can be rapid using galvanometers, it is necessary to adjust the objective focal plane either by moving the tissue or the objective. Both approaches generate problems. Moving the tissue, obviates electrophysiological methods, causes mechanical artefacts, and is slower than steering the light beam with galvanometers. Moving the heavy objective lens is slow, and also moves the recording medium, again causing mechanical artefacts. Moreover, the LLS, like other tomographic approaches, does not provide access to the sample phase modulation. This limits

speed and accuracy of tomographic imaging, and precludes gathering phase information, preventing access to critical information on the state of the imaged neurons. We sought an alternative approach to axial reconstruction, called incoherent holography lattice light-sheet (IHLLS), without the need to alter the emission z position and with minimal cost in speed. IHLLS was developed as a second detection module on the original LLS design. This has the advantage of utilizing the incoherent properties of fluorescence emission and the coherent properties of LLS to retrieve the sample phase information. We characterize an IHLLS optical system, and image with two excitation wavelengths 488nm and 561nm, which produce emission beams at 523 nm and 570 nm. The two-color technique uses self-interference properties of the emitted fluorescent light, in which 3 or 4 interference patterns are created using a phase shifting technique, to create Fresnel holograms of a 3D object. The spatial light modulation (SLM) optical design actively controls the dual diffractive lenses phase-shifting at two colors sequentially. This is repeated at each z-galvo scanning level. The technique allows both fast three-dimensional amplitude and phase imaging without moving either the sample stage or the detection objective, for extended FOV (208 x 208 mm^2) and depth. The scanning depth is a function of two variables, the numerical aperture of the LLS diffraction mask annulus and the z-galvanometer mirror scanning range. Using an anulus of 0.55 outer NA and 0.48 inner NA, the scanning depth could reach up to 80 µm, using 9 z-galvo positions within the range Δz_{galvo} = 80 µm, at z_{galvo} = ±40 µm, ±30 µm, ±20 µm, ±10 µm, and 0 µm.

Disclosures: **M. Potcoava:** None. **S. Alford:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.10

Topic: I.04. Physiological Methods

Support: U01NS113295
R35GM133802

Title: Development of photoactivatable derivatives of gastrin releasing peptide, oxytocin, cholecystokinin and substance P

Authors: *A. E. LAYDEN, J. X. HE, C. JOHNSON, X. MA, M. R. BANGHART;
Dept. of Neurobio., Univ. of California San Diego, La Jolla, CA

Abstract: Neuropeptides are ubiquitous in the nervous system, yet the logic of neuropeptide signaling is poorly understood. This is due, in part, to a lack of tools for delivering neuropeptides in neural tissue with high spatiotemporal precision in order to study the physiological and behavioral consequences of their action. Photoactivatable or “caged” ligands can greatly facilitate quantitative studies into the mechanisms and consequences of neurotransmission by providing a convenient, robust stimulus-response relationship that relies on a brief flash of light

to drive release. Building off our prior work with caged opioid neuropeptides, we have now developed a suite of caged neuropeptide derivatives that target diverse neuropeptide receptors. These include caged variants of gastrin releasing peptide (GRP), oxytocin (OXT), cholecystokinin (CCK), and substance P (SP), all of which contain a C-terminal carboxamide. Although several of these peptides were successfully caged by incorporating UV-sensitive nitrobenzyl-derived caging groups into amino acid side chains, a "one-size-fits-all" approach was explored for caging the C-terminal carboxyamide moiety with a charged, sterically bulky nitrophenyl peptide (NPP). Candidate caged peptides were first evaluated for inactivity at their cognate receptors in vitro using a GloSensor assay. The least active candidates were then evaluated for stability in the dark and for clean conversion to the target neuropeptide upon exposure to UV light. Top performing candidates were further evaluated for their ability to activate endogenous GPCRs in ex vivo brain slices in response to brief light flashes using electrophysiological recordings from receptor-expressing neurons. While standard side chain caging was successful as expected, the C-terminal extension strategy proved viable for all four target peptides. This work not only validates caged variants of GRP, OXT, CCK, and SP, but also establishes the peptide extension strategy as an apparently general solution for caging C-terminally carboxamidated peptides, which comprise >50% of the neuropeptides found in the nervous system.

Disclosures: A.E. Layden: None. **J.X. He:** None. **C. Johnson:** None. **X. Ma:** None. **M.R. Banghart:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.11

Topic: I.04. Physiological Methods

Support: U01NS113295

Title: A caged DAMGO for selective photoactivation of endogenous mu opioid receptors in vivo

Authors: *D. JOHNSON, X. MA, J. X. HE, A. LAYDEN, S. P. MCCLAIN, J. C. YUNG, M. R. BANGHART;
Dept. of Neurobio., UCSD, San Diego, CA

Abstract: Photoactivatable drugs and peptides are valuable tools that can drive quantitative studies into endogenous receptor signaling with high spatiotemporal resolution. In particular, such photopharmacological probes enable rapid (sub-second)triggering of drug action that is largely restricted to the area of illumination. The Banghart Lab synthesized a photoactivatable or"caged"derivative of the mu opioid receptor (MOR)-selective peptide agonist [D-Ala2,N-MePhe4, Gly-ol]-enkephalin(DAMGO). In this poster, I present the *in vitro* and *ex vivo* characterization of the caged DAMGO variant CNV-Y-DAMGO, to establish its use in

behavioral photopharmacology experiments that involve *in vivo* photorelease with ultraviolet light. To achieve site-specific DAMGO photorelease, optofluidic cannulas that deliver both light and peptide were implanted in the ventral tegmental area (VTA)of the mouse brain, where MOR activation increases locomotor behavior. Local administration of CNV-Y-DAMGO in the VTA was found to be inert, yet photoactivation with ultraviolet light produced a dramatic increase in locomotor behavior that was blocked with systemic administration of naloxone. Notably, the increase in locomotor behavior occurred within several seconds of illumination with a 200mslight flash, which reveals the rapid onset of drug action at endogenous receptors that is achievable with photopharmacology. These results demonstrate the power of *in vivo* photopharmacology for dynamic studies into animal behavior and establish CNV-Y-DAMGO as a useful reagent for biological studies.

Disclosures: **D. Johnson:** None. **X. Ma:** None. **J.X. He:** None. **A. Layden:** None. **S.P. McClain:** None. **J.C. Yung:** None. **M.R. Banghart:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.12

Topic: I.04. Physiological Methods

Support: NIH Grant DP2DK128800
NIH Grant DK114165
NIH Grant DK124731
NIH Grant DA033760
the Dana Foundation
the Whitehall Foundation
the Baxter Foundation

Title: Brain-wide in situ visualization of cellular drug targets

Authors: *Z. PANG[1], M. A. SCHAFROTH[2], D. OGASAWARA[2], Y. WANG[1], V. NUDELL[1], N. K. LAL[1], D. YANG[1], K. WANG[1], D. M. HERBST[4], J. HA[4], C. GUIJAS[4], J. L. BLANKMAN[4], B. F. CRAVATT[2], L. YE[1,3];
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Abstract: Precise mapping of drug actions in the central nervous system (CNS) has long been difficult due to the spatial, cell type and connection complexity. Although it is highly desirable, visualizing *in situ* drug target at cellular resolution in the mammalian brain had not been possible. Here, we develop clearing-assisted tissue click chemistry (CATCH) to optically image covalent drug binding across the brain. With an alkyne modified fatty acid amide hydrolase (FAAH) inhibitor PF7845-yne as our proof-of-concept compound, we demonstrated lipid

removal by tissue clearing is critical for the success of click chemistry drug labeling. With optimization of reaction ligand and copper, we were able to profile PF7845-yne targets across different brain regions and cell types. We demonstrated CATCH is highly specific with both parental drug competition and FAAH knock out mice (FAAH-/-). We revealed potential off target binding sites of another FAAH inhibitor BIA10-2474, which is known to have clinical toxicity, and a distinct binding pattern of a monoamine oxidase inhibitor pargyline. By complementing the use of direct and competitive CATCH, we uncovered unexpected drug binding profiles across different brain regions and dose-dependent shifts of drug engagement in different subcellular compartments. CATCH is compatible with multiple rounds of secondary staining, enabling rare drug-positive cell type identifications. More recently, we further optimized CATCH labeling kinetics, which allows for direct volumetric drug visualization, paving way for high-throughput, unbiased and brain-wide drug binding registration. In summary, CATCH represents the first endeavor to visualize *in vivo* drug binding with cellular resolution and opens exciting new opportunities for understanding drug actions in the brain.

Disclosures: **Z. Pang:** None. **M.A. Schafroth:** None. **D. Ogasawara:** None. **Y. Wang:** None. **V. Nudell:** None. **N.K. Lal:** None. **D. Yang:** None. **K. Wang:** None. **D.M. Herbst:** None. **J. Ha:** None. **C. Guijas:** None. **J.L. Blankman:** None. **B.F. Cravatt:** None. **L. Ye:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.13

Topic: I.04. Physiological Methods

Title: Near-infrared fluorescent nanosensor development for visualization of dopamine and other biologically relevant catechols

Authors: *A. T. KRASLEY, C. BULUMULLA, A. G. BEYENE;
HHMI Janelia Res. Campus, Ashburn, VA

Abstract: This work describes the use of near-infrared (NIR) fluorescent single-walled carbon nanotubes (SWCNT) for applications in neuroscience research. SWCNTs have several photophysical properties that make them attractive for imaging in biology. SWCNTs fluoresce in the near infrared region of the spectrum (~ 900-1300 nm), which is suitable for imaging in thick biological specimens because of reduced scattering of NIR photons and minimal tissue autofluorescence. They exhibit superior photostability and can be considered to be non-photobleaching on time scales of interest to imaging in biology. Their fluorescence in the NIR range of the spectrum is also suitable for multiplexing with existing optical tools that operate in orthogonal channels for neuroscience research. Functionalized SWCNT can be sensitized to molecules of interest in biology, and this offers additional opportunities for developing optical biosensors that are endowed with the unique photophysical properties of SWCNTs. In this work,

we describe the principles behind molecular recognition and sensor development from functionalized SWCNTs. We will put emphasis on SWCNT-based optical biosensors for monoamines and discuss how these probes have been used to image dopamine release in cultured primary dopamine neurons and acute brain slices. Owing to their synthetic nature, these biosensors can be deployed in unique preparations that afford imaging of dopamine release from axons terminals and dendrites. Using SWCNT-based optical biosensors, we have been able to characterize the spatiotemporal dynamics of canonical release of dopamine from axon terminals with single bouton resolution and quantal sensitivity. Furthermore, we have applied these tools to study somatodendritic release of dopamine, a phenomenon that has been insufficiently characterized, and enable visualization of the spatial spread of dopamine release from dendritic processes. When coupled with retrospective immunofluorescence, genetic perturbation, and super-resolution imaging, our method facilitates examination of the molecular correlates and determinants of release in axonal and dendritic processes.

Disclosures: **A.T. Krasley:** None. **C. Bulumulla:** None. **A.G. Beyene:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.14

Topic: I.04. Physiological Methods

Support: NIH Grant EY22122
NIH Training Grant 5T32GM132498-02
NIH Training Grant 5T32GM132498-03
NIH Training Grant 2T32MH019929-26

Title: A chronic head-fixed ferret preparation for uncovering the properties of feedforward connections between LGN and V1

Authors: ***L. MARTIN**[1], Z. C. KEELEY[2], Y. ZHU[3], M. D. VIVIAN[1], S. D. VAN HOOSER[4,2,5];
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Abstract: In the mammalian brain, there is a major transition of sensory response properties as one moves from relay neurons in the thalamus to the neurons of primary sensory cortex. In the visual system of carnivores and primates, there is a transition from primarily "spot detector" neurons in lateral geniculate nucleus (LGN) to orientation- and direction-selective neurons in primary visual cortex. While the understanding of circuit properties underlying the computation of direction selectivity in the retina of rodents, drosophila and lagomorphs are advanced, our understanding of its computation in carnivores and primates, where it arises de novo within

primary visual cortex and requires visual experience to develop, is immature. We already understand that convergence of LGN cells with co-linear receptive fields onto primary visual cortical neurons helps to confer orientation selectivity in cortex, but the feed-forward contributions that may underlie direction selectivity in visual cortex of animals that have functional maps of direction (carnivores and primates) remain unknown. Further, feed-forward input to inhibitory interneurons in these animals has never been described, despite the importance of understanding the key role of feed-forward inhibition for enhancing selectivity and stability in cortical neurons. Here we present progress on the development of a chronic approach that mimics a successful approach in the rabbit: a head-fixed ferret with chronically implanted micro-drives and electrodes that target the lateral geniculate nucleus and primary visual cortex, to scan for monosynaptic connections between these areas using cross-correlation methods. Ferrets are trained to tolerate head fixation for extended periods while they view a stimulus monitor and their eye movements are monitored with cameras to track their focus. By returning to the same animal day after day, we will build up a detailed understanding of the receptive field properties of the recorded neurons, further understand their connectivity, and explore the spatial-temporal properties of feedforward connections. These experiments will reveal important principles of the
connectivity that underlie the transformation of receptive field properties from thalamus to cortex.

Disclosures: L. Martin: None. **Z.C. Keeley:** None. **Y. Zhu:** None. **M.D. Vivian:** None. **S.D. Van Hooser:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.15

Topic: I.04. Physiological Methods

Support: R01NS111028

Title: Rapid imaging-guided automated craniotomy for small rodents

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Abstract: A majority of neural activity recording and modulation modalities require physical access to the brain via acuteports or chronically implanted transparent cranial windows. In mice, the most widely used mammalian model organism, such intracranial access is gained by performing delicate craniotomy procedures on sub-millimeter thick skull tissue with care taken to ensure no damage to the dura or brain occurs during the bone removal process. Efforts have been made recently to automate such delicate procedures, wherein a measurement of the surface

profile of the skull and additionally sparse measurements of skull thickness are used to guide a robotically controlled burr tool to remove the skull tissue at the desired craniotomy location. Current robotic craniotomy procedures utilize impedance sensing (Pak et al 2014) or contact force sensing (Ghanbari* Rynes* et al 2019). Profiling using impedance sensing is prone to false positives and false negatives, whereas contact profiling is time consuming and is useful only for measuring the top surface of the skull without any information about the thickness of the skull. In both cases, an accurate estimate of the skull thickness is lacking and thus the bone is robotically excised in an iterative process.Here we investigated the feasibility of using Optical Coherence Tomography (OCT) for non-invasive, single-shot profiling of the dorsal skull. OCT imaging can be used to image and computationally construct the 3D top and bottom surface of the skull within 3 minutes with an axial resolution in bone of 10 μm and a lateral resolution of 20 μm. The necessary accuracy and precision of the OCT was cross validated by comparison with Micro-Computed Tomography (μCT) scans of 33 C57BL6 mice. We observed that 98.5% of the time the height change within 20 μm of each location is less than 20 μm while the large gradients in skull thickness are all located near skull sutures. We next developed an automated computer-vision pipeline to segment and analyze the OCT scans. The scans are processed to isolate bone from the background and the thickness of the dorsal skull is measured in a 20 μm resolution grid. We algorithmically optimized the skull thickness measurements based on our previous μCT study of mouse skull morphology. We used the skull thickness along the path of craniotomy to guide a Cartesian robot to automatically perform coverslip implant craniotomies. Our work demonstrates the feasibility of using OCT imaging followed by computer vision for performing precise cranial microsurgery procedures such as circular bone removal for the implantation of cranial windows.

Disclosures: Z.S. Navabi: None. **B.R. Gulner:** None. **E. Hajare:** None. **S.B. Kodandaramaiah:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.16

Topic: I.04. Physiological Methods

Support: JSPS KAKENHI JP15H05917
JSPS KAKENHI JP20K12022
JSPS KAKENHI JP20H00614
JSPS KAKENHI JP19K22881
JSPS KAKENHI JP21H05820
Program for Leading Graduate Schools R03

Title: A fine scale and low invasive marking method for use with conventional tungsten microelectrodes

Authors: *T. OIKAWA[1], K. NOMURA[1], T. HARA[1], K. KOIDA[2,1];
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Abstract: Metal microelectrodes have been widely used for single-cell recording in vivo, however, there is difficulty in correlating the recording site with neuroanatomical structures. Various marking methods have been developed such as the electrolytic lesion, metal deposition, and fluorescent-dye coating, however, there still exist problems in its spatial resolution, tissue damage, and durability of the mark for chronic experiments. Here we show a novel marking method of simple, fine scale, and low invasiveness for use with tungsten electrodes. Tungsten needles are often processed by electrolytic polishing with alternating current, and small fragments of tungsten oxide appear and deposit around the tip. This tungsten oxide could be a mark if the electrolytic polishing is processed in vivo. We applied biphasic current stimulation (>4 μA, >4 V at 1 kHz) via tungsten electrodes (~1 MΩ, FHC) in a saline solution, and confirmed the deposition of the tungsten oxide. The size of the tungsten oxide increased depending on the current and stimulating duration. Next, we applied our proposed marking method to the cortex of a mouse and a macaque monkey. At the site where single-unit activity was measured, the electric current was applied (20-50 μA) for 1 to 7 minutes. The animals were perfused acutely (mouse) or two years (macaque) after the marking. Brain slices were then stained with cresyl violet. We observed small clusters of tungsten oxide (<50 μm in width) colored dark brown in bright field microscopy without any additional stain. The marking was clearly visible as a bright red in dark-field microscopy, probably due to the specular reflection of the tungsten oxide. Thus, even tiny fragments of tungsten oxide smaller than cellular size were visible in low magnification images, contributing prompt detections of the marking. The sites of marking were in good agreement with both the depth of penetration and the track of penetration visualized by fluorescent dye of the electrodes. Tissue damage due to the current was negligible for low currents (20 μA) and was partially confirmed for high currents (50 μA). The marking lasted for at least two years in vivo, thus our marking method can be used for chronic experiments.

Disclosures: **T. Oikawa:** None. **K. Nomura:** None. **T. Hara:** None. **K. Koida:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.17

Topic: I.04. Physiological Methods

Support: JSPS KAKENHI JP15H05917
JSPS KAKENHI JP20K12022
JSPS KAKENHI JP20H00614
JSPS KAKENHI JP19K22881
JSPS KAKENHI JP21H05820

Title: Metal deposition marking method for use with multielectrodes

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Abstract: Metal microelectrodes have been widely used for single-unit recording, however spatial reconstruction of the recording site with the anatomical structure is poorly limited. Various marking methods have been developed however there still exist limitations in its spatial resolution, tissue damage, and durability.
Here we introduce a novel marking method by applying a double-layer plating and electrolysis of the electrode tip to enable precise marking of the recording site. The double-layer plating is composed of a superficial layer (Pt) and a connecting deep layer (Au), they are electroplated onto the tip of the conventional microelectrodes. When an anode current is passed through the electrode at the recording site, the metal of the connecting layer is selectively dissolved and broken, then the superficial layer is detached from the electrode. As a result, the detached tip would become a very small marking of the recording site.
We demonstrated the proposed method by using platinum electrodes including single wire, tetrodes, and silicon probes (Neuronexus). The marking was successfully deposited for the Pt wire and tetrodes. For the tetrode, we found that multiple markings were made while reproducing the spatial arrangement and size of the electrode tip. On the other hand, the marking with Neuronexus was only rarely successful. These failures were accompanied by damage to the thin film of the electrode before the separation of the plating. Next, we demonstrated the proposed method in vivo. After inserting the tetrodes into an anesthetized mouse cerebral cortex, an anode pulsed current (80 μA, 1 ms ON / 9 ms OFF, 100Hz, total ON duration 6 s) was applied where single unit activities were obtained. Then the animal was perfused and the brain was sliced. We observed multiple markings at the recording sites. The markings were visible by a conventional microscope without any staining. The marking size was about ~20 μm in width, corresponding to the diameter of the individual Pt wire. Because tissue damage was observed primarily through tetrode insertion and bleeding, the extent of damage originating from the current pulse could not be assessed. These results suggest that our proposed marking method is applicable to the multielectrodes, which contribute to the identification of the recording cells.

Disclosures: **T. Matsuhira:** None. **T. Yamada:** None. **T. Hara:** None. **R. Numano:** None. **T. Kawano:** None. **H. Sawahata:** None. **K. Koida:** None.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.18

Topic: I.04. Physiological Methods

Title: Benchmarking of individual-level preprocessing strategies for functional ultrasound imaging

Authors: *S. DIEBOLT[1,2,3], J.-C. MARIANI[2], A. KLIEWER[4], L. BEYNAC[2], R. SANTOS[2], B.-F. OSMANSKI[3], T. DEFFIEUX[1], Z. LENKEI[2];
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Abstract: Functional ultrasound (fUS) imaging, a novel neuroimaging modality with high spatiotemporal resolution and high sensitivity, is becoming an increasingly important tool for the study of functional connectivity in awake animals. However, awake fUS data preprocessing presents significant challenges, in particular considering the confounding effects of artefacts caused by animal motion. Those artefacts can be partially mitigated by adequate preprocessing steps such as global signal regression (GSR), scrubbing and bandpass filtering. Here, we report benchmarking results of the performance of several preprocessing pipelines tailored to functional connectivity studies using fUS imaging, including new methods inspired by recent advances in fMRI preprocessing. We tested the algorithms on several fUS datasets from studies of resting-state functional connectivity in mice. Preprocessing pipelines were evaluated using previously established metrics of noise removal and seed-based maps strength. This study illustrates the effects that different preprocessing steps can have on subsequent statistical analyses and shows which steps can be used to improve the robustness of awake fUS connectivity analyses.

Disclosures: **S. Diebolt:** A. Employment/Salary (full or part-time):; Iconeus. **J. Mariani:** None. **A. Kliewer:** None. **L. Beynac:** None. **R. Santos:** None. **B. Osmanski:** A. Employment/Salary (full or part-time):; Iconeus. **T. Deffieux:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus. **Z. Lenkei:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.19

Topic: I.04. Physiological Methods

Support: EU Grant no 874721 (PREMSTEM project)

Title: Ultrasound multiparametric imaging of neuroinflammation

Authors: *S. RUINET[1], H. SOLEIMANZAD[1], Z. CSABA[2], N. IALY-RADIO[1], C. BOKOBZA[2], P. GRESSENS[2], M. TANTER[1];
[1]Physics for Med., Paris, France; [2]INSERM U676, Paris, France

Abstract: Background: Neuroinflammation is an inflammatory reaction that takes place in the central nervous system and can be induced by intrinsic (stroke, dysfunction of the immune system…) or extrinsic factors (infection, injury…). When it occurs during the perinatal period, neuroinflammation can impact critical phases of brain development and have long-term consequences on individuals' health (motor impairments, behavioral disorders, cognitive deficits…). **Aim:** The aim of this ongoing study is to develop a multiparametric imaging technique based on the sole use of ultrasonic waves in order to better understand the impact of neuroinflammation on brain development. More specifically, three aspects of brain activity will be examined: neurovascular response to task-evoked and spontaneous brain activity, vascular architecture and hemodynamics properties, and cerebral tissue biomechanics. **Methods:** This study is based on a mouse model of inflammation, at postnatal days 5 and 30. Two inflammatory molecules are tested: lypopolysaccharide (LPS) and polyinosinic:polycytidylic acid (poly I:C), which reproduce respectively a bacterial and a viral inflammation. A set of combined methods of ultrafast ultrasound imaging is developed in the same experimental session: functional ultrasound imaging, to map blood flows in the brain; shear wave elastography, to measure tissue elasticity; and ultrafast Ultrasound Localization Microscopy (ULM), to detect cerebral microvessels and microhemodynamics. **Results:** We implemented a simultaneous mapping of brain stiffness (300 um, 1.6 s) and Cerebral Blood Volume (CBV) measurements (100 um, 1.6 s) for structural and functional imaging of the mouse brain. Following these acquisitions, ULM sequence was performed to image the vascular system at microscopic scale (6 um), using a 10-min acquisition sequence. In the LPS inflammatory mouse model, we identified an alteration of the neurovascular coupling during whisker stimulations. The CBV increase relative to baseline was found to be lower in inflammated mice compared to control mice (respectively + 13 ± 3.4 % and + 17 ± 3.8 %). **Perspectives:** We implemented a full ultrasound-based imaging method in mice able to quantify multiple parameters in neuroinflammation. This multiparametric modality should enable us to identify new biomarkers of neuroinflammation both for the screening of inflammatory processes and the follow-up of therapeutic treatment efficacy in the context of drug discovery.

Disclosures: S. Ruinet: None. **H. Soleimanzad:** A. Employment/Salary (full or part-time):; Iconeus. **Z. Csaba:** None. **N. Ialy-Radio:** None. **C. Bokobza:** None. **P. Gressens:** None. **M. Tanter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

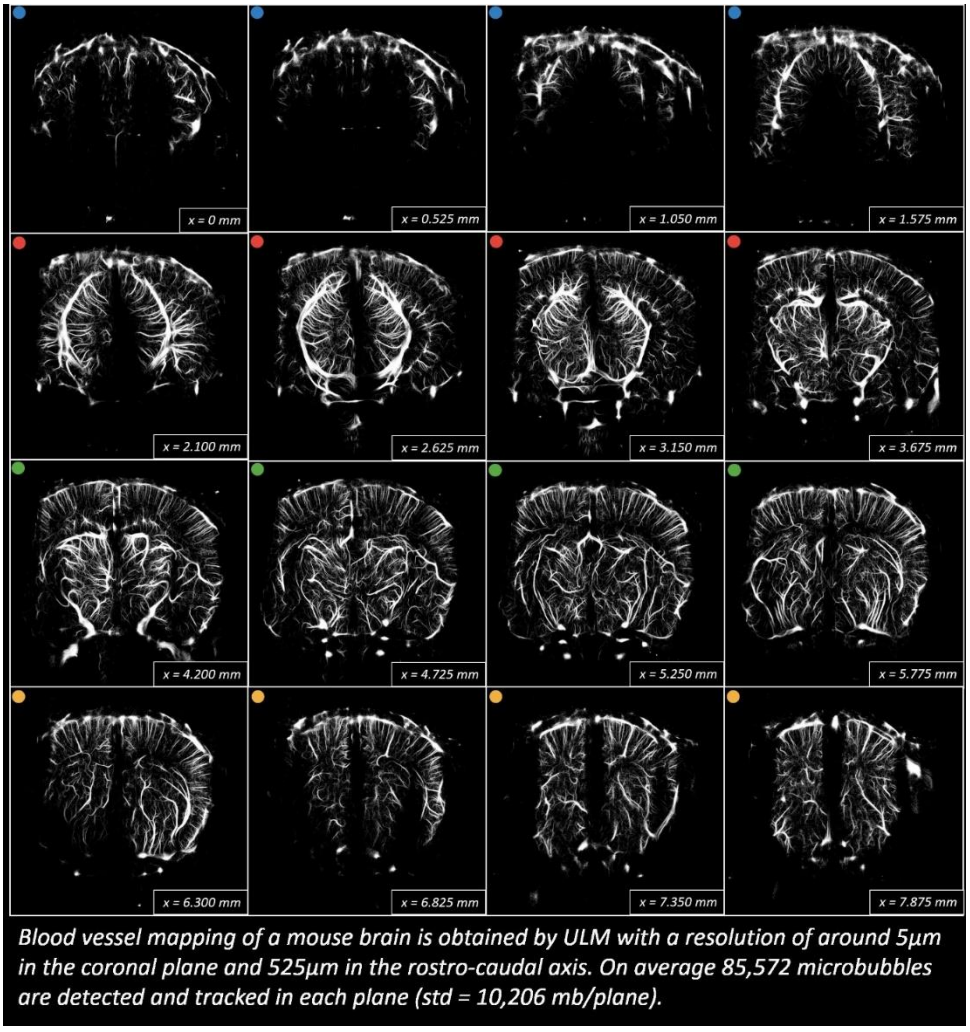
Program #/Poster #: 747.20

Topic: I.04. Physiological Methods

Title: Non-invasive transcranial whole brain angiography and hemodynamics quantification at the microscopic scale in rodents

Authors: *M. VERT[1,2], M. NOUHOUM[2], A. BERTOLO[1,2], T. DEFFIEUX[1], B. OSMANSKI[2], M. TANTER[1];
[1]Inst. Physics for Med. Paris, Inserm U1273, ESPCI Paris, CNRS UMR 8631, PSL Res. Univ., Paris, France; [2]Iconeus, Paris, France

Abstract: In the last decade, Ultrafast ultrasound imaging at thousands of frames per second combined with the intravenous injection of 1-3 µm gas microbubbles led to the concept of Ultrasound Localization Microscopy (ULM). This new modality breaks the fundamental trade-off between spatial resolution and penetration depth of Ultrasound imaging and enables the deep and non-invasive mapping of cerebral vasculature at the microscopic scale both in preclinical[1] and clinical[2] configurations. Additionally, ULM provides quantitative information about hemodynamics (local microbubble speed in the 1-30 mm/s range and microbubble flow). It exhibits several distinct compartments of the vascular tree (arterioles, first and second order branching capillaries, venules) and can be spatially linked to the functional and anatomic information through a process of registration to an atlas.
For now, ULM has mainly been restricted to single-plane imaging. For 3D imaging, matrix probes still lack sensitivity and impose a great electronic complexity. Here, we introduce a multilinear stacked probe combining four high sensitivity linear ultrasound probes (4x64 elements, 15MHz) - which high sensitivity is ensured thanks to geometrical lenses - to image the whole brain at once. Our protocol is implemented on the Iconeus One ultrasound scanner (256 channels) and consists in translating the probe to four positions to obtain sixteen super-resolution planes in 15 minutes. We achieve a whole-brain quantification of the mouse vascular properties and characterize the spatial heterogeneities of the hemodynamic response under the influence of a vasodilator drug (isoflurane) in different brain regions.
Whole-brain transcranial angiography at microscopic scale based on ULM imaging gives new insights on the spatial heterogeneities of the vascular system and its associated hemodynamics. [1] Errico C. et al, *Nature*, 2015, [2] Demene C. et al, *Nature Biomedical Engineering*, 2019



Blood vessel mapping of a mouse brain is obtained by ULM with a resolution of around 5µm in the coronal plane and 525µm in the rostro-caudal axis. On average 85,572 microbubbles are detected and tracked in each plane (std = 10,206 mb/plane).

Disclosures: **M. Vert:** A. Employment/Salary (full or part-time):; Iconeus. **M. Nouhoum:** A. Employment/Salary (full or part-time):; Iconeus. **A. Bertolo:** A. Employment/Salary (full or part-time):; Iconeus. **T. Deffieux:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus. **B. Osmanski:** A. Employment/Salary (full or part-time):; Iconeus. **M. Tanter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.21

Topic: I.04. Physiological Methods

Support: AG073040

Title: Continuous Transepithelial-endothelial measurements to track blood-brain-barrier integrity in a multi-organs recirculation system for Alzheimer's drug testing

Authors: *J. COLLINS[1], H. C. WONG[2], **A. J. COLLINS**[3], G. KATARA[2], C. J. COLLINS[3], J. A. J. JOSE[3], K. V. JOHNSTON[2], J. KOHANA[2], S. L. LIM[3], M. KITAZAWA[3], T. TEAFATILLER[3], V. SUBRAMANIAN[3], M. SUN[1];
[1]Biopico Systems Inc, Irvine, CA; [2]Biopico Systems, Irvine, CA; [3]Univ. of California Irvine, Irvine, CA

Abstract: A gravity-driven multiorgan system with media recirculating across liver-kidney-gut organs and multicellular brain organ was developed. A drug absorbed by the gut, metabolized in the liver and reabsorbed in the kidney is examined for BBB permeability and brain toxicity. These two recirculations are separated by a blood-brain-barrier (BBB) formed by endothelial cells, pericytes and astrocytes. In this research, we have developed a continuous recording system to monitor the Transepithelial-endothelial resistance (TEER) data across the BBB and imaged GFP labeled human microvascular endothelial cells during unidirectional flow. The plate was scaled for multiorgans and optimized according to surface-to-volume and non-linear metabolic rates. On either side of the BBB, brain organ and multiple organs connecting blood are accommodated in the 6-units multi-organ plate. In Fig. 1. OrganRX multi-organ recirculation system was coupled with continuous TEER measurements. An App was developed for showing TEER raw values acquired by Bluetooth signals from multi-organ 6 units plate. This is the first report of multi-organ recirculation system with continuous TEER measurement in a multi-well format. BBB is created with brain microvascular GFP-labeled endothelial cells using 2.5mg/ml Collagen I gel and will include pericytes and astrocytes. In Fig. 2 Immunohistochemistry data for low shear rate (0.2 dynes/cm2) and high shear rate (2.5 dynes/cm2) on the organ plate seeded with 25k and 40k endothelial cells is shown to verify stress genes expressed due to flow in the system. Multi-organ capability of the organ system is demonstrated with coupled multi-organs (liver, gut and kidney). The drug introduced in the organ plate is mixed across the organs within 1 hr. Toxicity studies in the flow system are compared to 12-well plate. The multi-organ platform is validated for drugs using CYP1A2 measurements. The results show dynamic culture in the organ plate with shear flow improves the enzymatic activities, proliferation and gene expression of the multi-organ culture system.

Fig. 1. OrganRX multi-organ recirculation system coupled with continuous TEER measurements (left). App showing TEER raw values acquired by Bluetooth signals from multi-organ 6 units plate.

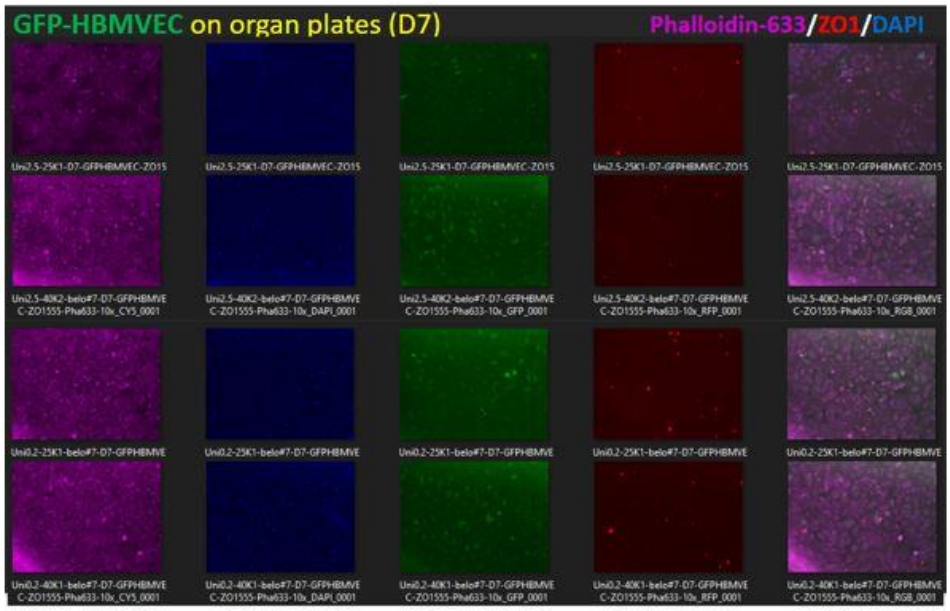


Fig. 2. Immunohistochemistry data from gravity-driven low shear rate (0.2 dynes/cm2) and high shear rate (2.5dynes/cm2) on 25k cells seeded in an organ plate.

Disclosures: **J. Collins:** A. Employment/Salary (full or part-time):; Biopico Systems Inc. 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. **H.C. Wong:** A. Employment/Salary (full or part-time):; Biopico Systems Inc. **A.J. Collins:** A. Employment/Salary (full or part-time):; Biopico Systems Inc. **G. Katara:** A. Employment/Salary (full or part-time):; Biopico Systems Inc. **C.J. Collins:** A. Employment/Salary (full or part-time):; Biopico Systems Inc. **J.A.J. Jose:** A. Employment/Salary (full or part-time):; Biopico Systems Inc. **K.V. Johnston:** A. Employment/Salary (full or part-time):; Biopico Systems Inc. **J. Kohana:** A. Employment/Salary (full or part-time):; Biopico Systems Inc. **S.L. Lim:** None. **M. Kitazawa:**

None. **T. Teafatiller:** None. **V. Subramanian:** None. **M. Sun:** A. Employment/Salary (full or part-time):; Biopico Systems Inc.

Poster

747. Methods for Studying Brain Structure and Function

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 747.22

Topic: H.08. Learning and Memory

Support: NIH Grant 1RF1NS113283

Title: Flexible blue μLED optoelectrodes for reduced stimulation artifact: design consideration

Authors: *E. KO, M.-L. HSIEH, J. R. LOPEZ RUIZ, E. YOON;
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Abstract: The introduction of optogenetics paved a new direction of studying complex neuronal structures through optical perturbation - excitation or inhibition - of a small or large group of cells of interest. Among the various types of light delivery methods, the micro-light-emitting-diode (μLED) integrated Michigan type probe (Wu et al., Neuron 2015; Kim et al., Nature Comm 2020; Vöröslakos et al., Adv Sciences 2022) demonstrated the reliable functionality of the device inside hippocampus of a mouse brain. Analyzing the recorded signals inside such a sea of cells requires the data to be less noisy, and one of the most disturbances comes from stimulation artifact, when it comes to the optogenetic probe, which should be suppressed. The initial version of Michigan optoelectrode was built on a rigid silicon substrate, in a 5 mm-long shank, electrically connected and controlled through metal bonding to the connector integrated on a printed circuit board (PCB). Stimulation artifacts originate from electromagnetic interference and photovoltaic effect and can be significantly reduced from a heavily doped silicon substrate and the metal shield between LEDs and recording sites. In this work, we report a flexible, polymer-based optoelectrode for longer and reliable chronic electrophysiology in the deep-brain of a mouse. The probe shank is 10 mm long, which is connected with an extra cable to the headstage PCB for the ease of surgery. The backend of the probe was connected to an interposer (6 mm x 6 mm, 200 μm thick silicon substrate), which was assembled to the headstage PCB through a flexible cable (20 mm in length). 1x phosphate-buffered saline (PBS) solution was used for in-vitro characterization of the stimulation-induced artifact of the fabricated flexible optoelectrode. Intan RHD2000 recording system was used for acquiring artifact data while driving the LEDs through OSC1Lite (12-channel current source driving module, https://github.com/YoonGroupUmich/osc1lite). The nondegenerate silicon-based interposer was used with a shield added to the probe site, both bottom and top, showed the artifact was suppressed < 200 μV peak-to-peak (wide band, non-high pass filtered). This is x30 reduced level of artifact amplitude. This poster will present the parametric design consideration for artifact reduction and their effects in multi-component flexible blue-LED optoelectrodes.

Disclosures: **E. Ko:** None. **M. Hsieh:** None. **J.R. Lopez Ruiz:** None. **E. Yoon:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.01

Topic: I.06. Computation, Modeling, and Simulation

Title: An artificial neural network trained on next-frame prediction of natural videos learns to disentangle abstract concepts from the spatio-temporal input pixel space

Authors: *Z. YE, R. WESSEL;
Dept. Physics, Washington Univ. in St. Louis, Saint Louis, MO

Abstract: To generalize and function in the real world, the brain must learn to extract latent variables beyond merely identifying statistical relations within the training dataset. However, it is unclear how the brain represents the often-entangled latent variables. To address this problem, we employed an artificial deep neural network ("PredNet") as a model of the brain and indicated a representation strategy that could computationally disentangle the latent variables. PredNet is an artificial deep neural network trained to predict future video frames, which had been shown to exhibit many biological plausible phenomena. We exposed the network to two types of moving stimuli commonly used in vision research: white bars moving at different speeds on a black background, and whole-field drifting gratings of different speeds. Unit population activity in each layer (or pixels' values when considering the input stimuli) was analyzed geometrically using the principal component analysis. We found the speed manifold (a trajectory with a fixed time but different speeds) overlapped with the temporal manifold (fixed speed by different time points) in the pixel space. In contrast, these two information manifolds split into different directions in the deeper layers of the network. Intuitively, splitting the information manifolds allows extracting the speed information out of an unknown network state by projecting it onto the speed manifold. On the other hand, extracting the speed information out of a single video frame is impossible due to the mixture of the temporal component in the pixel space. Together, these findings indicate that, after training with naturalistic videos, the network learned to disentangle latent variables (e.g. time and motion) by splitting their information manifolds. The evidence for disentanglement of latent variables in the model network motivates future searches for such disentanglement of latent variables in brains.

Disclosures: **Z. Ye:** None. **R. Wessel:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.02

Topic: I.06. Computation, Modeling, and Simulation

Support: National Institute of Mental Health of the National Institutes of Health; Award Number R01MH123687

Title: A recurrent reinforcement learning model solves a reversal-learning task with uncued switches using division of labor

Authors: X. LEI[1], T. WOMELSDORF[2], *P. H. TIESINGA[3];
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Abstract: A hallmark of executive control is the ability to flexibly acquire and adapt to changing task rules without explicit cues in a volatile environment. The exact neural substrate underlying the recognition of a rapid switch of reward contingencies remains unknown. The task rules could be encoded either by recurrent activity or/and plastic synaptic weights in the frontal network. Here we investigated the activity-based hypothesis by constructing a deep learning model (DLM) composed of Long-Short Term Memory (LSTM) units that was trained using reinforcement learning algorithms to execute a feature-based (FB) reversal learning task. Agents have to pick from among multiple presented objects the one that contains the current rewarding feature, which is switched to a new feature at a random trial within a block. The model was trained to perform the task for both deterministic and probabilistic rewards with convergence speed correlating with task difficulty level. After training, it settled down in a set of weights that support adapting to new rules, yielding learning performance trajectories similar to those observed in animal experiments. We fitted the agent's behavior by a FB Rescorla-Wagner model. The fit-parameter learning rate was lower in more difficult environments with probabilistic rewards or with a higher number of features.

By conducting dimension reduction analysis, we demonstrated distributed population encoding of task-relevant variables and a division of labor between cell states and hidden states of the LSTM units, within which the target and the object representation emerged, respectively. The trained network can generalize to novel objects, i.e. combinations of features not presented during training, which suggests a FB instead of object-based (OBLS) learning strategy. We further examined the network capacity and found that the number of neurons required for reaching criterion performance grows linearly with features rather than exponentially as expected for OBLS.

We analyzed the learning dynamics within one episode by calculating the neural activity difference vectors of two consecutive trials. We succesfully trained a classifier to classify four types of difference vectors, defined by the presence or absence of reward of two consecutive trials. This supports the hypothesis that the reward prediction errors act as a driving factor for learning the new rule.

Our study shows that DLMs can model flexible behavior in constantly changing environments and predicts how FB learning emerges in activity-based models, which can be validated in empirical data.

Disclosures: **X. Lei:** None. **T. Womelsdorf:** A. Employment/Salary (full or part-time):; Vanderbilt University. **P.H. Tiesinga:** A. Employment/Salary (full or part-time):; Radboud University.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.03

Topic: I.06. Computation, Modeling, and Simulation

Title: The allen cell and structure segmenter: an open source toolkit and napari plugin for segmenting 3D intracellular structures in microscopy images

Authors: *G. DUNSTER, K. R. CORDES METZLER, A. TEAM, S. M. RAFELSKI; Allen Inst. for Cell Sci., Seattle, WA

Abstract: The Allen Institute for Cell Science uses high-replicate live cell imaging to understand the principles by which cells reorganize in health and disease. We aim to predict cell behavior by building a state space of structural signatures in human induced pluripotent stem cells (hiPSCs) to differentiated cell types, while building open-source image analysis tools and reproducible datasets. We generated a dynamic imaging pipeline using endogenous fluorescently-tagged hiPSC lines. Each line expresses a monoallelic EGFP-tagged protein that represents a major cellular structure or organelle, including neuron-relevant structures such as the nuclear envelope (Lamin B1), mitochondria (Tom20), endoplasmic reticulum (Sec61 beta), cell membrane (CAAX), actin filaments (Beta-actin), microtubules (alpha-tubulin), and more. Thousands of high-resolution 3D images are acquired for each structure and used to develop quantitative image-based assays and computational models. However, accessible cell and structure segmentation tools remains a challenge in the field, limiting the extraction of meaningful information from imaging data. We developed the Allen Cell and Structure Segmenter, a Python-based open-source toolkit and Napari plugin for 3D segmentation of intracellular structures. This toolkit combines classic and iterative deep learning workflows to streamline the identification of successful 3D segmentation algorithms for a wide range of intracellular structures. Two of these workflows applied on different types of neurons achieved accurate 3D segmentation of the dendrites and axonal terminals. To make this tool broadly applicable across diverse cell types and structures, we 1) formulated a classic image segmentation workflow based on a minimal number of selectable algorithms and tunable parameters, 2) successfully applied this workflow to over 30 intracellular structures; whereby the workflows can be selected via a lookup table, 3) developed this workflow and lookup table into a user-friendly plugin for the open source image viewer Napari, and 4) implemented an iterative deep learning workflow using the results of these classic segmentation algorithms with minor manual inspection to generate a ground truth for training deep learning models. This open-source segmentation toolkit facilitates quantitative single-cell cell biology in cell types from pluripotent stem cells to neurons, leveraging state-of-the-art algorithms in computer vision for specific image segmentation needs and challenges. The

Allen Cell and Structure Segmenter is available free to the public on our website www.allencell.org/segmenter.html

Disclosures: G. Dunster: None. **K.R. Cordes Metzler:** None. **A. Team:** None. **S.M. Rafelski:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.04

Topic: I.06. Computation, Modeling, and Simulation

Title: Using a machine vision approach for automated pain measurements at millisecond timescales in rats

Authors: *M. JIWANJI[1], C. C. DRESSLER[1], W. FOSTER[2], B. DUNHAM[1], I. ABDUS-SABOOR[2], N. T. FRIED[3], M. E. WIMMER[1];
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Abstract: Chronic pain, one of the most common reasons adults seek medical attention, has been linked to limitations in mobility, opioid dependence, and a lower quality of life. One of the hurdles to improving available treatments for chronic pain is the difficulty to accurately measure pain, especially in rodents. The most commonly used assessment method in preclinical models is scoring the paw withdrawal reflex to a natural stimulus, with binary responsiveness used as an endpoint for inferring pain states. This is a widely accepted measure of pain that has led to important discoveries in the past. However, one limitation of this method is that it lacks resolution. This can now be overcome thanks to advancements in videography and automated tracking. We recently established a novel pain scale that combined paw kinematics and face grimaces into a single pain score using principle component analyses. This method consistently distinguished painful stimuli from those in the touch domain, and could help us improve the validity of pain therapeutics and the rate at which basic science findings can be translated to the clinic. However, this approach is time consuming, and still has subjectivity because humans have to score by hand. Here, we automated part of the analytical and scoring procedure using high-speed videography, as well as automated paw tracking powered by machine and deep learning approaches. A software known as sLEAP (Social LEAP Estimates Animal Poses), which was recently developed by Periera and colleagues, is a machine learning system for multi-animal pose tracking. It utilizes both top-down and bottom-up approaches and animal identity tracking via kinetic or image models. It includes an input-output layer that allows for data input in raw video or variety format, as well as annotation import from other pose-tracking software and standardized formats. Data can be labeled dynamically once imported using a versatile graphical user interface, which can then export images and annotations to facilitate remote training and data sharing. We previously used sLEAP with high speed videography in mice at baseline states

and here we apply sLEAP in a different experimental context in rats. By using this automated method, we intend to improve the consistency of the pain scoring even more by pinpointing the paw with high spatiotemporal resolution. To validate this pain scoring method, we compared our previous manual scores to this new automated scoring pipeline. In conclusion, this algorithmic pain quantification method may improve validity in collecting rigorous behavioral data and is compatible with other neural circuit dissection methods for analyzing rat pain states.

Disclosures: **M. Jiwanji:** None. **C.C. Dressler:** None. **W. Foster:** None. **B. Dunham:** None. **I. Abdus-Saboor:** None. **N.T. Fried:** None. **M.E. Wimmer:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.05

Topic: I.06. Computation, Modeling, and Simulation

Support: KAKENHI no. 19H04994
KAKENHI no. 18H05213

Title: Simplicial recurrent networks for memory and language processing

Authors: *T. BURNS, T. FUKAI;
OIST Grad. University, Neural Coding and Brain Computing Unit, OIST, Japan, Onna-son, Japan

Abstract: Hopfield networks are artificial neural networks which store memory patterns on the states of their neurons by choosing recurrent connection weights and update rules such that the energy landscape of the network forms attractors around the memories. How many stable, sufficiently-attracting memory patterns can we store in such a network using N neurons? The answer depends on the choice of weights and update rule. Inspired by setwise functional connectivity and connection weight modulations in biology, we extend Hopfield networks by adding setwise connections and embedding these connections in a simplicial complex. Simplicial complexes are higher dimensional analogues of graphs which naturally capture hierarchies of pairwise and setwise relationships. We show that our simplicial Hopfield networks increase memory storage capacity. Surprisingly, even when connections are limited to a small random subset of equivalent size to an all-pairwise network, our networks still outperform their pairwise counterparts. We also test analogous modern continuous Hopfield networks, offering a potentially promising avenue for improving transformer models used in machine learning for language processing.

Disclosures: **T. Burns:** None. **T. Fukai:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.06

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH R00MH116100

Title: Reinforcement learning reveals the contribution of distinct cell types and layers to predictive routing

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Abstract: Predictive coding is a major function of the cortex. Deficits in predictive coding may underlie mental disorders like depression and schizophrenia. Previous studies have shown that when stimuli are predictable they evoke larger alpha (8-14Hz) or beta (15-30Hz) power in PFC which feeds back to V4 via cortical deep cortical layers. Unpredictable stimuli were associated with increases in gamma-band (40-90Hz) strength in V4 which fed forward to the cortical hierarchy via superficial layers. The network specific mechanisms underlying these observed physiological changes remain unknown. Here, we assume that prediction tasks can be learned by trial-and-error and by updating synaptic weights on each trial to optimize an internal model. We therefore used Reinforcement Learning (RL) together with biophysically-detailed spiking neural networks (SNNs) to investigate the contribution of distinct cell types and network architectures to learning a predictive coding task. Here, we introduce DynaLearn, a flexible RL framework for SNNs that enables in silico investigations of this kind. This novel framework is built on top of the DynaSim toolbox, which enables learning to operate on dynamic models like neural networks with arbitrary cell types and network structure. It allows responses and error signals to be computed from any hypothesized response-encoding activity or metrics relatable to experimentally observed dynamics.
We demonstrate its application using thresholded firing rates of modeled response units and simultaneous neocortical beta-gamma rhythms at the network level which recapitulate published LFP findings in a predictive coding task. We repeated the training procedure for simulated knockout experiments eliminating one or more cell types from the network to investigate cell type specific contributions to learning to predict. The procedure highlights the role of distinct interneuron types (eg, SOM vs. PV) and layers. This work shows the power of DynaLearn for elucidating the biological mechanisms that account for brain dynamics observed while learning a predictive coding task. The model also realizes the specific laminar/dynamic circuitry proposed to implement predictive coding via predictive routing.

Disclosures: **H. Nejat:** A. Employment/Salary (full or part-time):; Vanderbilt University. **J. Sherfey:** A. Employment/Salary (full or part-time):; Javelin Biotech. **A. Bastos:** A. Employment/Salary (full or part-time):; Vanderbilt University. C. Other Research Support

(receipt of drugs, supplies, equipment or other in-kind support); NIH R00MH116100. Other; BastosLab.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.07

Topic: I.06. Computation, Modeling, and Simulation

Support: 2019976

Title: Modeling multi-region cortical interactions using task-specific data-constrained recurrent neural networks

Authors: *P. GUPTA[1], T. MURPHY[1], A. L. FAIRHALL[2];
[1]Univ. of British Columbia Grad. Program In Neurosci., Vancouver, BC, Canada; [2]Dept Physiol & Biophys, Univ. Washington, Seattle, WA

Abstract: During behavioral tasks, recent findings (e.g. Pinto et al., 2019) demonstrate the recruitment of widespread cortical areas. For any neuron within the network, its evolving activity can be mediated by a combination of unidirectional, bidirectional, or self-driven inputs from anatomically local neural populations as well as from distributed brain regions. In order to develop theories of neural processing, it is necessary to relate neural dynamics to the brain structure, but it is very challenging to infer connectivity from in vivo neural recordings.Recent pioneering work (Perich et al., 2021; Rajan, Harvey and Tank, 2016; Pinto et al., 2019) addresses this issue by modeling biological neural data using artificial, multi-region “network of networks” (Perich and Rajan, 2020) Recurrent-Neural-Network (RNN) models aim to dissociate inputs from self v/s other brain regions in a task-specific manner (Perich et al., 2021). We adapted this approach to model the large-scale Visual Behavior Brain-Observatory GCaMP6f functional imaging datasets from the Allen Institute (Hu et al., 2021; Orlova et al., 2020; de Vries et al., 2020; Garrett et al., 2020; Groblewski et al., 2020) which contains curated 2-photon recordings from multiple visual areas (Primary Visual Area ie. VISp, Anterolateral visual area ie. VISal, Anteromedial visual area ie. VISam, and Lateral visual area ie. VISl), from multiple cortical layers, different cell types (Pyramidal ie. PC, Somatostatin ie. SST, vasoactive intestinal polypeptide ie. VIP), over six days post-training, in a total of 19 mice performing a visual image change detection task. A multi-region RNN was iteratively trained and constrained to fit the biological neural data at each step, mimicking the activity of in vivo neurons. After the RNN is trained, we read out the connectivity weights between artificial neurons and between regions to infer driving inputs to a region from all other recorded regions during different task conditions. Our preliminary results from two mice (six sessions each) suggest distinct bottom-up inputs for familiar images and top-down inputs for novel images in excitatory cell populations, on different days during a successful trial. Our modeling also suggests a distinct role of inhibition by VIP neurons during task performance.

Disclosures: **P. Gupta:** None. **T. Murphy:** None. **A.L. Fairhall:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.08

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 1R01EB028154-01

Title: Remapping of task-relevant attractor dynamics in lesioned neural network models via low-dimensional feedback

Authors: *A. SCHWAMB, S. CHING;
Washington Univ. in St. Louis, St. Louis, MO

Abstract: Use of exogenous inputs to alter brain networks is a hallmark of systems neuroscience paradigms, and a long-held goal for clinical applications. Choosing these inputs generally relies on a dose-response framework in which graded amounts of stimulation are applied and behavioral correlates are measured, without overtly using information about ongoing network activity. We ask whether it is instead possible to create subject-specific external inputs that interact with brain networks in a manner that is synergistic with task-relevant neural dynamics. We begin with a model of working memory based on [1], wherein short-term representations of afferent stimuli are encoded within the fixed point attractors of the recurrent network dynamics. Then, using a model-free optimization strategy, we construct "synergistic networks," that interact with the memory network via low-dimensional input and feedback. We ask two questions: (i) Can the synergistic network learn to impart "individualized" inputs that enhance task performance, especially in contexts where the original network is lesioned, and (ii) how does the synergistic network alter the prior attractor landscape of the original memory networks. We show that synergistic networks can reliably improve memory function through low-dimensional feedback interaction. Rather than restoring the original dynamics, however, the combined network structure typically uses a different dynamic architecture, in which a new set of attractors are formed to encode memory representations. Analyzing the lesioned network sheds some light on why this occurs. In order to restore functionality, one of two scenarios must occur: (i) the original dynamics are undamaged and the synergistic network performs only trivial interaction, or (ii) the original dynamics are functionally destroyed and the synergistic network must modify the remaining vector field to remap the relevant memory representations. In fact, after remapping, the composite fixed point-limit cycle vector field identified in [1] is the most common. Since such dynamics rarely occur in "normal" memory networks, their prevalence here indicates a qualitative difference between the network architectures that arise from learning *tabula rasa*, versus those that can be built onto the fragments of a lesioned network. Moreover, this confirms that synergistic networks are learning to work *with* the residual dynamics, rather than simply "overwriting" them. In summary, our computational modeling study provides a

potential design framework for constructing individualized neural control strategies that remap network dynamics and restore or enhance function.

Disclosures: **A. Schwamb:** None. **S. Ching:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.09

Topic: I.06. Computation, Modeling, and Simulation

Support: NSERC Discovery Grant

Title: Comparison of deep learning architectures for subject-specific structural to functional brain connectome mapping

Authors: *M. FARHAN[1], A. B. ASHRAF[2], C. R. FIGLEY[3];
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Abstract: Earlier studies have reported a strong relationship between resting-state functional connectivity (FC) and structural connectivity through computational modeling, and more recently artificial intelligence (AI) based methods as well. However, very little optimization and no direct comparisons between different AI-based methods have been reported for this purpose. The purpose of the current study was therefore to systematically compare the performance of two different deep learning (DL) methods - i.e., U-Net and graph convolutional networks (GCNs) - with different sets of parameters to establish a more optimized DL-based approach for predicting brain FC from SC. To achieve this, we used subject-specific structural (diffusion MRI) and functional (resting-state fMRI) connectomes from 762 participants in the Human Connectome Project (HCP, S900 release) - each segmented into 360 bilateral regions of interest using the Glasser atlas - and used those to train two different neural networks by minimizing the mean squared error of the predicted vs. measured FC. Subjects were randomly subdivided into groups to perform a 5-fold cross-validation. In total, six GCN-based networks (with slightly different architectures and/or parameters) and two U-Net-based networks (with different parameters) were tested. These eight configurations were evaluated using both conventional performance metrics (mean squared error and correlation coefficient), as well as the recently proposed pairwise functional connectome fingerprinting approach (PFCF) to determine how closely matched each subject's predicted and measured FCs are, relative to inter-subject differences in measured FCs. These results show that for SC-FC prediction, all of the GCN architectures worked better than the U-Nets, achieving lower mean squared error values and higher correlation coefficients, as well as PFCF accuracies of almost 70% across all participants. Although other traditional performance metrics have indicated differences in performance for each structural variation, PFCF is quantitatively more rigorous. Therefore, we conclude that the current analysis based on

a comprehensive set of metrics will provide a new benchmark for future AI-based connectivity prediction.

Disclosures: **M. Farhan:** None. **A.B. Ashraf:** None. **C.R. Figley:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.10

Topic: I.06. Computation, Modeling, and Simulation

Title: Brain-inspired neuronal silencing mechanism to enable high-precision sequence identification

Authors: *Y. TZACH[1], S. HODASSMAN[1], Y. MEIR[1], I. BEN-NOAM[1], Y. TUGENDHAFT[1], A. GOLDENTAL[1], R. VARDI[1], I. KANTER[2];
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Abstract: Real-time sequence identification is a core use-case of artificial neural networks (ANNs), ranging from recognizing temporal events to identifying verification codes. Existing methods apply recurrent neural networks, which suffer from training difficulties; however, performing this function without feedback loops remains a challenge. Here, we present an experimental neuronal long-term plasticity mechanism for high-precision feedforward sequence identification networks (ID-nets) without feedback loops, wherein input objects have a given order and timing. This mechanism temporarily silences neurons following their recent spiking activity. Therefore, transitory objects act on different dynamically created feedforward sub-networks. ID-nets are demonstrated to reliably identify 10 handwritten digit sequences, and are generalized to deep convolutional ANNs with continuous activation nodes trained on image sequences. Counterintuitively, their classification performance with limited training datasets is high for sequences, but low for individual objects. ID-nets are also implemented for writer-dependent recognition, and suggested as a cryptographic tool for encrypted authentication. The presented mechanism opens new horizons for advanced ANN algorithms.

Disclosures: **Y. Tzach:** None. **S. Hodassman:** None. **Y. Meir:** None. **I. Ben-Noam:** None. **Y. Tugendhaft:** None. **A. Goldental:** None. **R. Vardi:** None. **I. Kanter:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.11

Topic: I.06. Computation, Modeling, and Simulation

Support: National Institute of Health U-19 program grant no. 5U19NS107609-03

Title: A modular recurrent neural network trained to perform un-cued task switching

Authors: *Y. LIU, X.-J. WANG;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Animals can switch rapidly between multiple well-learned tasks based solely on the outcome of their recent actions, without being explicitly instructed on which task to perform. The neural circuit mechanism underlying this un-cued task switching is not well known. Towards this end, we trained a two-module recurrent neural network on an un-cued task switching paradigm adapted from the context-dependent random dot motion task (Mante et al., Nature 2013). During this task, the network should make a response according to the color or motion coherence of a random dot pattern, depending on whether the current trial is under the color rule or the motion rule. Importantly, the correct rule is not explicitly cued, and switches with a small probability across trials.
The network model consists of a “prefrontal cortex (PFC)“ module that interacts with a "sensorimotor" module. Inspired by an influential theory of the PFC (Miller and Cohen, Ann. Rev. Neurosci. 2001), the PFC module receives an input about the trial outcome, and is trained to maintain the rule representation during correct trials and switch the rule representation after error trials, whereas the sensorimotor module receives the external sensory input and the top-down rule input from the PFC module, and is trained to generate the correct motor output. Each module consists of excitatory neurons and three genetically-defined types of inhibitory neurons (PV, SST and VIP). The connectivity between neuron types is constrained by the experimental data, while the connection strength between pairs of neurons is trained via gradient descent.
After training, we found two distinct subpopulations of excitatory neurons emerge from the PFC module. The neurons in one subpopulation are selective for the current task rule (rule neurons) and the ones in the other subpopulation show non-linear mixed selectivity for the outcome and the rule (error x rule and correct x rule neurons). We uncovered the connectivity pattern between different subpopulations of neurons that supports un-cued task switching. In particular, the connectivity from and to the error x rule neurons is critical for the error-induced transition between rule attractors. Interestingly, this circuit structure is reminiscent of the one that underlies the updating of the head-direction representation in the Drosophila's central complex (Turner-Evans et al. eLife 2017). We further found that this connectivity pattern is preserved across dozens of trained networks with different hyperparameters. Finally, we discovered specific top-down connectivity patterns from the PFC module to the sensorimotor module that gates the sensorimotor mapping based on the rule signal.

Disclosures: **Y. Liu:** None. **X. Wang:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.12

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R01MH062349

Title: Toward a neural mechanistic understanding of economic decisions

Authors: *A. BATTISTA, X.-J. WANG;
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Abstract: Economic choice is the behavior observed when individuals decide on one good over others based on subjective preference. One prominent theory assumes that individuals assign each available item a value during choice, and a decision is made by comparing them. One prediction of this theory is that economic decisions are made in the space of goods rather than actions. A key finding in neuroeconomics was the discovery of single neurons in primates' orbitofrontal cortex (OFC) that explicitly encode values. Specifically, studies found neurons encoding the value of individual goods, the value of the chosen good, and the outcome of the choice. This finding suggests that a neural circuit within OFC is sufficient to implement economic decisions because these neurons encode the input and output of the decision process. So far, little is known about the putative decision circuitry. It is unknown whether these different neuron types have a specific anatomical identity and how they are connected. Furthermore, these results focus on individual neurons and lack a neural population analysis. To answer these questions, we trained excitatory-inhibitory recurrent neural networks using state-of-the-art reinforcement learning algorithms, which are well suited to study problems where optimal behavior depends on subjective preferences. Networks have been trained to choose between two goods that vary on two dimensions: type of good and quantity. The analysis of the networks after training revealed that there are three types of neurons, as observed in OFC, with temporal dynamics reflecting the decision process. Previous theoretical models force the three types of neurons to have positive value encoding and predict the chosen value neurons to be inhibitory. In contrast, our model shows more heterogeneous activity, admitting both excitatory and inhibitory chosen value neurons, and without constraining the sign of the encoding value. In addition, population analysis shows that the dynamics of the networks is low-dimensional, with the relevant dimensions (which explain most of the variance) associated with decision quantities. Lastly, with our approach, we can inspect the connectivity between the different types of neurons and propose new hypotheses on the neural mechanisms of economic decisions. These predictions can be tested in the future by experiments in mice, in which the necessary technologies for recording and perturbing neural activity are available.

Disclosures: A. Battista: None. **X. Wang:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.13

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF BCS-1749430
NIH NIBIB R01EB018297

Title: Spatially heterogeneous cholinergic release facilitates preferential learning of external stimuli

Authors: Y. YANG[1], *V. BOOTH[2], M. R. ZOCHOWSKI[3];
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Abstract: Forebrain acetylcholine (ACh) signaling has been shown to drive theta and gamma rhythms and their cross-frequency coupling, which has been linked to attention and learning. Recent experimental evidence of spatially and temporally constrained cholinergic signaling has sparked interest to investigate how it facilitates stimulus-induced learning. We use biophysical excitatory-inhibitory (E-I) multi-module neural network models to show that external stimuli and ACh signaling can mediate spatially constrained learning patterns. The effects of ACh on neural excitability are simulated by varying the conductance of a muscarinic receptor-regulated K^+ current (m-current). Each network module consists of an E-I network with local excitatory connectivity and global inhibitory connectivity. The modules are interconnected with plastic excitatory synaptic connections, that change via a spike-timing-dependent plasticity (STDP) rule. Our results indicate that spatially constrained ACh release influences the information flow represented by network dynamics resulting in selective learning among the plastic synapses. Activity in high ACh regions induced firing bursts in other modules and thus strengthened the outgoing synapses while at the same time weakening the incoming ones. Besides unidirectional strengthening, similar ACh release patterns between the modules led to synchronized network bursts across different modules and thus reciprocal strengthening of connections. The multi-module E-I network also demonstrated flexibility in storing representations, driven by changing directions of information flow between the modules. These mechanisms allowed for storage of temporal activation interdependencies between the modules (i.e. relative activation delays). Overall the modeling results provide insights into the mechanisms for spatial and temporal information storage mediated by temporally and spatially constrained ACh release.

Disclosures: Y. Yang: None. **V. Booth:** None. **M.R. Zochowski:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.14

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R01NS110079

Title: Analysis of Parvalbumin and Somatostatin Interneurons Patchseq data reveals that Spike-frequency Adaptation is a Subtype Identifier and Its Relationship with Fast-spiking Feature

Authors: Y. KANG[1], ***J. H. MENG**[2], B. RUDY[3], X.-J. WANG[2];
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Abstract: Parvalbumin-expressing (PV) and somatostatin-expressing (SST) interneurons (IN) account for about 70% of the GABAergic interneurons in the neocortex. These two subtypes have a distinct molecular profile, morphology, electrophysiology, and connectivity. However, because of the heterogeneity and variability of PV and SST INs, it is not trivial to distinguish individual INs of these two subtypes from electrophysiological parameters without applying a genomic tagging methodology directly. Here, we systematically studied how to best distinguish PV cells and SST cells from electrophysiological features by analyzing the Patch-seq data from the Allen Institute. To minimize the heterogeneity within each subtype, we first analyze only the data from Layer 2/3 of the visual cortex. Although many of the parameters are significantly different between PV and SST IN populations, it is difficult to infer which subtype an individual cell belongs to based on electrophysiological features. We demonstrated that the first four features that can distinguish PV and SST INs, ranked by the accuracy of a single-parameter classification, were the membrane time constant (tau), the adaptation index (AI), the slope of the firing rate, and spike half-width (HW). Combining tau and AI, a trained linear decoder was able to distinguish the PV and SST INs with 100% accuracy. The method was also tested in a dataset from Layer 2/3 of the somatosensory cortex with similar results. An analysis of the data from all the layers in V1 showed a qualitatively consistent conclusion but with reduced classification accuracy. We next asked whether the RNA expression can explain the significant adaptation difference between the PV and SST INs. The adaptation is believed to be a result of a strong medium after-hyperpolarization current (mAHP), mediated by small-conductance calcium (Ca)-dependent potassium (SK) channels. However, the SK channel coding genes are not significantly differentially expressed between PV and SST INs. Since SK channels depend on the influx of Ca2+ during spikes, we investigated the upstream mechanisms that may control Ca2+ influx. Previous experiments showed that blocking voltage-gated Kv3 channels abolishes the fast-spiking (FS) features of PV INs and, surprisingly, increases adaptation, suggesting that the Kv3 channel-mediated fast repolarization of the action potential of these INs limits the time window for Ca2+ influx. We also found that HW and the expression levels of genes encoding Cav channels are correlated with AI on a single-cell level. These results suggest that the adaptation differences between PV and SST INs may result from Ca influx-related upstream mechanisms.

Disclosures: Y. Kang: None. **J.H. Meng:** None. **B. Rudy:** None. **X. Wang:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.15

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 1U19NS107609

Title: Comparing rapid rule-learning strategies under ambiguous contextual cues in monkeys and humans

Authors: *V. GOUDAR[1], J.-W. KIM[1], Y. LIU[1], A. J. O. DEDE[2], M. J. JUTRAS[2], I. SKELIN[3], M. RUVALCABA[4], W. CHANG[4], J. J. LIN[3], R. T. KNIGHT[4], E. A. BUFFALO[2], X.-J. WANG[1];
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Abstract: Context-dependent behavioral adaptation is a hallmark of volitional control. Often, it is contingent upon determining the context from ambiguous cues. We compared this ability of humans (n=5) and monkeys (n=4) in a version of the Wisconsin Card Sorting Task that required learning which one "rule" feature out of 12 visual features produces a reward when selected in a block of trials. Even though rule switches were uncued and reward outcomes only partially informative about the rule, both species learned rules rapidly (within tens of trials). But monkeys were over 3 times slower than humans. To assess whether this reflects different learning strategies, we fit Hidden Markov Model-Generalized Linear Models (HMM-GLM) to the choices of each species. The best-fit models identify: (i) 4 hidden states akin to levels of feature-based attention that modulate the probability of choosing a feature; ii) across-trial dynamics of these states that culminate in rule learning; and (iii) sensitivity of underlying choice- and state transition probabilities to the previous trial's choice and outcome. The models enabled an inter-species comparison of learning strategies: First, both species adopt information-seeking exploration, testing and rejecting features until they learn the rule. The number of such exploration trials strongly determines a subject's learning speed (Monkeys mean +/- sd: 50% +/- 8% trials; Humans: 52% +/- 7% trials). Both species frequently explore multiple features in parallel, but monkeys do not easily disambiguate the rule from other features - they spend much longer simultaneously exploring the rule and other features (M: 14.2 +/- 3.4 trials; H: 3.5 +/- 0.8 trials). Second, both species exhibit inferential reasoning - a feature under exploration is determined as the rule when negative feedback is received for not choosing it. But monkeys are less likely to do so (rule inference probability - M: 12% +/- 5%; H: 87% +/- 9%). Monkeys also continue exploring a feature after being rewarded for choosing another feature (continuation probability - M: 83% +/- 25%; H: 0.3% +/- 0.6%). These oversights prolong exploration and degrade monkey learning. Third, only monkeys perseverate on the previous rule after a rule switch (M: 4.2 +/- 2.6 trials; H: 0.5 +/- 0.4 trials), responding weakly to negative feedback once a rule is learned. Fourth, monkeys choose the rule less consistently after learning it (choice probability - M: 80% +/- 5% trials; H: 99% +/- 0.5%), thus taking longer to reach the learning criterion. Our results offer testable neural predictions on divided attention to features across trials and species-dependent attentional and feedback modulation of choice behavior.

Disclosures: V. Goudar: None. **J. Kim:** None. **Y. Liu:** None. **A.J.O. Dede:** None. **M.J. Jutras:** None. **I. Skelin:** None. **M. Ruvalcaba:** None. **W. Chang:** None. **J.J. Lin:** None. **R.T. Knight:** None. **E.A. Buffalo:** None. **X. Wang:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.16

Topic: I.06. Computation, Modeling, and Simulation

Support: University of Miami Institute for Data Science & Computing

Title: Deep neural networks trained for speech recognition do not generalize to sine-wave speech

Authors: *Y. ZHU[1], O. SCHWARTZ[2], A. R. DYKSTRA[3];
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Abstract: Sine-wave speech (SWS) is a sparse acoustic signal comprising 3-4 time-varying sinusoids. Naive listeners typically perceive SWS as noise, but readily perceive SWS as speech after priming. To better understand how humans learn to perceive SWS like natural speech (NS), we examined the ability of deep neural networks (DNNs) trained on NS words to recognize SWS words. We tested DNN SWS word recognition both before and after fine-tuning the network based on SWS words derived from NS word counterparts. The DNN trained to recognize NS words did so with an accuracy of 0.91. However, such high word-recognition performance did not transfer to SWS (accuracy: 0.55), even after fine-tuning the network on the SWS words with variable learning rates (max accuracy: 0.67). In contrast, a naive model trained only to recognize SWS words was much more accurate (0.88), and better transferred to recognizing NS words (0.58, 0.75 after NS recognizing). Furthermore, representational similarity analysis showed that the outputs of the naive model trained only on SWS are closer to the outputs of the original speech model than the model transferred from NS to SWS. This suggests that the accuracy of DNNs trained on NS typically derives from speech features other than those preserved in SWS. Furthermore, given that humans are readily able to perceive SWS as speech with minimal training, this, in turn, suggests that DNNs recognize speech in a manner fundamentally different from humans, and likely will require additional top-down mechanisms to be effective models for human speech perception.

Disclosures: Y. Zhu: None. **O. Schwartz:** None. **A.R. Dykstra:** None.

Poster

748. Deep Learning: Theory and Application

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 748.17

Topic: I.06. Computation, Modeling, and Simulation

Title: A recurrent neural network model of excitatory-inhibitory imbalance in autism spectrum disorders

Authors: *D. ZAVITZ, G. J. GOODHILL;
Washington Univ. in St. Louis, St. Louis, MO

Abstract: The proportion of excitation and inhibition neurons receive is critical to sensory processing and a fundamental measurement of activity in neuronal network. Furthermore, an imbalance of excitation and inhibition is a leading hypothesis for the mechanism underlying autism spectrum disorders (ASDs). Numerous studies of ASD mouse models have found genetic, neuronal, and circuit changes that implicate disruption to excitation or inhibition. However, the precise sense in which excitation and inhibition are imbalanced in cortical circuits, what physiological changes might result from such an imbalance, and which circuit functions may be disrupted, remain unclear. To explore these questions, we constructed a recurrent neural network (RNN) model of cortical circuits consisting of separate excitatory and inhibitory populations and trained the RNN to perform a variety of tasks. Once trained, we systematically perturbed network parameters into hyperexcitable or hypoexcitable regimes in which there is relatively more excitation or inhibition respectively and tracked the resulting shifts in task performance. We found that the two regimes have distinct effects on task performance, which can then be related to neurological disorders. Altogether, our study illuminated the computational significance of excitatory-inhibitory balance and its implications for ASD.

Disclosures: D. Zavitz: None. **G.J. Goodhill:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.01

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF Grant 1552946
NSF Grant 1807216
NSF Grant 2032649
NIH Grant 1U19NS107464-01

Title: Inferring directional connectivity from spiking observations via latent variable modeling

Authors: *S. KHOSRAVI[1,2], A. RUPASINGHE[1,2], B. BABADI[1,2];
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Abstract: Recent advances in neural data acquisition technology have paved the way for recording the simultaneous activity of large neuronal populations. Extracting directional connectivity among such neuronal ensembles is a key step in understanding the underlying mechanisms of brain function. To this end, Granger causality (GC) is a well-established and widely used methodology. However, existing methods for inferring GC from neuronal observations have various shortcomings. First, commonly used approaches typically proceed in two stages, by first estimating the latent processes that drive neural spiking, then followed by GC inference based on said estimates. As a result, biases induced by time-domain latent variable estimation propagate to the subsequent GC inference stage. Secondly, current models that are used to directly extract GC links from spiking observations do not account for both the endogenous and exogenous processes that govern spiking activity. Third, neural dynamics that are captured by latent variable models pertain to instantaneous correlations and do not account for delayed interactions between neurons. Here, we propose a methodology to bypass intermediate time-domain estimation and directly recover the underlying GC from spiking observations. We use point process and multivariate autoregressive modeling to explicitly account for both spontaneous and stimulus-driven neuronal activity and develop a variational Bayesian inference methodology and a statistical testing framework to infer GC links among the neurons in the ensemble. We demonstrate the utility of our proposed method through simulation studies and application to experimentally recorded spiking data from rat cortical neurons during sleep. Our method provides a robust and reliable alternative to conventional methods for inferring GC links with significant improvements in terms of hit and false alarm rates. In addition, application of our method to experimentally recorded data identified network-level changes in the connectivity of putative pyramidal cells (PE) and putative interneurons (PI) during rapid eye movement (REM) and non-rapid eye movement (nonREM) stages of sleep. Our analysis revealed that the average number of GC links from PE to PI populations significantly decrease during REM compared to nonREM sleep, whereas there was no significant change in the number of GC links from PI to PE neurons.

Disclosures: **S. Khosravi:** None. **A. Rupasinghe:** None. **B. Babadi:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.02

Topic: I.06. Computation, Modeling, and Simulation

Support: ARC grant number DP170101815
European Research Council (FP/2007-2013)/ERC Grant Agreement no. 616268
European Union's Horizon 2020 Framework Programme for Research and Innovation under Specific Grant Agreement No. 785907 and 945539 (Human Brain Project SGA2 and SGA3)
Agence Nationale de la Recherche grant number ANR-21-NEUC-0005-01

Melbourne Research Scholarship
NHMRC of Australia APP1118153

Title: Modeling the propagation of electrical stimuli through the human connectome at high spatiotemporal resolution

Authors: *C. SEGUIN[1], M. JEDYNAK[2], O. DAVID[3], S. MANSOUR L.[1], O. SPORNS[4], A. ZALESKY[5];
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Abstract: 1. INTRODUCTION
Understanding the mechanisms governing the propagation of stimuli through brain networks is crucial for the design of clinically effective brain stimulation protocols for psychiatric conditions. We use invasive intracranial electroencephalography (iEEG) recordings of thousands of direct electric stimulation experiments to investigate the propagation of signals through the human connectome at high-spatiotemporal resolution.
2. METHODSThe F-TRACT project compiled invasive iEEG recordings from 29,055 direct electrical stimulation experiments, performed across 550 individuals with epilepsy, into a matrix of cortico-cortical evoked potential (CCEP) amplitudes. A group-level normative structural connectome was mapped from 1,000 participants of the Human Connectome Project. Computational models were used to perform in silico simulations of stimuli propagation through the connectome according to a range of putative mechanisms of neural signalling. Empirical measures of CCEP amplitudes were compared to computational estimates of communication efficiency between gray matter regions.
3. RESULTS
Computational estimates of network communication were strongly associated with CCEP amplitudes. We found that network communication models provide reliable and parsimonious predictors (out-of-sample correlation coefficient r=0.8) of the CCEP amplitude evoked in downstream cortical regions following stimulation of an arbitrary gray matter locus.
4. CONCLUSIONS
Our computational model equips clinical researchers with a tool to select brain stimulation targets for neuropsychiatric interventions. Importantly, the model facilitates the non-invasive modulation (e.g., via TMS) of deep structures through estimates of polysynaptic propagation of stimuli delivered to the cortical surface. We envision future work combining our model with patient-specific white matter connectivity data for the identification of personalized stimulation targets in treatment-resident MDD and OCD.

Disclosures: C. Seguin: None. **M. Jedynak:** None. **O. David:** None. **S. Mansour L.:** None. **O. Sporns:** None. **A. Zalesky:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.03

Topic: I.06. Computation, Modeling, and Simulation

Support: "Institut de Convergence ILCB" (ANR-16-CONV-0002)
USIAS 2020 Fellowship -D Battaglia

Title: Decomposing neural circuit function into information processing primitives

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Abstract: Cognitive functions must arise from the coordinated activity of neural populations distributed over large-scale brain networks. However, it is challenging to understand and measure how specific aspects of neural dynamics translate into operations of information processing, and, ultimately, cognitive function. An obstacle is that simple circuit mechanisms - such as self-sustained or propagating activity and nonlinear summation of inputs- do not directly give rise to high-level functions. Nevertheless, they already implement simple transformations of the information carried by neural activity. Here we show that distinct neural circuit functions, such as stimulus representation, working memory, or selective attention stem from different combinations and types of low-level manipulations of information, or information processing primitives.
To prove this hypothesis, we combine approaches from information theory with computational simulations of canonical neural circuits involving one or more interacting brain regions that emulate well-defined cognitive functions. More specifically, we track the dynamics of information emergent from dynamic patterns of neural activity, using suitable quantitative metrics to detect where and when information is actively buffered ("active information storage"), transferred ("information transfer") or non-linearly merged ("information modification") as possible modes of low-level processing. We find that neuronal subsets maintaining representations in working memory or performing attention-related gain modulation are signaled by their boosted involvement in operations of active information storage or information modification, respectively.
Thus, information dynamics metrics, beyond detecting which network units participate in cognitive processing, also promise to specify how and when they do it, i.e. through which type of primitive computation, a capability that may be exploited for the parsing of actual experimental recordings.

Disclosures: **N. Voges:** None. **J. Hausmann:** None. **A. Brovelli:** None. **D. Battaglia:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.04

Topic: I.06. Computation, Modeling, and Simulation

Support: Howard Hughs Medical Institute

Title: Statistics of sub-threshold voltage dynamics in cortical networks

Authors: O. AMSALEM[1], H. INAGAKI[2], J. YU[3], K. SVOBODA[4], ***R. DARSHAN**[5]; [1]Harvard Med. Sch., Boston, MA; [2]Max Planck Florida Inst. for Neuroscienc, Jupiter, FL; [3]Sch. of Life Sci., Peking Univ., Beijing City, China; [4]Allen Inst. for Neural Dynamic, Seattle, WA; [5]Janelia Res. Campus, Ashburn, VA

Abstract: Cortical neurons exhibit temporally irregular spiking patterns and heterogeneous firing rates. These features arise in model circuits operating in a 'fluctuation-driven regime' (FDR), in which fluctuations in membrane potentials emerge from the network dynamics. However, it is still unclear whether the cortex operates in the FDR. We evaluate the FDR hypothesis by analyzing spiking and sub-threshold membrane potentials of neurons in sensory and frontal cortex recorded during a decision-making task. Standard FDR models account for spiking statistics but fail to capture the heterogeneity in sub-threshold activity. We present a network model that effectively incorporates dendritic conductances into the FDR framework. It accounts for sub-threshold heterogeneities and suggests that frontal cortex operates in FDR. In contrast, excitatory neurons in layer 4 of barrel cortex are not fluctuation-driven; they spike in response to occasional synchronous inputs. Our work reveals fundamental differences between cortical areas, suggesting that they operate in different dynamical regimes.

Disclosures: O. Amsalem: None. **H. Inagaki:** None. **J. Yu:** None. **K. Svoboda:** None. **R. Darshan:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.05

Topic: I.06. Computation, Modeling, and Simulation

Title: The neural basis of generalization from one example

Authors: *M. A. NUNEZ-OCHOA, L. ZHONG, F. DU, C. STRINGER, M. PACHITARIU; Janelia Res. Campus, Ashburn, VA

Abstract: Learning general principles from single examples is a hallmark of higher cognitive functions in humans and animals. To study this form of generalization, previous studies have looked either at human behavior or at the neurons which may support generalization. For

example, neurons that encode visual categories have been found in the inferior temporal cortex in primates. However, it is still not known how these neurons obtain their tuning properties or how the neurons give rise to behavior, because it is very difficult to record them during learning and behavior.
Mice are an attractive model organism due to the wide range of available neuroscience techniques. However, it is not known if mice can be trained to learn general principles from single examples, and their capacity for visual cognition is thought to be modest. We trained mice to discriminate between two images chosen from different natural object categories, such as rock or leaves. After successful learning, the mice were presented with new images from the same categories and they responded to the new images according to their category. This demonstrates that mice can in fact learn general categories from single examples of those categories.
To take advantage of the neuroscience toolset available in mice, we developed the task in a head-fixed condition. This allowed us to record simultaneously from up to 70,000 neurons in the visual cortex using calcium imaging. To investigate the neural basis of learning in this task, we recorded neural responses to different visual textures before and after learning, and found a subset of neurons in primary and higher-order visual cortex that had invariant tuning properties to the visual textures. To explain these tuning properties, we fit the neural responses with a multi-layer neural network and investigated the ability of the model to generalize from a single example.
We will use the recordings from this task together with machine learning theory to explain: 1) which neural properties are used for generalization, 2) how the brain constructs good features for learning, 3) what algorithms does the brain use to identify relevant features to be learned in the context of a task and 4) which circuit changes and computations are supporting this.

Disclosures: **M.A. Nunez-Ochoa:** None. **L. Zhong:** None. **F. Du:** None. **C. Stringer:** None. **M. Pachitariu:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.06

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF Grant #1704436
NSF DBI Grant 201531

Title: Benchmarking a new software tool for designing and simulating large-scale synthetic nervous systems

Authors: *W. R. P. NOURSE[1], N. S. SZCZECINSKI[3], R. D. QUINN[2];
[1]Electrical, Computer, and Systems Engin., [2]Mechanical and Aerospace Engin., Case Western Reserve Univ., Cleveland, OH; [3]West Virginia Univ., Morgantown, WV

Abstract: Animals have long provided inspiration for the development of adaptable robots. One current approach being explored is simulating networks of conductance-based models of neurons and synapses, also known as Synthetic Nervous Systems (SNS), to model animal systems and for robotic control. There is a wide variety of neural simulators which have existed for years, such as NEURON, NEST, and Brian, and simulators capable of large networks using reduced models such as BindsNET. While these and many other simulators are available, it is difficult to interface any of these programs in real-time with robotic hardware. Additionally, many of these simulators that are designed for high performance are incompatible with cyclic neural networks, eliminating the ability to simulate feedback loops.
To address this discrepancy, we introduce SNS-Toolbox, our new Python-based software package for the design and simulation of SNS networks. SNS-Toolbox implements non-spiking and spiking neuron models in multiple software backends, and is capable of simulating cyclic networks with thousands of neurons in real-time. Neural states are computed at each time-step, allowing straightforward data transfer between the neural simulation and external systems.
We have benchmarked the toolbox simulation speed across multiple network sizes and characterized the upper limits on network size in various scenarios. Using consumer hardware (NVIDIA GeForce RTX 2060), a cyclic network with over 3000 non-spiking (or over 1000 spiking) neurons can be simulated in real-time. If real-time performance is not a concern, networks can be simulated with over 150,000 neurons before encountering memory issues. We also present an example network created using the toolbox, showing the implementation of a network inspired by functionality within the *Drosophila melanogaster* optic lobe. Results are shown verifying the network behavior when presented with example image data.

Disclosures: W.R.P. Nourse: None. **N.S. Szczecinski:** None. **R.D. Quinn:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.07

Topic: I.06. Computation, Modeling, and Simulation

Support: NRF-2021R1I1A1A01059755

Title: A computational method for effective brain controls based on degeneracy and free energy principles

Authors: *J. KANG[1], H.-J. PARK[2];
[1]Dept. of Scientific Computing, Pukyong Natl. Univ., Busan, Korea, Republic of; [2]Dept. of Nuclear Med., Yonsei Univ. Col. Med., Seoul, Korea, Republic of

Abstract: The Brain is a highly complex system, and predicting effects of treatments of brain diseases is a challenging problem. For example, the self-restorative property of the brain can protect itself from external damage, but it makes difficulties in treatments of brain diseases since

an initial plan of treatment could not always be the best solution. To overcome such problems, in the present study, we formulate a self-restoration process in the brain, and suggest a computational framework to explore appropriate treatments based on the free energy principle and degeneracy of the brain.To describe non-linear brain dynamics, we adopted the pairwise maximum entropy model, which considers regional activity and pairwise interactions between two regions. We modeled a normal brain based on the resting state fMRI signals obtained from the 470 subjects in human connectome projects. In this study, we assumed that the recovery process could be explained by the free energy principle to satisfy environmental demands by reconfiguring the remained resources after treatment, and we developed a computational framework to use the degeneracy principle of the complex brain, i.e., we explored effective treatments that can recover brain dynamics rather than original brain network parameters. Using the proposed computational scheme, we determined the best treatment target area (nodes or edges in the network) and the strength of the treatment within a source system (disease system) to induce microstate dynamics of the desired goal system (healthy system).To generate diseased brain systems that show different brain dynamics from the normal healthy brain, we perturbed brain networks. Then, our computational scheme was applied to explore effective treatments. Our simulations showed that optimal control of the abnormal brain system successfully approached the brain dynamics of the healthy brain under restrictions that mimic various clinical treatments. Although more studies using experimental data should be done, we think the suggested computational framework would aid in achieving the optimal brain control of the dynamic self-restorative brain following treatment.
[1] Park, H.-J., and Kang, J. (2021). *Front. in Compt. Neurosci.* 15.

Disclosures: **J. Kang:** None. **H. Park:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.08

Topic: I.06. Computation, Modeling, and Simulation

Title: Multi-scale modeling of spike and field potential activity using neurobiologically-driven ordinary differential equation model

Authors: *Y.-J. CHANG[1], Y.-I. CHEN[1], H.-C. YEH[1], S. R. SANTACRUZ[1,2,3];
[1]Biomed. Engin., [2]Electrical & Computer Engin., [3]Inst. for Neurosci., The Univ. of Texas at Austin, Austin, TX

Abstract: Brain mechanism depends on neural dynamics spanning multiple spatiotemporal scales of population activity. However, the lack of integrative multi-scale analysis prevents us from illustrating the brain computation precisely and comprehensively. Here we developed a neurobiological model-driven deep learning method, termed neural ordinary differential equation-based multi-scale dynamics modeling (msDyNODE), as a generic framework for multi-

scale neural activity. To date, the investigation of the neural population dynamics is mostly limited by the single-scale analysis. Although in neuropsychiatric conditions, neural circuit-wide pathological activity impacts dynamics at multiple scales, either directly or indirectly, there is no broadly accepted multi-scale dynamical model for the collective activity of neuronal populations. Traditionally, the analysis has largely proceeded without formal neurobiological models of the underlying multi-scale neuronal activity. Whereas cross-correlation or coherence have been employed to measure the coupling of activities at different scales (e.g., spiking and local field potential (LFP) for neuronal synchronization), they only capture patterns of statistical dependence. Instead, dynamical modeling, which is seldom explored at multi-scale level, infers the causal interactions among brain regions or sources and potentially yields mechanistic understanding of brain computations. In addition, distinct modalities generally have different sampling rates. Down-sampling the one with higher sampling rate to match the lower counterpart can lose the fast dynamics information. Our proposed msDyNODE not only discards the need of adjusting the sampling rate but also uncovers multi-scale brain communications governing cognitive behaviors.

Disclosures: **Y. Chang:** None. **Y. Chen:** None. **H. Yeh:** None. **S.R. Santacruz:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.09

Topic: I.06. Computation, Modeling, and Simulation

Support: Allen Institute

Title: Neural Population Dynamics of Computing with Synaptic Modulations

Authors: *K. AITKEN, S. MIHALAS;
Allen Inst., SEATTLE, WA

Abstract: In addition to long-time scale rewiring, synapses in the brain are subject to significant modulation that occurs at much shorter time scales and allow them to process short-term information. Despite this, models of the brain like recurrent neural networks (RNNs) often have their weights frozen after training, relying on an internal state stored in neuron activity to process temporal information. Although networks with dynamical synapses have been explored previously, often said dynamics are added to networks that also have recurrent connections and thus the short-time scale computational capabilities of synapse modulation alone remain unclear. In this work, we analyze the dynamics of a network that relies solely on synaptic modulations to process short-time scale information, the multi-plasticity network (MPN). We thoroughly examine the neural population dynamics of the MPN trained on integration-based tasks and compare it to known RNN dynamics, findings the two to have fundamentally different behavior and attractor structure. We find said differences in dynamics allow the MPN to outperform its

RNN counterparts on several neuroscience-relevant tasks. Of note, the MPN has a significantly simpler attractor structure that allows it to be more flexible in training and sequential-learning settings. Lastly, how the dynamics change for MPNs trained on contextual and continuous integration tasks is also investigated.

Disclosures: K. Aitken: None. **S. Mihalas:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.10

Topic: I.06. Computation, Modeling, and Simulation

Support: Start-up funds from Johns Hopkins University (SPM, HA)

Title: Synergistic information encoded by neuronal ensembles

Authors: *X. FAN[1], G. SHAH[2], H. ADWANIKAR[3], S. P. MYSORE[2];
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Abstract: Synergistic information encoded by neuronal ensembles
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Synergistic information is the information that emerges only from the joint activity of multiple sources but remains unavailable in single sources alone. Such "synergy" occurs frequently (and intuitively) in everyday scenarios. For example, the visual recognition of an object in a picture requires knowing the collective activity of pixels forming a picture, whereas every single pixel only encodes brightness or color at a spot un-indicative of the object. Similarly, in the XOR operation in computer science, which takes two binary inputs and yields one binary output (00 or 11 yielding 0; 01 or 10 yielding 1), each input bit, by itself, has zero mutual information about the output, but the two inputs, taken together, unambiguously predict the output. Despite the importance of understanding the contribution of the information encoded by ensembles that may exceed the simple summation of individual contributions, there does not yet exist a systematic approach to quantitatively estimate synergistic information in multivariate datasets. Here, using ideas of partial information decomposition and destruction of synergistic information, we develop a practical algorithm that can estimate the synergy within data of high dimensions. We apply it to neural calcium dynamics imaged in the medial prefrontal cortex of freely behaving mice during navigation of the elevated zero maze, to estimate the amount of task-relevant synergistic information encoded in prefrontal ensembles (imaging done using the nVoke miniscope, Inscopix Inc). We show that synergy is the key contributor to the encoding of distinct behavioral states in the maze by the ensemble of neurons that are individually non-selective. This

novel approach to quantify synergistic information can help provide new insights into neural population coding.

Disclosures: **X. Fan:** None. **G. Shah:** None. **H. Adwanikar:** None. **S.P. Mysore:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.11

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R01MH122957

Title: Scaling laws in connectome topology across mammalian brains

Authors: *M. PUXEDDU[1], J. FASKOWITZ[2], Y. YOVEL[3], Y. ASSAF[4], O. SPORNS[2]; [2]Psychological and Brain Sci., [1]Indiana Univ., Bloomington, IN; [3]Sch. of Neurobio., Tel-Aviv, Israel; [4]Tel Aviv Univ., Tel Aviv, Israel

Abstract: The brain connectome is an embedded network of anatomically interconnected brain regions. Unlike other networks (e.g. social networks), brain connections incur material and energetic cost and their length and density is constrained by the overall brain volume (Laughlin and Sejnowski, 2003). One open question is how differences in brain volume, for example across different species, can impact the topological organization of the connectome. In this study, we tackle this issue by investigating the MaMI database (Assaf, Bouznach et al. 2020, Suárez, Yovel et al. 2022), a diverse set of mammalian structural brain networks reconstructed from post-mortem anatomical and diffusion MRI. The data covers 12 taxonomic orders/super-orders and 125 different species with brain size varying over more than three orders of magnitude. For each mammal, white matter tracts were reconstructed using diffusion tractography, and networks have been built from a volume-normalizing streamline count between 200 grey matter regions. We investigated the topology of the networks in this mammalian dataset and specifically, we focused on modular organization. We identified modules at different scales through a multi-resolution approach (Jeub et al., 2018) and observed how their properties vary with the brain size (Fig). We found that the modules tend to be denser and composed by stronger and more expensive connections in bigger brains rather than in the smaller ones. Moreover, we observed a negative correlation between brain size and Euclidean distance between nodes belonging to the same cluster. Finally, we found that long-distance connections are used to connect modules more and more as the brain size increases. Collectively, our results suggest that brain volume is systematically related to the connectome's topology and we quantify this influence in its modular organization.

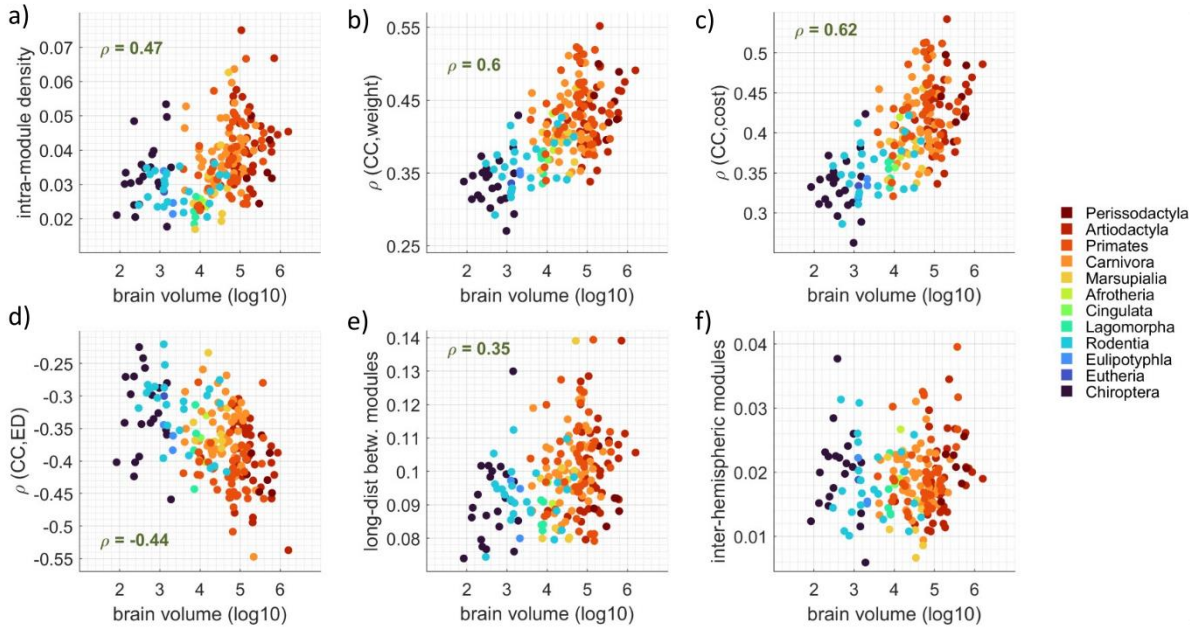

Figure. In each one of the panels, we report the trends of the properties of the modular structure (y-axis) with the brain volume (x-axis) highlighting the different orders through a color code. Specifically, we report on the y-axis: (a) density of connections within modules; correlation between the probability that two nodes belong to the same module and (b) weight (c) cost and (d) Euclidean distance of the connection connecting those two nodes; (e) number of long-range connections linking two modules; (f) number of inter-hemispheric modules.

Disclosures: **M. Puxeddu:** None. **J. Faskowitz:** None. **Y. Yovel:** None. **Y. Assaf:** None. **O. Sporns:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.12

Topic: I.06. Computation, Modeling, and Simulation

Title: Multi-policy models of interregional communication in the human connectome

Authors: ***R. BETZEL**[1], J. FASKOWITZ[1], B. MISIC[2], O. SPORNS[1], C. SEGUIN[1]; [1]Indiana Univ., Indiana Univ., Bloomington, IN; [2]McGill Univ., McGill Univ., Montreal, QC, Canada

Abstract: Network models of communication, e.g. shortest paths, diffusion, navigation, have become useful tools for studying structure-function relationships in the brain. These models generate estimates of communication efficiency between all pairs of brain regions, which can then be linked to the correlation structure of recorded activity, i.e. functional connectivity (FC). At present, however, communication models have a number of limitations, including difficulty

adjudicating between models and the absence of a generic framework for modeling multiple interacting communication policies at the regional level. Here, we present a framework that allows us to incorporate multiple region-specific policies and fit them to empirical estimates of FC. Briefly, we show that many communication policies, including shortest paths and greedy navigation, can be modeled as biased random walks, enabling these policies to be incorporated into the same multi-policy communication model alongside unbiased processes, e.g. diffusion. We show that these multi-policy models outperform existing communication measures while yielding neurobiologically interpretable regional preferences. Further, we show that these models explain the majority of variance in time-varying patterns of FC. Collectively, our framework represents an advance in network-based communication models and establishes a strong link between these patterns and FC. Our findings open up many new avenues for future inquiries and present a flexible framework for modeling anatomically-constrained communication.

Disclosures: R. Betzel: None. **J. Faskowitz:** None. **B. Misic:** None. **O. Sporns:** None. **C. Seguin:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.13

Topic: I.06. Computation, Modeling, and Simulation

Support: IVADO Postdoctoral Fellowship
NSERC Discovery Grant: RGPIN-2020-05105
NSERC Discovery Accelerator Supplement: RGPAS-2020-00031
Healthy Brains, Healthy Lives (New Investigator Award: 2b-NISU-8)
CIFAR (Canada AI Chair; Learning in Machine and Brains Fellowship)
This research was enabled in part by computational resources provided by Calcul Québec
This research was enabled in part by computational resources provided by Compute Canada

Title: Exploring learning in neural networks with brain-inspired geometries

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Abstract: There are many differences between biological and artificial neural networks (ANNs). However, based on the fundamental assumption that biological neural networks have been optimized by evolution, the two fields have long shared a synergistic relationship. A simple question we might therefore ask is: “How similar are the parameter update rules that govern learning in biological and artificial networks?”. In Artificial Intelligence, neural networks are

generally trained using stochastic gradient descent (SGD). As such, network parameters are updated additively with the negative gradient of the loss function at every training iteration. In contrast, recent biological experiments have shown that synaptic weight updates in the brain are predominantly multiplicative in nature. In this work we show how these two forms of update can arise from the choice of distance generating function in Mirror descent, and leverage our recent work building networks with sign-constrained weights to explore the use of multiplicative updates and non-euclidean distance functions for training ANNs.

Disclosures: **J. Cornford:** None. **A. Ghosh:** None. **G. Gidel:** None. **B.A. Richards:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.14

Topic: I.06. Computation, Modeling, and Simulation

Support: Simons Foundation / Simons-Emory International Consortium on Motor Control (I.N., A.S.)
University of Minnesota Medical School (A.J.S.)
NIH Grant R01-NS084844 (A. J. S. and I. N.)
NIH Grant No. R01-EB022872 (I. N.)
NIH Grant No. R01-NS099375 (I. N.)
NSF Grant No. BCS-1822677 (I. N.)
Minnesota Supercomputing Institute (MSI)

Title: Critical behavior is a generic phenomenon in large neural populations with distributed coupling to latent dynamical variables

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Abstract: Nearly two decades ago, the observation [1] that neural systems produce activity events whose size and duration were power-law distributed and consistent with a critically tuned system sparked numerous studies across organisms and scales. This ‘avalanche criticality’ appears to be remarkably widespread, from cultured neurons in a dish to zebrafish recordings to EEG in humans and has been hypothesized to provide various functional advantages. Recently, a different form of criticality was reported based on the analysis of 2000 neurons in the mouse hippocampus [2]. In this analysis, an averaging procedure, known in the physics community as coarse-graining, was applied to neural recordings from the mouse hippocampus. This analysis showed over two decades of scaling in the coarse-grained activity variance, eigenvalue spectra, and correlation time, hinting that this system operates in a critical regime. Despite the seeming ubiquity of the observation of signatures of criticality in neural systems, it is unclear what

mechanisms generate signatures of a critical state. In recent work, we showed that a large network of neurons in which activity is determined by a small number of latent dynamical variables could reproduce, within experimental error bars, the scaling relationships reported under coarse-graining analysis [3]. For this result, multiple latent variables were required. Inspired by previous work linking a single latent variable to avalanche criticality, we extended our model to determine the conditions under which avalanche criticality is observed with multiple latent variables. We systematically examined how adjusting two parameters, the input gain and firing threshold, determined whether critical behavior was observed. Consistent with past work, we find that a single, quasi-static latent variable can generate critical behavior, but that a population coupled to multiple latent variables will exhibit critical behavior in a broader parameter regime, including when the latent dynamics evolve on faster timescales. Finally, we computed how much information population activity carries about the latent variables, and we found that avalanche criticality is observed when the network activity is informative of the value of the latent field. Our results suggest that power laws and scaling relationships are a common feature in neural systems in which (a) there is an emergent dynamical variable or shared inputs creating an effective latent dynamical variable, and (b) this variable can be read out from the population activity.
[1] Beggs and Plenz, J Neurosci, 2003. [2] Meshulam et al., Phys Rev Lett, 2019. [3] Morrell et al., Phys Rev Lett, 2021

Disclosures: **M. Morrell:** None. **I. Nemenman:** None. **A.J. Sederberg:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.15

Topic: I.06. Computation, Modeling, and Simulation

Title: The Topology and Geometry of Brain Representations

Authors: *B. LIN, N. KRIEGESKORTE;
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Abstract: To evaluate how well a model can account for a brain representation, we need to develop inference methods for model comparison. Previous studies have compared models and brains in terms of their representational geometries and related statistics such as singular-vector canonical correlation analysis (SVCCA) and centered kernel alignment (CKA). Characterized by the matrix of distances between representations of the input patterns in a model layer or cortical area, the representational geometry is defined by these Representational Dissimilarity Matrices (RDMs) as the summary statistic or, equivalently, by the second moment of the activity profiles. The RDM constitutes an intermediate summary statistic: it discards some information contained in the distribution of activity profiles, but retains more information than a linear decoding approach. In this study, we propose to explore these summary statistical descriptions of

representations in models and brains as part of a broader class of statistics that emphasize the topology as well as the geometry of brain representations. The topological summary statistics build on topological data analysis (TDA), information-based functional mapping and other graph-based methods. To abstract from idiosyncrasies of individual brains and highlight the representational properties key to their computational function, we seek an optimal upper distance threshold above which we consider stimuli distinct, but do not consider differences between distances meaningful (i.e., the stimuli are disconnected in the graph capturing the topology at a proper scale). To suppress noise, we seek a lower distance threshold below which we consider stimuli as co-localized (i.e., the stimuli have collapsed into the same node in the graph). We evaluate these statistics in terms of the sensitivity and specificity that they afford when used for model selection, with the goal to relate different neural network models to each other and to make inferences about the computational mechanism that might best account for the representations of black box systems including both the cortical areas of the biological brains and neurons of global surrogate models of these brain activity patterns, such as an artificial neural network. Benchmarked on fMRI data of human subjects viewing 62 images, its surrogate neural network models, and Allen Brain Observatory calcium imaging data, we demonstrate that these new methods enable brain and computer scientists to visualize the dynamic representational transformations learned by brains and models, and to perform model-comparative statistical inference in a more flexible and expressive way.

Disclosures: B. Lin: None. **N. Kriegeskorte:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.16

Topic: I.06. Computation, Modeling, and Simulation

Support: Marie Curie Fellowship

Title: Inferring data-consistent spiking neural network models with simulation-based inference

Authors: *R. GAO, M. DEISTLER, J. H. MACKE;
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Abstract: Variations in cellular and network parameters shape neural dynamics and computation. Mechanistic models, such as biophysical spiking neural networks, are instrumental for quantitatively linking observed circuit dynamics with their underlying structural parameters. However, such models often lack analytical expressions for inference (i.e., model-fitting), making it difficult to systematically identify a single parameter configuration that reproduces experimental data, let alone the full space of data-consistent models and their associated uncertainty. Recent progress in simulation-based inference (SBI) approaches has made it possible to apply Bayesian inference on “black-box” mechanistic models in neuroscience, but it

remains unclear if SBI scales to large-scale network models with complex high-dimensional parameter landscapes and arbitrary data features.Here, we assess the effectiveness of Neural Posterior Estimation (NPE) for inferring parameters of spiking network models. By training on parameter-data pairs generated from model simulations, NPE learns a probabilistic mapping between network parameters and neural activity with a conditional density estimation network. We apply NPE on synthetic data from two network models to evaluate its performance against ground truth data. First, for balanced linear integrate-and-fire networks, NPE accurately estimates network parameters of held-out simulations from population spike-train statistics, while posterior covariance recovers known phase transitions over input strength and synaptic E:I ratio. Second, we apply NPE to adaptive exponential integrate-and-fire networks with 15 parameters. Posterior samples—especially maximum a posteriori estimates—recover model parameters that lie close to the ground truth and produce data-consistent simulations. Furthermore, recovery accuracy of samples scales with their posterior probability, and is strongly dependent on training set coverage around a given test sample in both parameter- and data-space. In summary, we demonstrate how SBI can be applied to large-scale circuit models for recovery and characterization of parameter landscapes, paving the way for efficient and automated discovery of black-box mechanistic models from experimental neural recordings.

Disclosures: **R. Gao:** None. **M. Deistler:** None. **J.H. Macke:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.17

Topic: I.06. Computation, Modeling, and Simulation

Support: R01GM134363

Title: Estimating neuronal timescales

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Abstract: Neuronal timescales are functionally dynamic and hierarchically distributed across the cortex. Recent evidence has implicated alterations in neuronal timescales in a variety of neurological and psychiatric disorders, with shortened neural timescales in aging. Current methods for quantifying timescales involve fitting an exponential decay to the autocorrelation function (ACF) or a Lorentzian to power spectral density (PSD). However the accuracy and/or stability of these estimates are biased in the presence of neural oscillations, finite duration signals, or in dynamic processes with non-constant timescales. Given the clear importance of

neuronal timescales in cognition and disease, having a robust and reliable method for estimating short-time timescales is critical. However, as a signal becomes shorter in time, non-parametric PSD methods, such as Welch's method, produce increasingly unstable spectra. Here, we demonstrate how parametric methods, specifically AR models, rectify PSD instability. AR models use weighted past values to predict future values in a signal, and conveniently these AR models have PSD representations that may be subsequently parametrized for more precise estimates of short-time timescales. In addition, we introduce a novel approach for simulating neural spike trains with a desired timescale, which provides us with ground truth data against which we can test the accuracy of our AR-based timescale estimation method. This spike simulation method also allows us to quantify the sources of bias using spectral parameterization and autoregressive (AR) modeling. We show that oscillations can be accounted for in the PSD with the inclusion of Gaussian peaks when parameterizing spectra, and finite duration is minimized using AR-PSD estimates. Rat hippocampal data is used to extend simulation findings and demonstrates how timescales may be tracked over time in the presence of oscillations, using short time windows, and with dynamic timescales.

Disclosures: R. Hammonds: None. **B. Martin-Burgos:** None. **T. McPherson:** None. **R. Gao:** None. **B. Voytek:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.18

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant MH099045
NIH Grant MH121841
NIH Grant EY022951
NIH Grant MH113852
NIH Grant EY031133
NIH Grant EB026936
Yale Kavli Institute of Neuroscience

Title: Rapid fluctuations in functional connectivity of cortical networks encode spontaneous behavior

Authors: *H. BENISTY[1], A. H. MOBERLY[1], S. LOHANI[1], D. BARSON[1], R. R. COIFMAN[2], J. A. CARDIN[1], M. J. HIGLEY[1], G. MISHNE[3];
[1]Yale Sch. of Med., Yale Univ., New Haven, CT; [2]Applied Math, Yale, New Haven, CT; [3]Univ. of California San Diego, UCSD, La Jolla, CA

Abstract: Experimental work across a variety of species has demonstrated that spontaneously generated behaviors are robustly correlated to variation in neural activity within the cerebral

cortex. Indeed, functional magnetic resonance imaging (fMRI) data suggest that functional connectivity in cortical networks varies across distinct behavioral states, providing for the dynamic reorganization of patterned activity. However, these studies generally lack the temporal resolution to establish links between cortical signals and the continuously varying fluctuations in spontaneous behavior typically observed in awake animals. Here, we take advantage of recent developments in wide-field mesoscopic calcium imaging to monitor neural activity across the neocortex of awake mice. Diverging from traditional analysis of functional connectivity as a static entity, we explored the temporal dynamics of connectivity as expressed by instantaneous correlations between functional brain parcels. We develop a novel analysis, termed "graph-of-graphs", that views the temporal fluctuations of correlations as high dimensional observations of a dynamical system and aims to extract their latent dynamics. We use Riemannian geometry and diffusion geometry to extract a low dimensional representation capturing the intrinsic dynamics of the functional connectivity. Using this novel approach, we demonstrate that spontaneous behaviors are more accurately represented by fast changes in the connectivity structure versus the activity of large-scale network. Moreover, the dynamics of the extracted functional connectivity representation reveals subnetworks that are not evident in traditional anatomical atlas-based parcellation of the cortex. For a small-scale network such as cells in the primary visual cortex, we show that there is no significant difference in the representation of behavioral variables using either embedded activity or embedded correlations, which means that the internal mechanisms of behavior encoding vary with scale. These results provide insight into how behavioral information is represented across the mammalian neocortex and demonstrate a new analytical framework for investigating time-varying functional connectivity in neural networks.

Disclosures: H. Benisty: None. **A.H. Moberly:** None. **S. Lohani:** None. **D. Barson:** None. **R.R. Coifman:** None. **J.A. Cardin:** None. **M.J. Higley:** None. **G. Mishne:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.19

Topic: I.06. Computation, Modeling, and Simulation

Title: Feedback Controllability as a Normative Measure of Neural Dynamics

Authors: *A. KUMAR[1], K. BOUCHARD[2];
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Abstract: Brain computations underlying cognition and behavior are produced through the collective dynamics of networks of neurons. Concomitantly, the structure and variability within diverse behaviors can be accounted for by theories of optimal control, by which behavior arises from the brain optimizing task-dependent control objectives. In particular, prior work has demonstrated variability in tasks such as motor coordination can be accounted for by models of

optimal feedback, as opposed to feedforward, control. However, to date, the implications of this normative description of behavior for the dynamics of the underlying neural circuits have not been explored. In this work, we put forward the theory that functionally relevant brain dynamics should be feedback controllable, and test this theory in electrophysiological recordings across diverse brain areas. We develop Feedback Controllable Components Analysis (FCCA), a statistical method to identify subspaces of neural population dynamics that are most controllable under feedback. In neural data, we show that FCCA subspaces and feedforward controllable (i.e. variance-maximizing) subspaces diverge from each other, and recruit fundamentally different populations of neurons. We show that FCCA subspaces robustly outperform feedforward controllable (FC) subspaces in decoding of reaching behavior from macaque M1, location from rat hippocampus, and syllable production from human vSMC. In M1 recordings, we demonstrate that single neuron leverage scores in FCCA subspaces cannot be predicted from single unit statistics, indicating that feedback controllability is an emergent, population level, feature. Furthermore, we find that FCCA subspaces contain more stereotyped rotational dynamics than FC subspaces. The decoding performance of FCCA vs. FC subspaces is also found to be largest during high acceleration reaching periods. Finally, we show, through analytic results, numerical simulations, and dynamical systems inference on electrophysiology data, that the divergence between FCCA and FC subspaces is modulated by the degree of non-normality in neural dynamics. Taken together, our results demonstrate feedback controllability is a novel, normative characterization of neural dynamics, and provides insights into how specific features of dynamical systems shapes their controllability under feedback and feedforward policies.

Disclosures: **A. Kumar:** None. **K. Bouchard:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.20

Topic: I.06. Computation, Modeling, and Simulation

Support: NRF-2022R1A2C3008991
NRF-2019M3E5D2A01058328
NRF-2021M3E5D2A01019544

Title: Random imitation for evolution in multi-agent systems

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Abstract: Imitation, the act of copying the behavior of others, is widely observed in social animals, including humans (Laland, 2004). Previous studies on adaptive learning rules suggest that human and animals imitate more effective traits as a payoff-based strategy for social

learning (Morgan, 2012). On the other hand, intriguingly, it has also been proposed that even unbiased imitation, i.e., random copying, can be a simple mechanism for describing certain cultural phenomena (Bentley, 2004) and that it can be a particular form of social learning to improve and inherit traits across generations (Gonzalez, 2017). Nonetheless, a detailed mechanism of how unbiased or random imitation works as an adaptive learning rule remains elusive. Here, using a computational model of a multi-agent system, we show that random imitation can function as a key mechanism of population evolution. In our multi-agent survival model, we found that non-selective imitation can be an effective strategy to increase the survival time of individual agents. The model was designed such that an individual agent has a single trait parameter which determines its shape, with the shape modulating the agent's energy collection and consumption efficiency. An agent's trait is randomly mutated initially, but later it is modulated by unbiased imitation by copying the trait of an agent chosen randomly. When only mutation was allowed, we observed that the average lifespan of agents does not differ from that of the initial trait. Interestingly, however, when unbiased imitation is introduced, we observed a significant increase in the average lifespan, which converges to the optimal value theoretically estimated for the environment. Next, we examined the effect of random imitation under variation of the duration and timing of random copying. Interestingly, the increase in the average lifespan was maximized when only a single imitation at each agent's birth was allowed, implying that unbiased imitation can work adaptively under certain environmentally constrained conditions. Lastly, we compared the effect of unbiased imitation with that of payoff-biased imitation using three models in which the imitation targets are selected by different rules. We found that the unbiased imitation condition results in comparable or even higher average lifespans than other payoff-biased imitation conditions, implying that the unbiased imitation can serve as a better strategy than payoff-biased imitation, which can be easily biased by limited observations in the environment. Our results suggest that unbiased imitation or random copying can play an important role in the evolution of a multi-agent system.

Disclosures: **M. Kang:** None. **H. Lee:** None. **Y. Park:** None. **M. Song:** None. **S. Paik:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.21

Topic: I.06. Computation, Modeling, and Simulation

Title: A predictive plasticity rule explains the anticipation of spike patterns at the single neuron level and the emergence of spike-timing-dependent plasticity mechanisms

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Abstract: Intelligent behaviour depends on the brain's ability to anticipate future events. Neurons can exploit the rich temporal structure of sensory stimuli to learn their predictive relations and to guide actions accordingly. However, the learning rules that enable neurons to predict and fire ahead of sensory inputs remain largely unknown. There is abundant but contrasting evidence on the role of pre- and post-synaptic spike times in the synaptic learning rules, yet a formal understanding of their role for prediction of sensory inputs is still missing. Here we propose a plasticity rule based on predictive processing, where neurons use their membrane potential as a tunable readout for the temporal relations in the inputs. Neurons thereby amplify those synapses that maximally predict other synaptic inputs based on their dynamics, providing a solution to an optimization problem that can be implemented at the single-neuron level. Consequently, neurons learn spike patterns over long timescales and shift their spikes towards the first inputs in the sequences. The plasticity rule enables neurons to learn multiple predictive components of their own synaptic inputs, providing a mechanism for fast processing of sensory inputs. Furthermore, we demonstrate that the learning rule gives rise to several STDP (spike-timing-dependent plasticity) mechanisms. The model predicts that the STDP rules observed experimentally emerge as a consequence of learning predictive relations in the input spike patterns. Finally, we show that this mechanism can explain the development of anticipatory motion signalling and recall in the visual system. These findings suggest prediction as a guiding principle to orchestrate learning and synaptic plasticity in single neurons.

Disclosures: **M. Saponati:** None. **M. Vinck:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.22

Topic: I.06. Computation, Modeling, and Simulation

Support: DOD VBFF
NIH U19NS107609-01

Title: Artificial Neuronal Ensembles

Authors: *M. J. TILLEY[1], Z. DONG[4], B. M. SWEIS[5], A. BAGGETTA[6], M. MILLER[2], D. M. MORALES-RODRIGUEZ[3], D. J. FREEDMAN[1], D. J. CAI[7];
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Abstract: There is evidence to suggest that many biological neural networks encode memories in distinct neuronal ensembles. However, when training artificial neural networks on a set of tasks, there is usually no mechanism for selectively producing an equivalent to these ensembles.

Artificial neural networks suffer from catastrophic forgetting, where the network's performance rapidly deteriorates as tasks are learned sequentially. By contrast, sequential learning is possible for a range of biological organisms. We aim to alleviate this problem of catastrophic forgetting and create a model for ensemble dynamics in biological neural networks. We introduce a method to flexibly allocate and recall artificial neuronal ensembles, using a particular network structure and a set of regularization terms. Activities in the hidden layers of the network are modulated by 'gates', which are dynamically produced during training. For example, if there are 2 hidden layers with 2000 neurons in each layer, there will be 2 associated gates of size 2000. The gates are outputs of networks themselves, trained with a sigmoid output activation. Neurons that have an associated gate value of ≈1 are included in an 'artificial ensemble'. The regularization terms we have introduced correspond to properties exhibited by biological neuronal ensembles. The first term deals with sparsity, ensuring that only a specified fraction of the network is used. For example, we can specify that approximately 20% of the neurons should be included for each task. The second term ensures that old ensembles are recalled when the network is presented with examples of old input data. Finally, there is a regularization term responsible for ensuring that new tasks are encoded in ensembles that are as orthogonal as possible from previously used ones. We demonstrate the ability of this method to alleviate catastrophic forgetting on a range of continual learning benchmarks. On the benchmark 'permuted MNIST' the model achieves greater than 95% mean performance across 50 tasks. By contrast, performance for the same network without the use of the regularization terms reduces to 27%. By studying neuronal ensembles in mice, we can compare this model with experiment. We use a spatial task where mice must receive water rewards from 8 ports on a circular track. Only 2 ports are active for each context. Visual context cues are provided by different patterned walls. The ensembles used to encode these tasks can be investigated using calcium imaging. We have produced a virtual 3D task, similar to that performed by the mice, trained via reinforcement learning. With this, we may assess the suitability of the networks as models for ensemble dynamics.

Disclosures: **M.J. Tilley:** None. **Z. Dong:** None. **B.M. Sweis:** None. **A. Baggetta:** None. **M. Miller:** None. **D.M. Morales-Rodriguez:** None. **D.J. Freedman:** None. **D.J. Cai:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.23

Topic: I.06. Computation, Modeling, and Simulation

Support: MSTP Training Grant T32GM007281
Pritzker Endowment for the Neurosciences

Title: Unique Characterization of Spatiotemporal Neural Network Activity

Authors: *S. S. DESHPANDE[1,2], G. SMITH[2,3], W. VAN DRONGELEN[2,3];
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Abstract: Analyses of spatiotemporal network patterns can be limited by heuristic approaches and traditionally utilize second-order statistics (e.g. auto- and cross-correlation). Here, we use the proof that third-order motifs and phase relationships between frequency bands are sufficient to fully characterize spatiotemporal network activity. This follows from applying the Triple Correlation Uniqueness (TCU) theorem from optical science to show that all finite data have both unique triple (third-order) correlation and unique bispectrum. The triple correlation formalism is defined by the relationships among three nodes: one reference node and up to two other nodes separated by spatial and temporal lags from the reference node, which generates 169 possible one-, two-, and three-node motifs. We show that these motifs fall into 14 qualitatively distinct motif-classes, which can embody well-studied network properties such as synchrony, feedback, feedforward, convergence, and divergence. Adding together the triple correlations within these motif-classes summarizes structure underlying the network data. Per the TCU theorem, we need not seek beyond third-order statistics to characterize network functionality in both the time and frequency domains, demonstrating the power of triple-node motifs as complete statistical representations of network activity. We test this methodology using spiking activity recorded from microelectrode arrays implanted in the motor cortex of rhesus macaques completing an instructed, delayed reach-to-grasp task. Preliminary analyses show that the triple correlation captures different network structures underlying various time periods during various tasks. Since these triple-node motifs generalize across recording modalities, we present and illustrate our analysis as a potential avenue for investigation throughout the field.

Disclosures: S.S. Deshpande: None. **G. Smith:** None. **W. van Drongelen:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.24

Topic: I.06. Computation, Modeling, and Simulation

Support: Brain/MINDS from AMED No. JP15dm020700
MEXT KAKENHI Grant No. JP18H0543
MEXT KAKENHI Grant No. JP19K2036

Title: Chaotic neural dynamics facilitate representations for probabilistic computation through their intrinsic variability

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Abstract: Cortical neurons exhibit time- and trial-varying responses when the same stimulus is presented or even without sensory inputs. While recurrent neural network models hypothesize that this variability is generated by chaotic network dynamics of strongly coupled neurons, it is unknown how the irregular neural dynamics could contribute to computation and learning in the brain. Here, we demonstrate the benefit of chaotic neural dynamics in the representation of probability distributions, which is essential for Bayesian computation. We train recurrent neural networks for tasks that require the integration of multiple sources of information and demonstrate that chaotic neural dynamics serve as the source of variability for probabilistic sampling. Our results with the use of a local learning rule suggest that probabilistic sampling by chaotic network dynamics is a biologically plausible mechanism to achieve Bayesian computation in the brain.

Disclosures: Y. Terada: None. **T. Toyoizumi:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.25

Topic: I.06. Computation, Modeling, and Simulation

Title: Power law scaling of frequency spectrum and eigenspectrum in neural population data

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Abstract: Neural data of many recording modalities exhibit power law-like statistics, which has been interpreted as evidence that the brain operates at the edge of criticality. Indeed, systems at criticality display scale-free temporal and spatial correlations, which can be characterized by their frequency spectrum (i.e., power spectral density, PSD) and population eigenspectrum (ES), respectively. Previous works have found that PSDs of neural data often follow a 1/f power law. More recently, it's been shown that the ES decays similarly. Here, we investigate whether power law scaling of temporal correlation in neural population recordings is related to that of their spatial (or, population) correlation, and whether this relationship depends on the fraction of the system observed, by comparing the decay exponents of PSD and ES in subsets of the data at various sizes. We examine this in two simulated systems—"populations" of independent colored noise, and the Ising model—as well as in Neuropixels data from 3 mice. Comparing the dynamics in neural activity with those of established power law models found in other domains, we aim to explain the extent to which the critical systems interpretation of neural computation is tractable. First, we find that in colored noise simulations, the decay exponents of the ES and PSD

are closely related, despite being independently generated processes. Next, we simulate the Ising model at various temperatures, repeat the same analysis, and observe a lack of consistent correlation between the two exponents at a given temperature or subset size. Finally, in population spiking data recorded across the mouse brain, we find that power law exponents in the PSD and ES were correlated in some brain regions, such as V1, but were again inconsistent across subset sizes and mice. In summary, we attempt to integrate recent findings of high-dimensional (i.e., power law) geometry in neural manifolds into the theoretical framework of complex systems at criticality, and find inconsistent relationships between temporal and spatial power law scaling at different system sizes.

Disclosures: B. Barry: None. **B. Voytek:** None. **R. Gao:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.26

Topic: I.06. Computation, Modeling, and Simulation

Support: NDSEG Fellowship
arie Sklodowska-Curie Individual Fellowship Grant (839179)
NIH R01-EB02695
DARPA's VIP (Super-HD Project) and AIE (HyDDENN Project)
AFOSR FA9550-19-1-024
Intel THWAI program

Title: An Algebraic Theory of Neural Population Codes Enabling Computation on Variables and Functions

Authors: *C. J. KYMN[1], E. P. FRADY[1,3], D. KLEYKO[1,4], B. A. OLSHAUSEN[1,2], F. T. SOMMER[1,3];
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Abstract: A central problem for computational neuroscience is how neural populations can compute over variables and functions. Such encodings are required for not only sensory data but also to form a 'cognitive map' of an animal's environment. How can these representations be constructed, operated over, and retrieved in an efficient yet robust manner?
Inspired by models using distributed population codes for symbolic reasoning, known as Vector Symbolic Architectures [1,2], we propose *Vector Function Architectures* (VFA), an algebraic theory of population coding for variables and functions. In VFA, *vectors* correspond to encodings of continuous variables or functions over continuous variables, *algebraic operations* correspond to manipulations over variables or functions, and *inner products* reflect the similarity

of the encoded objects. Unlike many current neural network models, VFA provides a fully transparent method for computing with distributed representations. Thus, it provides a normative framework for interpreting how the brain represents functions or associations between variables. To demonstrate how our framework uncovers structure in neural activity patterns, we construct a model of hippocampus (HC) and entorhinal cortex (EC). First, we define a *sparse* VFA, in which sparse vectors (with few non-zero elements) are mapped onto sparse neural circuits (with few neurons firing at any time). The complex values of the sparse vectors are mapped onto spike timing of neurons. We show how neural circuits can implement the algebraic operations and inner product comparisons required for a VFA. Second, we analyze the individual units in our model to compare their coding properties to neurophysiological findings. We find that the model's single unit responses mimic those observed experimentally in HC/EC. Specifically, we show that our model can replicate phase precession phenomena, and it leads to useful single-cell representations of reward functions over environments. Finally, we compare our model to other models of HC/EC, showing that it provides a bridge between observed single cell phenomena and population coding approaches such as Representational Similarity Analysis [3].
References: [1] Gayler (2004) *arXiv*, [2] Kanerva (2009) *Cognitive Computation*, [3] Kriegeskorte (2008) *Frontiers in Systems Neuroscience*

Disclosures: **C.J. Kymn:** None. **E.P. Frady:** None. **D. Kleyko:** None. **B.A. Olshausen:** None. **F.T. Sommer:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.27

Topic: I.06. Computation, Modeling, and Simulation

Title: A neurophysiological data driven investigation of linear versus nonlinear patterns of neuronal dynamics with applications to data representation and modeling brain functions

Authors: A. ARDALAN[1], ***A. ASSADI**[2];
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Abstract: Advances in neuronal data acquisition are accompanied with progress in powerful computational modeling and geometric insights into dynamics in neuronal circuits and higher structures. Consider the following: 1) What are the main assumptions for validity of a geometrical view of the brain? 2) What are the choices for the geometric models of the brain activity, e.g., alternatives to Euclidean spaces? 3) What is the neurophysiological evidence to support the choices above.Representation of data in Euclidean space or as Riemannian manifolds reflects neuroscientists' preference for mathematical tools to distinguish patterns of dynamics as linear or nonlinear, and to extract nonlinear features as proxies to diverse dynamic phenomena. We have taken a neurophysiological-data-driven approach, without prior preference for the

choice of geometry or any assumptions. This approach is akin to discovering structure in observation in physics and cosmology, which continues to new insights. In our preliminary computations of several data sets (e.g. D. Tank et al) we are led to a broader view of this dichotomy. This research reports the following results:a) Design of algorithms to decide "regularity" versus "singularity" in portions of data sets that we call "topologically local".b) Design of algorithms for hierarchical organization of topologically local data sets and design of a relational database.c) Design of unsupervised statistical learning architectures to classify topologically local data sets in two classes. The first class provides topologically local models for REGULAR structures, while members of the second class are models for deviation from regularity (SINGULAR). Members of both classes are assigned biologically relevant phenotypic labels. By design, neurophysiology support these models. Despite very large initial number of topologically local subsets, the number of members in REGULAR are much smaller, robust subject to perturbation of temporal duration, and functional vicinity of neuronal circuits. SINGULAR members represent deviation from regularity, a much smaller number of most informative representatives, not necessarily robust to perturbations. Global geometric models for REGULAR follow modified versions of topological "local-to-global". SINGULAR members are useful as local models to distinguish and analyze separately. In a typical data set, SINGULAR representatives occur less often than the REGULAR subsets, thus potential for broad applicability and computational feasibility in larger data.Conclusion - A neurophysiological local geometric model based on REGULAR vs. SINGULAR is a viable alternative to Linear vs. Nonlinear.

Disclosures: **A. Ardalan:** None. **A. Assadi:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.28

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 1R01DC017695

Title: The computational benefitsof divisive normalization - insights from olfaction

Authors: *Y. SHEN, A. BANERJEE, D. ALBEANU, S. NAVLAKHA;
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Divisive normalization is a canonical computation used by many sensory systems to keep neural firing rates in informative regimes, despite wide changes in stimulus intensity levels. This process has been shown to maintain invariant representations (e.g., contrast invariance in the visual system, concentration invariance in the olfactory system) and to improve discrimination between similar stimuli by decorrelating output neural representations. Here, we started from first principles and derived three properties of divisive normalization: 1) the mean

response of the population is normalized to be independent of the intensity level; 2) single second-order neuron responses after normalization are non-monotonic as stimulus intensity increases, despite first-order (sensory) neurons being monotonic; and 3) stimulus intensity level can be decoded from population responses of the second-order neurons, despite mean normalization. We also describe sufficient conditions for how monotonic responses of first-order neurons can be transformed into non-monotonic responses of second-order neurons by divisive normalization, and not by alternative operations, such as gain control and subtractive normalization. Finally, we re-analyzed olfactory response data of second-order neurons in mice, zebra fish, and locusts, and find striking evidence of all three properties across species. Overall, our results highlight an evolutionarily conserved principle of sensory coding and paint a clearer picture of how divisive normalization transforms neural representations.

Disclosures: Y. Shen: None. **A. Banerjee:** None. **D. Albeanu:** None. **S. Navlakha:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.29

Topic: I.06. Computation, Modeling, and Simulation

Support: DFG JA 1999/5-1

Title: Neuronal implementation of representational geometry in prefrontal working memory

Authors: *X.-X. LIN[1,2], A. NIEDER[3], S. N. JACOB[1];
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Abstract: It is nowadays considered state-of-the-art in systems neuroscience to explain behavior in terms of computation over representations at the level of neuronal populations, rather than in terms of representations at the level of individual neurons comprising such neuron populations. This modern approach maps activity into spatial reference frames and thus emphasizes the geometrical structure of population activity. Importantly, a given geometry can be implemented in different ways, that is by different distributions of individual neurons' contributions. Implementations are not arbitrary, but subject to biological constraints and imply different potential readout mechanisms. The relationship between population-level representational geometry and its implementation is rarely addressed. Considering that a downstream readout neuron can only access a very small proportion of upstream neurons, we hypothesized that the representational geometry can be expressed by components that have sparse contributions from individual neurons. Supporting our hypothesis using single unit data recorded from the lateral prefrontal cortex (PFC) of monkeys performing a working memory task, we found three sparse components representing task-relevant information that were sequentially activated and matched

the structure of the task performed by the animals. To determine whether different implementations were equally likely in the recurrently connected PFC, we trained a recurrent neural network (RNN) model to reproduce the activity of the population of recorded PFC neurons. The model's accuracy dropped significantly when the sequential sparse implementation found in the data was destroyed. This study provides the perspective of neuronal implementation as an important complement to representational geometry, which helps to bridge the gap between single-neuron activity and population-level dynamics.

Disclosures: **X. Lin:** None. **A. Nieder:** None. **S.N. Jacob:** None.

Poster

749. Network Computation IV

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 749.30

Topic: I.06. Computation, Modeling, and Simulation

Support: Howard Hughes Medical Institute (HHMI)-Wellcome international Scholar Awards from the Wellcome Trust (208468/Z/17/Z)
Creative-Pioneering Researchers Program through Seoul National University (SNU)
Basic Science Research Program through the National Research Foundation of Korea (NRF)(2020R1A2C20072B5)
Samsung Science and Technology Foundation [SSTF-BA1602-11]

Title: Aging Lévy walk with model for Arc and β-actin mRNA transport in neurons

Authors: ***H. AHN**[1], X. DURANG[2], J. SHIM[3], G. PARK[3], J.-H. JEON[2], H. PARK[1]; [1]Dept. of Electrical and Computer Engin., Univ. of Minnesota, Minneapolis, MN; [2]Dept. of Physics, Pohang Univ. of Sci. and Technol., Pohang, Korea, Republic of; [3]Dept. of Physics and Astronomy, Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Localization of mRNA in dendrites is an essential mechanism for regulating gene expression involved in long-term memory formation. mRNA binds to RNA-binding proteins (RBPs) to form messenger ribonucleoprotein (mRNP) complexes, which are transported by motor proteins along microtubules to their target synapses. However, the dynamics by which mRNPs find their target locations in the dendrite have not been well understood. Here, we investigated the motion of endogenous β-actin and Arc mRNPs in living hippocampal neurons using the MS2 and PP7 stem-loop systems, respectively. We analyzed the statistical properties of each type of mRNP movement and found that an aging Lévy walk model could explain the transport process of both β-actin and Arc mRNPs. In dendrites, mRNP movement exhibited two distinct phases: the motor-driven ballistic run and static localization. Our model reproduced the experimentally measured dynamic characteristics of both mRNPs in proximal dendrites. The critical difference between β-actin and Arc mRNPs was the aging time, defined as the elapsed

time from the transport initiation to the measurement initiation. The longer aging time of β-actin mRNP (~100 s) compared to that of Arc mRNP (~30 s) reflects the longer half-life of constitutively expressed β-actin mRNP. This study establishes a robust theoretical model for mRNP transport, which offers insight into the general target search mechanism of mRNPs in neurons.

Disclosures: H. Ahn: None. **X. Durang:** None. **J. Shim:** None. **G. Park:** None. **J. Jeon:** None. **H. Park:** None.

Poster

750. Experimental Tools: Real-time Analysis and Closed Loop Experiments

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 750.01

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant EY014924
NIH Grant NS116623

Title: Real-time Spike-sorting of Neuropixel Neuronal Recordings for Neurofeedback Experiments

Authors: *S. MURALIDHARAN[1], L. E. ORTS[1,2], B. SIMONS[5], S. WEINGÄRTNER[5], R. XIA[3], M. PANICHELLO[4], K. V. SHENOY[6,1], T. MOORE[7];
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Abstract: A major challenge of studying cognitive processes (e.g. attention and decision-making) is that cognitive processes rely on internal neural states that lack direct behavioral correlates and must therefore be decoded directly from neural activity(e.g., [1]). Efficient study of temporal dynamics of cognitive processes via closed-loop experiments requires real-time decoding. Pinpointing the contributions of different cell-types to these cognitive processes requires isolating individual neuron spike activity. Employing a recently developed real-time spike-detection method [2] and newly available high-density, high-channel count, silicon probes (Neuropixels probes, IMEC, Inc.) specifically designed for use in nonhuman primates (NHPs), we have designed a system that decodes neural states in real time using single-neuron spiking activity from 100s of neurons. These decoded neural states can be used with behaving NHPs to dynamically adjust task parameters (e.g. stimuli), allowing for real-time, closed-loop experiments.
Our approach involves a two step process. First, during an initial recording period, waveform templates (~300) are determined through Kilosort 3 [3]. Subsequently, a compressed sensing spike detection method, optimized via CUDA programming, uses those templates to compute the

spiking activity of isolated neurons. Based on the spiking activity, an SVM-based decoder determines the neural state which is then used to modify or update behavioral conditions (e.g., adjust a visual stimulus display viewed by the NHP). During decoding of online sorted spiking activity, the stability of spiking data is continuously evaluated via continuous measures of neuronal inter-spike-intervals, spiking autocorrelation, channel voltage characteristics, and pairwise cross-correlations. Current performance demonstrates real-time spike sorting and decoding of 100 channels in real time (~300 neurons). Neuronal data binned into 50ms intervals are fully processed in an average of 38ms.

Disclosures: S. Muralidharan: None. **L.E. Orts:** None. **B. Simons:** None. **S. Weingärtner:** None. **R. Xia:** None. **M. Panichello:** None. **K.V. Shenoy:** F. Consulting Fees (e.g., advisory boards); MIND-X Inc., Inscopix Inc., Heal Inc., CTRL- Labs, Reality Labs, Neuralink. **T. Moore:** None.

Poster

750. Experimental Tools: Real-time Analysis and Closed Loop Experiments

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 750.02

Topic: I.07. Data Analysis and Statistics

Support: GE-2-2-023A (REXO)
IT-2-2-023 (VAFES)

Title: Adaptive SpikeDeep-Classifier: Self-organizing and self-supervised machine learning algorithm for online spike sorting

Authors: *M. SAIF-UR-REHMAN[1], O. ALI[3], C. KLAES[3], I. IOSSIFIDIS[2];
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Abstract: ***Objective.*** Invasive brain-computer interface (BCI) research is progressing towards the realization of the motor skills rehabilitation of severely disabled patients in the real world. The size of invasively implanted microelectrode arrays and the selection of an efficient online spike sorting algorithm are two key factors that play pivotal roles in the successful decoding of the user intentions. Recently, a very small but dense microelectrode array with 3072 channels was developed and implanted to decode the intention of the user. The neural data recorded with microelectrode arrays is time-varying and contaminated with non-stationary noise. Unfortunately, currently available state-of-the-art spike sorting algorithms are static in nature and are incapable to handle the massively increasing amount of data resulting from the dense microelectrode arrays, which makes the spike sorting one of the fragile components of the online BCI decoding framework. The process of spike sorting includes the selection of channels that record the spike activity (SA) and determines the SA of different sources (neurons), on selected

channels individually. ***Approach.*** This study proposed an adaptive, self-organized, and online spike sorting algorithm. Our algorithm uses SpikeDeeptector for the channel selection, an adaptive background activity rejector (Ada-BAR) for discarding the background events, and an adaptive spike classifier (Ada-Spike classifier) for classifying the SA of different neural units. By concatenating SpikeDeeptector, Ada-BAR and Ada-Spike classifier, the process of spike sorting is accomplished. ***Results.*** The proposed algorithm is evaluated on three different categories of data: a human dataset recorded in our lab, a publicly available non-human primate (NHP) dataset, and a publicly available simulated dataset to avoid subjective biases and labeling errors. The proposed algorithm achieved 93% average classification accuracy in the preliminary analysis. ***Significance.*** To the best of our knowledge, the proposed algorithm is the first spike sorting algorithm that automatically learns the abrupt changes in the distribution of noise and SA. The proposed algorithm is completely artificial neural network based, which makes it an ideal candidate for its hardware implementation on neuromorphic chips that is also suitable for wearable invasive BCI.

Disclosures: **M. Saif-ur-Rehman:** None. **O. Ali:** None. **C. Klaes:** None. **I. Iossifidis:** None.

Poster

750. Experimental Tools: Real-time Analysis and Closed Loop Experiments

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 750.03

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant NINDS U19NS107464

Title: Real Time Analysis of Neuronal Populations

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[1]Univ. of Maryland Col. Park, College Park, MD; [2]Fraunhofer Inst. USA, Cary, NC; [3]Univ. of Maryland, College Park, MD

Abstract: Two-photon (2P) calcium imaging allows for the activity readout of large populations of neurons at single cell resolution, and holographic optogenetics makes the population accessible for targeted stimulation. However, significant pre- and post-processing is required to interpret signals from large 2P imaging datasets, that leads to the selection of stimulation targets based only on rudimentary qualitative criteria. We have developed NeuroART (Neuronal Analysis in Real Time), a software that accesses microscope data streams to provide real-time readout of neuronal activity, downstream analysis, and photostimulation during image acquisition. NeuroART has been tested on a range of different imaging systems, imaging software and image formats. The software package includes automatic neuronal cell identification routines (e.g., CaImAn) to facilitate real time neuronal activity analysis. Utilizing NeuroART, experimenters gain knowledge of the data quality in real time and can identify neurons of interest for targeted photostimulation based on quantitative analysis of the

ΔF/F traces of each neuron. As a first demonstration of capabilities, NeuroART employs a pairwise correlation-based analysis to construct functional networks and identify the most population correlated neurons in the field of view. The software is linked to a fast switching Spatial Light Modulator (Boulder Nonlinear Systems) that enables fast holographic optogenetic stimulation. The downstream analysis within the real-time loop runs rapidly enough (at 30Hz for 250 neurons) to be computed at the graphical user interface (GUI) update rate (1 Hz) on a Windows laptop.

Disclosures: **D. de Zoysa:** None. **Z. Bowen:** None. **W. Losert:** None.

Poster

750. Experimental Tools: Real-time Analysis and Closed Loop Experiments

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 750.04

Topic: I.06. Computation, Modeling, and Simulation

Support: NINDS U24NS109043

Title: The Open Ephys GUI: A collaboratively developed platform for high-channel-count electrophysiology data acquisition

Authors: ***P. KULIK**[1], A. DOSHI[1], A. CUEVAS LÓPEZ[2], J. VOIGTS[3], J. H. SIEGLE[1]; [1]Allen Inst., Seattle, WA; [2]Open Ephys Production Site, Lisbon, Portugal; [3]HHMI Janelia Res. Campus, Ashburn, VA

Abstract: The Open Ephys GUI (https://open-ephys.org/gui) is an open-source, cross-platform application for acquiring data from multichannel implanted electrodes. The GUI was designed from the ground up with collaborative development in mind. Modules for real-time analysis and visualization are encapsulated within plugins that adhere to a standardized interface, providing a straightforward way for users to write their own extensions without needing to understand the entire code base. To streamline the distribution of plugins developed by scientists, we have created a centralized repository for pre-compiled plugins, which can be downloaded and installed via a single click. We have now collected, polished, and documented over a dozen community-developed plugins that expand the capabilities of the software. Priority has been given to plugins that can be used with Neuropixels probes, a new type of silicon probe capable of detecting single unit activity across dozens of cortical and subcortical structures simultaneously. Providing free, user-friendly, and performant software for recording spiking activity makes extracellular electrophysiology experiments more accessible to labs around the globe.

Disclosures: **P. Kulik:** None. **A. Doshi:** None. **A. Cuevas López:** A. Employment/Salary (full or part-time):; Open Ephys Production Site. **J. Voigts:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Open Ephys, Incorporated. **J.H. Siegle:** E. Ownership Interest (stock, stock options,

royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Open Ephys, Incorporated.

Poster

750. Experimental Tools: Real-time Analysis and Closed Loop Experiments

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 750.05

Topic: I.06. Computation, Modeling, and Simulation

Support: CRCNS Grant R01NS115327

Title: Closed-loop identifiability in neural circuits

Authors: *A. WILLATS[1], M. O'SHAUGNESSY[2], C. ROZELL[2];
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Abstract: The necessity of using experimental interventions to infer causal interactions has long been understood in neuroscience. Recent work has highlighted the limitations of passive observation and single-site lesion studies in accurately recovering causal circuit structure. The advent of optogenetics has facilitated increasingly precise forms of intervention, including closed-loop control that may help reduce confounding influences. However, it is not yet clear how best to apply closed-loop control to leverage this increased inferential power.
In this project, we use tools from causal inference, control theory, and neuroscience to show when and how closed-loop interventions can more effectively reveal causal relationships. We also examine the performance of standard network inference procedures in simulated Gaussian networks under passive, open-loop and closed-loop conditions. We demonstrate a unique capacity of feedback control to distinguish competing circuit hypotheses by disrupting connections that would otherwise result in equivalent patterns of correlation. We also demonstrate the increased range of correlations achievable under closed-loop intervention, leading to increased signal-to-noise ratio for connection-related measures. Our results build toward a practical framework to improve design of neuroscience experiments to answer causal questions about neural circuits.

Disclosures: **A. Willats:** None. **M. O'Shaugnessy:** None. **C. Rozell:** None.

Poster

750. Experimental Tools: Real-time Analysis and Closed Loop Experiments

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 750.06

Topic: I.06. Computation, Modeling, and Simulation

Support: NINDS Grant R01NS115327
NIBIB T32EB025816

Title: Bridging model and experiment with CLEOsim: a testbed for in-silico prototyping of complex neuroscience experiments

Authors: K. JOHNSEN[1], ***N. A. CRUZADO**[2], A. WILLATS[1], C. ROZELL[2];
[1]Biomed. Engin., Georgia Inst. of Technol. & Emory Univ., Atlanta, GA; [2]Electrical and Computer Engin., Georgia Inst. of Technol., Atlanta, GA

Abstract: Recent advances in neuroscience methods enable exciting new kinds of experiments. One of these is closed-loop optogenetic control, which combines simultaneous photostimulation and electrode recording to precisely control mesoscale neural activity on the order of milliseconds. Experiments such as these often require significant effort and resources to implement, which can slow development, limit opportunities to optimize experimental parameters, and pose a barrier to adoption. A potential solution is simulating an experiment—creating an in-silico prototype or proof-of-concept—which can demonstrate feasibility or reveal promising experiment designs for a fraction of the cost. Moreover, a virtual experiment with inputs and outputs resembling data collected in the lab allows for the realism of a spiking neural network model to be more directly evaluated. However, a convenient tool does not exist integrating optogenetics, electrode recording, and flexible closed-loop processing with neural population simulations. Thus, we have developed and now present Closed Loop, Electrophysiology, and Optogenetics Simulator (CLEOSim)—a Python package built around the Brian 2 simulator enabling closed-loop control as well as the injection of recording and stimulation devices into spiking neural network simulations.

These three components are designed to bring a degree of experimental realism to simulations. The closed-loop processor updates stimulator devices in response to measurements after a specified delay reflecting compute latency. The electrode module can detect spikes probabilistically with distance or read out a spike-based LFP proxy at arbitrary locations in the simulation, allowing the simulation of recording techniques such as a shank-style array. Finally, the optogenetics module simulates optic fiber light propagation and Markov state opsin dynamics for easily injecting photocurrents into user-provided model neurons. Beyond closed-loop intervention, CLEOSim is also useful for simulating electrode recording and photostimulation in open-loop experiments.

We demonstrate CLEOSim's utility in establishing proof-of-concept in two closed-loop optogenetics case studies. In the first, we inhibit a sparse traveling wave upon detection in a somatosensory cortex model, and in the second, we clamp firing rates to manipulate plasticity in a visual cortex model.

The package is accompanied by detailed online documentation including user-friendly tutorials, found at the links below:
Documentation: https://cleosim.readthedocs.io
Code Repository: https://github.com/Sensory-Information-Processing-Lab/cleosim

Disclosures: K. Johnsen: None. **N.A. Cruzado:** None. **A. Willats:** None. **C. Rozell:** None.

Poster

750. Experimental Tools: Real-time Analysis and Closed Loop Experiments

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 750.07

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH R01NS115327
NIH T32EB025816

Title: CLOCTools: A library of tools for closed-loop neuroscience

Authors: A. A. WILLATS[1], M. F. BOLUS[1], ***K. A. JOHNSEN**[1], G. B. STANLEY[1], C. J. ROZELL[2];
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Abstract: Closed-loop control enables engineers and scientists to adapt stimulation based on measured activity to drive a system towards a target. In neuroscience, the ability such closed-loop experiments to reduce variability and decouple connected systems has proven to be valuable. However, despite the promise of enabling stronger inference from experimental measurements, it remains challenging to implement fast, real-time feedback control. To address this obstacle, we are releasing CLOCTools, an open-source software collection designed to accelerate the use of closed-loop optogenetic control (CLOC).
CLOCTools is designed to assist neuroscientists in online estimation, decoding, and control by providing fast, cross-platform C++ libraries implementing core algorithms. The first of these is ldsCtrlEst, which features linear dynamical systems with Gaussian or Poisson observation models, as well as adaptive or switching control options and system identification functions. The second is hmm, implementing system identification and decoding algorithms for Hidden Markov Models (HMMs) with the intent of informing the state-switching control capability of ldsCtrlEst. Wrapper modules are provided for implementing the above methods in the Real-Time eXperimental Interface (RTXI) system in tandem with Tucker-Davis Technologies (TDT) electrophysiology data acquisition. This software suite has been demonstrated to perform well on real-time hardware with sub-millisecond compute times and low jitter.
Furthermore, the collection contains support tools for profiling new algorithms, as well as multi-language compatibility in the form of Python and MATLAB interfaces. An example pipeline for moving from a MATLAB prototype to a high-performance C++ implementation is also included to serve as a guide for future development of fast closed-loop methods.
CLOCTools thus provides a unified set of user-friendly open-source tools for developing and deploying powerful new closed-loop stimulation approaches for deciphering the function of complex neural circuits.
Key papers:
Bolus, M. F., Willats, A. A., Rozell, C. J., & Stanley, G. B. (2021). State-space optimal feedback control of optogenetically driven neural activity. Journal of neural engineering, 18(3), 036006.
Bolus, M. F., Willats, A. A., Whitmire, C. J., Rozell, C. J., & Stanley, G. B. (2018). Design strategies for dynamic closed-loop optogenetic neurocontrol in vivo. Journal of neural

engineering, 15(2), 026011.
Software links:
CLOCTools documentation: https://cloctools.github.io/
CLOCTools repositories: https://github.com/CLOCTools

Disclosures: **A.A. Willats:** A. Employment/Salary (full or part-time):; Medtronic. **M.F. Bolus:** None. **K.A. Johnsen:** None. **G.B. Stanley:** None. **C.J. Rozell:** None.

Poster

750. Experimental Tools: Real-time Analysis and Closed Loop Experiments

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 750.08

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH 1OT2OD030535-01

Title: Short-term hemodynamic effects of atrial fibrillation in a closed-loop human cardiac-baroreflex system

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[2]Chem. & Biomolecular Engin., [1]Lehigh Univ., Bethlehem, PA; [3]Chem. & Biol. Engin., Univ. of Delaware, Newark, DE; [4]Emory Univ., Alpharetta, GA; [5]Thomas Jefferson Univ., Philadelphia, PA

Abstract: Background: Atrial fibrillation (AF) is the most common type of arrhythmia and remains the leading cardiac cause of stroke. Heart palpitations are one of the well-known consequences of AF and result from the conduction of errant electrical activity from the sinoatrial node. However, the impact of AF on other hemodynamic variables is not as well established since other cardiac comorbidities (hypertension, heart failure) often prevent a direct, in-vivo evaluation. Our goal is to elucidate the short-term impact of AF on hemodynamic quantities under the influence of central autonomic regulation.
Methods: Our starting point is the closed-loop model of the human baroreflex from Park et al. (2020). The model features functionally distinct neuroanatomical sub-groups in the modulation of parasympathetic activity to investigate the role of neuronal remodeling under systolic heart failure conditions. We extend this delay differential algebraic equation (DAE) system to simulate AF conditions by making three modifications. Previously defined as constant, we recast the sinoatrial contribution to instantaneous heart period as a stochastic variable with an exponentially modified Gaussian distribution to describe the typical “irregularly irregular” AF inter-beat (R-R) interval. The R-R profile is validated with an AF detection algorithm based on a plot of successive R-R intervals versus successive changes in R-R intervals. Secondly, to quantify the loss of atrial systole associated with AF, we augment the description of the left atrium with a time-varying elastance function such that under healthy conditions, it successively operates as a

reservoir, conduit, and pump during a heart cycle. AF has also been linked with the suppression of cardiovascular autonomic function that manifests as a reduction in baroreflex sensitivity. Thus, our third modification involves the development of a valid baroreflex sensitivity metric to quantify the extent of impairment.
Result: Our simulations indicate that the impact of standalone AF on systolic and diastolic pressures trends from normotensive to hypotensive as the degree of impairment to the baroreflex increases. Such insights can help to improve the assessment of treatment strategies and the specificity of AF detection algorithms.
Reference: James H Park, Jonathan Gorky, Babatunde Ogunnaike, Rajanikanth Vadigepalli, and James S Schwaber. “Investigating the effects of brainstem neuronal adaptation on cardiovascular homeostasis.” Frontiers in Neuroscience, 14:470, 2020.

Disclosures: O. Adeodu: None. **M. Gee:** None. **B. Mahmoudi:** None. **R. Vadigepalli:** None. **M.V. Kothare:** None.

Poster

750. Experimental Tools: Real-time Analysis and Closed Loop Experiments

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 750.09

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Award 1 R03 HD099426-01A1
FAPESP Grant 2018/04964-8

Title: A subject-specific forward and inverse dynamics models for the real-time simulations of the human leg in swing

Authors: *S. BAHDASARIANTS[1], O. BACCA[2], J. A. BARELA[3], A. M. F. BARELA[2], S. YAKOVENKO[1];
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Abstract: Neural system predicts and executes complex motion of body segments actuated by the coordinated action of muscles. The closed-loop control system is thought to embed limb dynamics to overcome transmission delays and generate appropriate commands. When a stroke or other traumatic injury disrupts neural processing, the impeded behavior has both kinematic and kinetic attributes that require interpretation through biomechanical models because the musculoskeletal system plays an important role in the control of movement and posture. Any assistive technology designed to overcome movement disabilities requires real-time processing when computing dynamic models. In this study, we have developed a simulation method that relies on the *inverse and forward models* of lower-limbs with 17 rotational degrees of freedom (DOF)—describing hip, knee, ankle, and standing foot contact—and optimized to generate an

accurate description of motion at reduced simulation steps (400 Hz and above). This was achieved by the analysis of *optimal stabilizing joint impedance* to resist numerical noise, promoting stable simulations at low sampling rates. The addition of linear viscoelastic elements defined as neutral in the middle of the DOF range of motion provided an accurate reconstruction of kinematic (err < 2% peak-to-peak) and kinetic (err < 5% peak-to-peak) signals during gait. This model can be further used to analyze pathomechanics of the post-traumatic gait. Combined with novel muscle recording-stimulation techniques, this development can improve the existing rehabilitation strategies, equipping patients with the real-time human-in-the-loop system to improve limb control.

Disclosures: S. Bahdasariants: None. **O. Bacca:** None. **J.A. Barela:** None. **A.M.F. Barela:** None. **S. Yakovenko:** None.

Poster

750. Experimental Tools: Real-time Analysis and Closed Loop Experiments

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 750.10

Topic: I.06. Computation, Modeling, and Simulation

Support: Brain Initiative Grant R34-EB026951- 01A1
Swartz Foundation Postdoctoral Fellowship for Theory in Neuroscience
Whitehall Foundation

Title: Adaptive Bayesian optimization of population-wide neural responses in real time

Authors: *A. DRAELOS, M. D. LORING, M. NIKITCHENKO, E. A. NAUMANN, J. M. PEARSON;
Duke Univ., Durham, NC

Abstract: A common task in neuroscience is to characterize neurons' responses to different types of external stimuli as a way of understanding neural circuitry and computation. Frequently, our goal is to identify stimuli that produce the strongest responses per neuron or neural population. For a typical *in vivo* experiment, a researcher would select a set of stimuli to present to the organism, record the neural responses during the stimulation period, and analyze the results after the experiment is over. The number of stimuli one can present to a given neural population in a single experiment is inherently limited. If we want to search a larger stimulus space using the same fixed stimulus budget, then finding the peak neural responses becomes increasingly unlikely, as our measurements more sparsely sample stimulus space.
We propose a method that adaptively selects stimuli in real time, while the experiment is ongoing, to better utilize our limited number of measurements even in large stimulus spaces. We make use of streaming neural data analyses to provide current estimates of the neural tuning, coupled with a Bayesian optimization approach to search for projected optimal responses. As a result, we can adaptively determine the next best stimulus to present to the organism. We apply

this optimization method to the problem of finding peak neural responses to visual stimuli in larval zebrafish using two-photon calcium imaging. The visual stimuli are presented to the zebrafish from below as moving square gratings, with different orientations shown to each eye. While there are more than 500 unique stimuli we might display, we find that our approach allows us to determine individual peak neural responses for hundreds of neurons using only 50-60 presented gratings (15 minutes of experiment time). In simulation, we also demonstrate the considerable speed-ups this method offers when exploring stimulus spaces of 5-10 dimensions and tens of thousands of possible unique stimuli. Our method is highly generalizable and can enable fast and efficient closed-loop stimulus optimizations across many different kinds of stimuli or model organisms.

Disclosures: A. Draelos: None. **M.D. Loring:** None. **M. Nikitchenko:** None. **E.A. Naumann:** None. **J.M. Pearson:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.01

Topic: I.07. Data Analysis and Statistics

Support: Stanford University Wu Tsai Neurosciences Institute
Stanford Bio-X Seed Grant Award IIP9-104

Title: A minimally disruptive acquisition framework to build repositories of high-resolution, human intracranial electroencephalography and its application to an information theoretic seizure detection algorithm

Authors: *L. YAMADA[1], T. OSKOTSKY[2,3], P. NUYUJUKIAN[2,3,1,4,5];
[1]Electrical Engin., [2]Bioengineering, [3]Neurosurg., [4]Wu Tsai Neurosciences Inst., [5]Bio-X Inst., Stanford Univ., Stanford, CA

Abstract: Intracranial electroencephalography (iEEG) studies from people with refractory epilepsy have largely advanced human neuroscience research. Common clinical practice acquires data at a sampling rate below 2 kHz, which is sufficient for manual review of EEGs; however, the development of robust quantitative EEG (qEEG) methods for applications like seizure detection may require higher sampling rate. A multielectrode, high-resolution iEEG repository may enable identification of EEG features (e.g., high frequency oscillations and synchronicity) that are not traditionally observed and allow researchers to reliably test qEEG methods across numerous datasets. In this work, we introduce an acquisition infrastructure deployed in the adult and pediatric Stanford hospitals that facilitates the routine collection of high-resolution iEEG data with minimal research hardware presence. The addition of a pocket-sized router in the patient room enables 10 kHz research-quality iEEG data of up to 256 electrodes to be simultaneously acquired with the clinical data and securely routed from the patient room to the

hospital server room via an encrypted GRE tunnel. Since September 2017, all eligible patients undergoing iEEG clinical evaluations at both Stanford hospitals were recruited, resulting in over 250 TB (800+ days) of neuroelectrophysiology from 150+ participants, spanning diverse age, gender, and ethnicity. Using this higher quality data repository, we proposed and evaluated the seizure detection performance of the inverse compression ratio (ICR), an information theoretic technique that leverages changes in information content due to the oscillatory and synchronous nature of epileptiform EEG activity. Across 30 participant datasets (15 adults and 15 children, 17 males and 13 females, 240+ total seizures), ICR achieved a F1 score of 0.80, outperforming conventional qEEG methods and showing promise as a qEEG method for seizure detection. It demonstrated the efficacy of multidimensional estimation techniques like ICR and may hold potential usefulness in other domains of biomedical signal processing. To the best of our knowledge, this is the first clinical study that analyzed intracortical EEG for quantitative methods at scale. Our scalable, minimally disruptive iEEG acquisition framework only requires a single additional Ethernet connection to the clinical infrastructure and serves as a potential solution towards building comprehensive data repositories with consistent, higher fidelity specifications to advance the translation of qEEG methods into clinical practice.

Disclosures: L. Yamada: None. **T. Oskotsky:** None. **P. Nuyujukian:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.02

Topic: I.07. Data Analysis and Statistics

Support: NielsenIQ

Title: Longitudinal analysis of P300 and alpha activity in a large population utilizing home-based EEG

Authors: *K. ANDERSON[1], K. KASINATHAN[1], A. SHESTYUK[1], G. VENKATRAMAN[1], K. PERRY[1], V. KARAPOONDINOTT[1], N. KARNAM[1], M. LEVINSON[1], M. SEIGLIE[1], R. T. KNIGHT[2,3];
[1]BASES Product Leadership, NielsenIQ, Berkeley, CA; [2]Helen Wills Neurosci. Inst., [3]Dept. of Psychology, Univ. of California, Berkeley, CA

Abstract: Two of the most robust and well-studied signals which can be measured in the human EEG are the P300 ERP component and the occipital alpha oscillation. The P300 is most commonly elicited when a salient or unexpected stimulus is perceived. Modulation of occipital alpha activity is commonly noted over posterior contacts when the participant closes their eyes as well as by changes in attention. Both signals are affected by various cognitive states and can be used as biomarkers reflecting these states. These signals have found uses outside of research, partly due to their ubiquity and strong signal to noise ratio. Quantifying and understanding the

variability of both P300 and alpha across a large population as well as their consistency within individuals may help to further their potential uses.
In this study, participants recorded EEG at home using 32-channel Emotiv Flex EEG headsets (256 Hz sampling). Participants performed a standard visual oddball task, as well as a 30 second eyes-closed segment. Following each recording, the data were uploaded to the secure cloud for further analysis. P300 metrics (amplitude, latency, waveform shape) and Alpha metrics (amplitude, center frequency, width) were estimated utilizing custom Python scripts and verified by comparing with manual estimation.
As expected, we observe a significant variability in P300 latency, amplitude, and waveform shape across different participants. Within participants, we see a generally strong consistency in these measures. A similar pattern (high between-participant/ low within-participant variability) is seen with the amplitude and frequency of eyes-closed occipital alpha oscillations. These patterns are consistently observed over long time frames. Excessive within-participant variability in one or many sessions can be indicative of abnormal conditions during the recording.

Disclosures: **K. Anderson:** A. Employment/Salary (full or part-time):; Nielsen IQ. **K. Kasinathan:** A. Employment/Salary (full or part-time):; Nielsen IQ. **A. Shestyuk:** A. Employment/Salary (full or part-time):; Nielsen IQ. **G. Venkatraman:** A. Employment/Salary (full or part-time):; Nielsen IQ. **K. Perry:** A. Employment/Salary (full or part-time):; Nielsen IQ. **V. Karapoondinott:** A. Employment/Salary (full or part-time):; Nielsen IQ. **N. Karnam:** A. Employment/Salary (full or part-time):; Nielsen IQ. **M. Levinson:** A. Employment/Salary (full or part-time):; Nielsen IQ. **M. Seiglie:** A. Employment/Salary (full or part-time):; Nielsen IQ. **R.T. Knight:** F. Consulting Fees (e.g., advisory boards); NielsenIQ.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.03

Topic: I.07. Data Analysis and Statistics

Support: NielsenIQ

Title: Democratizing neuroscience research: Home-based high-resolution EEG and eye-tracking data collection at scale

Authors: *A. SHESTYUK[1], K. KASINATHAN[1], G. VENKATRAMAN[1], K. PERRY[1], V. KARAPOONDINOTT[1], N. KARNAM[1], M. LEVINSON[1], M. SEIGLIE[1], K. ANDERSON[1], R. T. KNIGHT[2];
[1]BASES NielsenIQ, Berkeley, CA; [2]Univ. of California, Berkeley, CA

Abstract: The COVID pandemic halted in-person data collection in labs across the world. It also highlighted difficulties in access to in-person research for vulnerable populations or individuals living far away from centralized medical and research facilities. These issues underscored the

need to develop alternative approaches to data collection that would combine high-quality neural data acquisition with the convenience of participating from one's home.
While there have been some attempts to introduce in-home data collection using simple limited-channel EEG devices and webcam eye-tracking, they typically suffer from poor data quality (low temporal and spatial resolution), limited utility, and insufficient participant compliance. We have developed a unique research ecosystem for collecting research-grade EEG and eye-tracking data from 500+ participants at their homes. Participants were recruited from across the US. To collect EEG data, we use Emotiv Flex EEG headsets with 32 channels, 256 Hz sampling rate, and custom firmware. Eye-tracking data are collected using Tobii Nano. Both devices are integrated into a custom-built data acquisition app that also controls and times stimulus presentation. Participants undergo rigorous online screening, are sent the equipment kit, and complete a 2-hr online training. They are then ready to collect EEG and eye-tracking data on their own with as little as 5 min setup time. The data acquisition app navigates participants through the setup process and ensures good data quality and proper calibration. Data is uploaded automatically to the secure cloud and are analyzed offline using Matlab and Python based scripts.
We observed 95% compliance across participants, with an average data yield of 75%. 80% of participants successfully record data on a weekly basis. To validate home-collected EEG and eye-tracking data, we compared signal quality with similar in-lab study recordings using a BioSemi Active2 EEG system and iScan eye-tracking. While we found convergent eye-tracking results (95% convergence), we observed higher power across all frequency bands and greater variability in EEG data collected at home. This can be overcome with in-person baseline correction and increased sample size (e.g., 32 home participants vs. 24 lab participants to obtain stable test-retest comparability at 95% confidence).
In summary, we demonstrate viability of at-home EEG and eye-tracking data collection that can be utilized to scale cognitive research and provide unique opportunities for longitudinal studies. This approach can also be used by clinicians for epilepsy monitoring in cases where in-person visits are not possible or costly.

Disclosures: **A. Shestyuk:** A. Employment/Salary (full or part-time):; NielsenIQ. **K. Kasinathan:** A. Employment/Salary (full or part-time):; NielsenIQ. **G. Venkatraman:** A. Employment/Salary (full or part-time):; NielsenIQ. **K. Perry:** A. Employment/Salary (full or part-time):; NielsenIQ. **V. Karapoondinott:** A. Employment/Salary (full or part-time):; NielsenIQ. **N. Karnam:** A. Employment/Salary (full or part-time):; NielsenIQ. **M. Levinson:** A. Employment/Salary (full or part-time):; NielsenIQ. **M. Seiglie:** A. Employment/Salary (full or part-time):; NielsenIQ. **K. Anderson:** A. Employment/Salary (full or part-time):; NielsenIQ. **R.T. Knight:** F. Consulting Fees (e.g., advisory boards); NieqlenIQ.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.04

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant 1R24MH117529

Title: What's new with RAVE: reproducible analysis and visualization of intracranial EEG data

Authors: *Z. WANG, J. F. MAGNOTTI, X. ZHANG, M. S. BEAUCHAMP;
Neurosurg., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Intracranial electroencephalography (iEEG) is a fast-growing and powerful technique in human neuroscience. However, analysis and visualization of iEEG data is extremely challenging. RAVE (R Analysis and Visualization of intracranial EEG data) is a freely-available software package that makes neuroscience discoveries with iEEG easier and more reliable (Magnotti, Wang, Beauchamp, NeuroImage, 2020). Here we describe three new features in RAVE: an electrode localization pipeline; multimodal data support in the 3dViewer; and improved support for group-level analysis and visualization.

Electrode localization. Localizing iEEG electrodes often requires complicated combinations of legacy scripts. To simplify the process, RAVE provides an integrated electrode localization tool using familiar software: FSL FLIRT for CT/MRI alignment and FreeSurfer for anatomical parcellation. The RAVE GUI displays any combination of the CT, MRI, and surface model and provides tools for quickly obtaining the locations of depth and surface electrodes, following the natural curvature of the cortical surface. Electrode information is saved in tabular format, including labels, MNI and T1 coordinates, and FreeSurfer atlas information.

Multimodal data in 3dViewer. A popular feature in RAVE is the ability to visualize electrode-level data on a cortical surface or volumetric MRI. RAVE can now visualize arbitrary volume data including fMRI data and lesion maps). iEEG data and volume data are combined by projecting both data types onto the cortical surface. Using an MNI-space template surface, users can combine group-level iEEG data with existing fMRI connectivity datasets such as the Human Connectome Project.

Group analysis and visualization. An area of active development in RAVE is group analysis. iEEG data is hierarchical, with electrodes nested in patients, resulting in unequal sample sizes. Making reproducible neuroscience discoveries requires analysis tools that model these intricacies correctly. RAVE will soon implement a GUI-driven linear mixed-effects model tool that guides users in the specification of a statistical model that accurately reflects their neuroscience question. The tool will automatically display analysis and visualizations results in a data dashboard containing cortical surface and volumetric MRIs and a slew of visualizations comparing data at multiple levels, from violin plots for assessing the consistency of the response in different brain areas to heat maps showing individual trials sorted by condition within electrode.

Visit the poster for a live demo and help installing RAVE on your own machine. http://rave.wiki for more details.

Disclosures: Z. Wang: None. **J.F. Magnotti:** None. **X. Zhang:** None. **M.S. Beauchamp:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.05

Topic: I.07. Data Analysis and Statistics

Support: NIH R24 MH117529

Title: Hierarchical clustering for iEEG data with HiCiE

Authors: *X. ZHANG, Z. WANG, J. F. MAGNOTTI, M. BEAUCHAMP, Y. ZHANG; Univ. of Pennsylvania, Philadelphia, PA

Abstract: Studies using intracranial electroencephalography (iEEG) may enroll dozens of patients, each with one hundred or more implanted electrodes. Because electrode location is driven by clinical need, there is usually sparse coverage within any individual brain area. Researchers must combine data across patients to make reliable findings, but manually searching for electrodes with similar electrodes is difficult. We describe a new group analysis tool, "*HiCiE*" ("hierarchical clustering for iEEG", pronounced High C). HiCiE is built on top of the RAVE iEEG analysis and visualization platform but is compatible with data exported from other popular iEEG tools such as EEGLAB and MNE. HiCiE uses common clustering algorithms and validity indices to automatically find groups of electrodes with similar neural responses, within individual patients or across patients. The GUI provides access to all parameters for each clustering algorithm while providing sensible default values to guide users to a useful result. Clustering is performed on the iEEG time-series data per electrode; trial types can be grouped and the analysis time window customized. Here we present an example application of HiCiE to differentiate electrodes based on iEEG responses to speech, using a dataset from *Karas et al., eLife*, 2021. Patients were presented with words in either auditory-alone (A), visual-alone (V), or audiovisual (AV) formats. Each electrode's broadband high-frequency activity (70 Hz to 150 Hz) for each trial type was averaged in a window from 0 to 1.5 seconds after stimulus onset using RAVE. The dataset included 470 electrodes across 5 patients. Using HiCiE, the average response to each of the three stimulus conditions (A, V, AV) in each electrode was concatenated. The response timecourses were then z-scored within each electrode so that clustering would be based on the *shape* of the response rather than differences in mean amplitude across electrodes. HiCiE found the best fitting number of clusters to be 4 based on both the silhouette and the explained variance indices. HiCiE clusters corresponded to clear differences in response properties. Cluster 1 (n=61) electrodes were *multisensory* (high responses to A, V, and AV). Cluster 2 (n=17) electrodes were *auditory* (high responses to A and AV), while Cluster 3 (n=2) electrodes were *visual* (high responses to V and AV). The largest cluster, cluster 4 (n = 390) had little to no response to any stimuli. Visit the poster for a live demo of *HiCiE* or see https://rave.wiki for more details.

Disclosures: X. Zhang: None. **Z. Wang:** None. **J.F. Magnotti:** None. **M. Beauchamp:** None. **Y. Zhang:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.06

Topic: I.07. Data Analysis and Statistics

Title: Ear-to-scalp eeg fraction of explained variance during common cognitive tasks using temporal metrics

Authors: *D. ADAIR[1], M. NONTE[2], T. V. DANG[3], W. HAIRSTON[4];
[1]United States Army Res. Lab., Baltimore, MD; [2]DCS Corp., Alexandria, VA; [3]DCS Corp, Alexandria, VA; [4]Human Res. and Engin., US Army Res. Lab., Aberdeen Proving Ground, MD

Abstract: AbstractElectroencephalograph (EEG) is a useful tool for measuring the cognitive state of a person, but is historically time consuming to apply and has primarily been limited to highly controlled seated laboratory tasks. In-ear measurement of EEG data provides a potentially more streamlined, compact, low-impact modality for real-world neuroimaging. While promising, understanding the relative amount of signal captured using this limited “keyhole” view into the brain as compared to other conventional methods is critical for connecting with prior work and predicting the usefulness of this technique. Thus, it is important to understand the overlap between the signal observed from ear EEG recordings with the signal measured at traditional scalp sites. Here, we explore the fraction of explained variance (FVE) between the ear and scalp as a useful metric of the utility of in-ear EEG recordings. We have collected simultaneous scalp, in-ear and around-ear EEG data during four cognitive tasks (AEP, RSVP, ASSR, and SSVEP) in eighteen subjects (n=18). EEG was recorded using a BioSemi amplifier with 64 channels on the scalp, 10 channels around each ear, and 2 channels within each ear. The in-ear electrode was a foam insert style with conductive fabric akin to those in Goverdovsky et al, 2017. Common temporal features were defined for each of the four tasks and the FVE was computed from a regression between all electrodes for a given site (e.g., in-ear, around-ear, combined in and around ear) and each individual scalp electrode based on the specified feature. SSVEP and ASSR features were the total power at stimuli frequency (15, 20, 30, and 42 Hz, and 20, 30, and $0 Hz, respectively. RSVP and AEP features were the area under the curve of the N1-P1-N2-P3 ERP component and N1 P250 and P3 ERP components respectively. Mean FVE values of each feature were computed for each task by averaging across all scalp electrodes, trial conditions (e.g. target), and finally across subjects. A smaller FVE was observed for all in-ear conditions compared with around ear, regardless of cognitive task, suggesting less general overlap in signal across features. However, the steady state tasks (ASSR and SSVEP) show a higher FVE than single-item evoked potentials (either the AEP or RSVP tasks). Because those tasks have a lower overall sign-to-noise ratio and require averaging over a high number of trials – we believe that there is a direct link between the inherent signal power and the degree to which it is observable at the ear. Specifically, these results suggest that in-ear EEG is closest to the scalp data during strongly evoked potentials, while weaker sources may be difficult to parse.

Disclosures: **D. Adair:** None. **M. Nonte:** None. **T.V. Dang:** None. **W. Hairston:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.07

Topic: I.07. Data Analysis and Statistics

Title: Anti-static devices reduce cadence artifact in mobile EEG

Authors: *M. NONTE[1], T. DANG[1], D. ADAIR[2], A. YU[2], W. D. HAIRSTON[2];
[1]DCS Corp., Alexandria, VA; [2]Human Res. and Engin. Directorate, United States Army Res. Lab., Aberdeen Proving Ground, MD

Abstract: In recent years, interest in mobile electroencephalography (EEG) recording has increased. One impediment to this research is the prevalence of motion-related artifacts in mobile EEG recordings. When participants walk at a constant cadence frequency, a characteristic artifact is induced into the EEG recording. In this work, we demonstrate how anti-static devices can be used to eliminate the cadence artifact in mobile EEG recordings Participants wore a 22-channel mBrainTrain Smarting Mobi EEG system to record neural signal and cadence artifact. Prior to each walking segment, participants stood stationary while a baseline EEG recording was made. During walking segments, participants walked on a conductive flooring in a circular pattern at a constant cadence. Participants wore anti-static heelstraps to create a conductive path from their body to the conductive flooring to remove excess charge. EEG recordings were made when the conductive flooring was connected to ground and when the conductive flooring was not grounded to determine if removing excess charge improved data quality. A band-pass filter with cutoff frequencies of 1Hz and 50Hz was applied to EEG data. The mean of each channel was subtracted to zero-center each recording. Independent component analysis (ICA) was used to remove eye artifacts from the data. The power spectral density (PSD) of each recording was computed and cadence artifact power was measured by integrating the PSD curve under each cadence peak. Walking power was divided by baseline power and decibel transformed. Walking data were segmented into 10 second windows and the power ratio relative to baseline was computed for each. We performed a 3-way ANOVA with floor grounding (grounded or ungrounded), front-back location (front, middle back), and left-right location (left, midline, right) as factors. The main effect of floor grounding was significant ($p<0.05$). We performed a multiple comparisons test using a Tukey-Kramer correction. This revealed that the power ratio in the ungrounded condition was significantly higher than during the grounded condition ($p<0.05$). Visual inspection of the walking PSDs revealed that the cadence artifact is not present when the participant is grounded. These results reflect a great step forward in the field of mobile EEG data collection. The method presented here will enable researchers to obtain cleaner EEG recordings in mobile overground and treadmill data collections. This will allow researchers to extend their experimental designs beyond seated laboratory settings to observe neural activity in more ecologically valid environments.

Disclosures: M. Nonte: None. **T. Dang:** None. **D. Adair:** None. **A. Yu:** None. **W.D. Hairston:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.08

Title: WITHDRAWN

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.09

Topic: I.07. Data Analysis and Statistics

Title: A method to compare motion artifacts in mobile ear EEG systems

Authors: *T. V. DANG[1], M. NONTE[1], D. ADAIR[2], W. HAIRSTON[3];
[1]DCS Corp., Alexandria, VA; [2]CCDC Army Reserach Lab., Aberdeen Proving Ground, MD;
[3]Human Res. and Engin., US Army Res. Lab., Aberdeen Proving Ground, MD

Abstract: Mobile electroencephalography (EEG) research has been a hot topic for the last decade. Unfortunately, mobile EEG recordings are plagued by motion-related artifacts which are difficult to characterize and remove. This contaminant can interfere with the analysis of neural activity. In this work, we propose a novel method for comparing motion artifact susceptibility of EEG systems and use it to compare commercial ear electrodes to a new design.
Participants wore a Vive Pro Eye head-mounted display (HMD) and performed a “Red Light/Green Light” task where they attempted to move quickly in a straight line during “Green” periods and stop abruptly when the light turns "Red". We expected large deflections in amplitude to occur when participants stop abruptly. Therefore, we epoched EEG data around stop events to utilize the deflections as a measure of comparison between different electrode types.
Data was collected using custom in-ear electrodes provided by Imperial College London (ICL), and separate recordings were made using Cognionics (CGX) Auris in-ear electrodes. In addition, we used motion trackers on the head, torso, and legs to identify when subjects initiated and completed stopping motions. We collected two five-minute recordings of the paradigm for each set of ear electrodes and a two-minute stationary baseline recording after each movement recording. To reduce anticipatory behavior by the subject, the light duration is randomly varied between 2.5 and 4 seconds.
We performed pre-processing using MATLAB and the EEGLab package. EEG data was band pass filtered with cutoff frequencies at 1 Hz and 50 Hz. Onset and offset periods were detected by thresholding head acceleration magnitude in the direction of forward movement. We epoched

EEG data around stop events and computed the power spectral density (PSD) for each epoch using Welch's method with a frequency resolution of 0.5 Hz. A power ratio was computed using the baseline and bin band power and then decibel transformed, resulting in 638 samples between ICL (n=424) and CGX (n=214).
We performed a one-way ANOVA analysis on the power ratios, using electrode type (CGX or ICL) as a factor. The main effect of electrode type has a significant effect on power ratio ($p<0.05$). ICL has a higher median and greater spread of values than CGX, indicating that the CGX is less susceptible to the stopping motion artifact. Using this method, we can compare electrode systems and determine suitable conditions for use.

Disclosures: **T.V. Dang:** None. **M. Nonte:** None. **D. Adair:** None. **W. Hairston:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.10

Topic: I.07. Data Analysis and Statistics

Title: Unbiased and efficient models of brain networks and gradients

Authors: *A. NANDA[1], M. RUBINOV[2];
[2]Biomed. Engin., [1]Vanderbilt Univ., Nashville, TN

Abstract: Brain networks and gradients represent two of the most influential paradigms in human neuroimaging. Networks denote groups of brain regions that form modular, functional units. Gradients denote continuous variations in cortical microstructure such as cortical thickness, myelination and cytoarchitecture. Despite broad adoption of these paradigms, there is a lack of methods for reconciling these descriptions in individual datasets. Specifically, to the best of our knowledge, the current literature lacks efficient methods to generate surrogate datasets with preserved networks or gradients. This makes it difficult to study interdependencies and statistical significance of these features in data.
Here, we present two independent methods to generate timeseries that preserve empirical brain network structure or cortical gradients in timeseries data but impose no other structure. We use these methods to develop models of brain networks and gradients. We present two models of brain networks: one that preserves all average within-network correlations, and another that preserves all within- and between-network correlations. Concurrently, we consider two models that preserve gradients: one model that preserves only the primary cortical gradient and another that preserves primary, the second and third cortical gradients (Figure).
We tested these methods and models on resting-state data from the Human Connectome Project. We used the 7-network 400-parcel Schafer parcellation. For each timeseries, we use a seed-based based approach to quantify network maps (Figure). This works paves the path forward to principled comparisons of brain networks and cortical gradients in future studies.

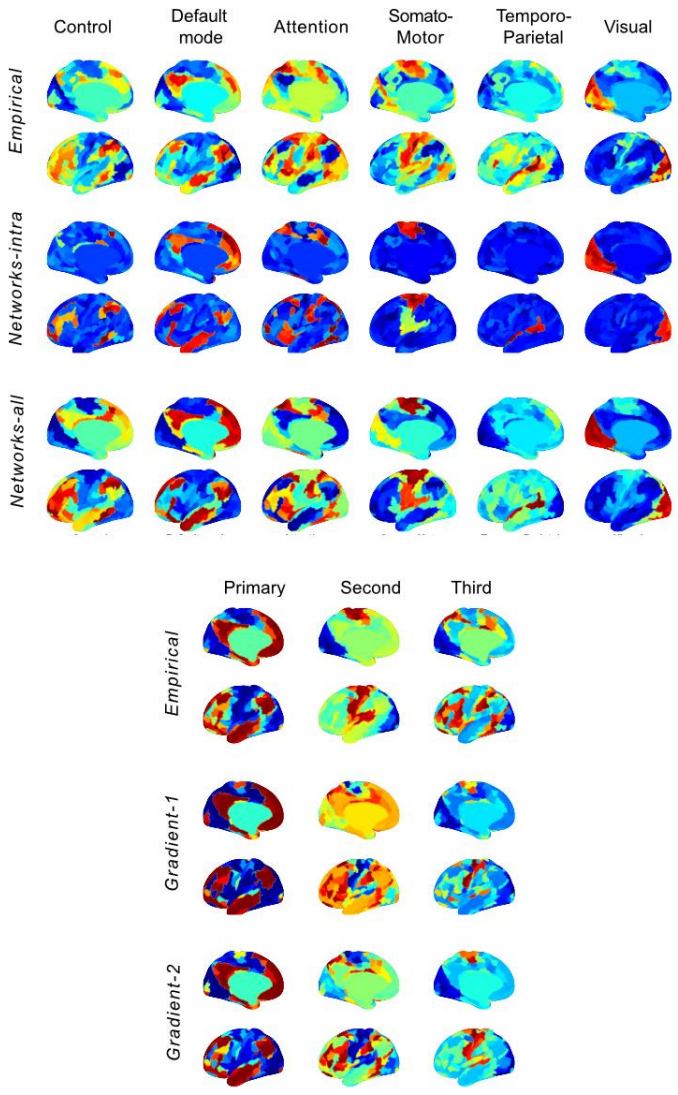


Figure 1: Performance of network and gradient models: Network activations in *Networks-intra* and *Networks-all* compared against empirical. Gradients obtained from *Gradient-1* and *Gradient-2* models compared with empirical gradients

Disclosures: **A. Nanda:** None. **M. Rubinov:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

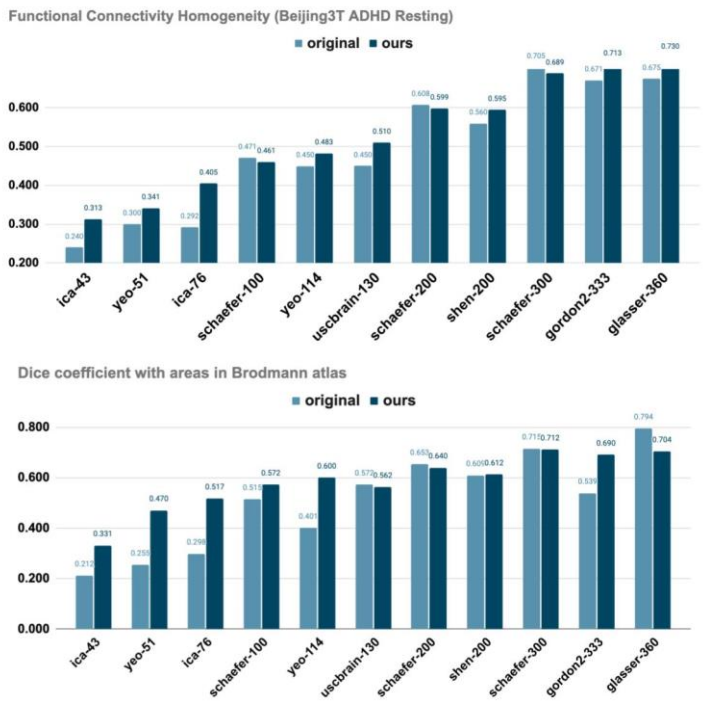
Program #/Poster #: 751.11

Topic: I.07. Data Analysis and Statistics

Title: Functional parcellation of the cerebral cortex based on brain network identification using resting-state fMRI

Authors: *Y. LIU[1], J. LI[4,5], J. L. WISNOWSKI[6,2], R. M. LEAHY[3];
[2]Keck Sch. of Med., [3]Signal and Image Processing Inst., [1]USC, Los Angeles, CA; [4]A. A. Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp. and Harvard Med. Sch., Charlestown, MA; [5]Ctr. for Neurotechnology and Neurorecovery, Dept. of Neurol., Massachusetts Gen. Hosp. and Harvard Med. Sch., Boston, MA; [6]Radiology and Pediatrics, Div. of Neonatology, Children's Hosp. Los Angeles, Los Angeles, CA

Abstract: Many functional parcellation schemes that use resting-state functional MRI (rs-fMRI) have been described in the literature. Although several schemes use applied graph-based analysis (e.g., Craddock et al., 2012 and Shen et al., 2013), no clear relationships between these parcellations have been described. Here, we explored these relationships. Moreover, we demonstrate that a more general graph-based method (NetMF) can unify several graph-embedding approaches by approximating graph-embedding as a matrix factorization procedure. Using 3T rs-fMRI data from 1000 subjects from the Human Connectome Project, we first computed group spatial activation maps using a temporal synchronization approach (Group BrainSync) combined with tensor decomposition (NASCAR). Unlike ICA, the spatial maps of different networks' activations obtained by NASCAR are not constrained to be independent of each other, and hence can be more physiologically plausible. We then construct a graph where each vertex on the cortical surface defines a node. The correlation of the previously identified spatial maps across all networks defines the edge strength between a pair of nodes. To ensure spatial contiguity of parcels, we place a k-hop neighbor spatial constraint. NetMF maps this graph to a low-dimensional latent space. The parcellation in then derived using k-means clustering on these low-dimensional embeddings. We show that our parcellation can achieve state-of-the-art performance compared with many other parcellation schemes in several metrics of interest, such as functional homogeneity, concordance with cytoarchitectonics, and delineation of function activation.



Results of (1) Functional connectivity homogeneity of all parcellations evaluated on the 3T Beijing ADHD resting-state fMRI dataset (2) Overlap with Brodmann areas measured using dice coefficient score. We match the number of parcels with all other existing parcellation schemes using our approach

Disclosures: **Y. Liu:** None. **J. Li:** None. **J.L. Wisnowski:** None. **R.M. Leahy:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.12

Topic: I.07. Data Analysis and Statistics

Support: NSF Grant 2112455
NIH Grant R01DA040487
NIH Grant R61NS120249

Title: An inclusivity index to evaluate the performance of harmonization algorithms on dynamic functional connectivity data

Authors: B. BOSTAMI[1], *F. ESPINOZA[2], V. CALHOUN[2], V. VERGARA[2];
[1]Computer Sci., [2]Tri-Institutional Ctr. for Translational Res. in Neuroimaging and Data Science, Georgia State Univ., Atlanta, GA

Abstract: Brain dynamic functional connectivity (dFC) use clustering to identify repeating time varying patterns of functional connectivity known as dFC states. Data collected from different

sites may be affected by site-effects, but these effects can be mitigated by performing data harmonization. Our research showed that site-effects significantly influence the dFC states. We developed a new method called “The Inclusivity Index” based on sites samples distribution among clusters to measure how site-effects influence the clustering of dFC states before and after harmonization. The method is applied to resting-state fMRI data collected from two country sites USA and The Netherlands. A total of 170 samples including controls and patients were obtained. Fig 1 presents the overview of the inclusivity index method; the exclusivity index measures site distribution for each cluster and the inclusivity index measures the overall sample distribution for each number of clusters in the k-means algorithm. In fig 2 we present the data inclusivity index values for different number of clusters; the results show that removal of site-effects produces fair sites samples distribution among clusters. We suggest that inclusivity index can be extended and used as a metric for multisite dFC data analysis.

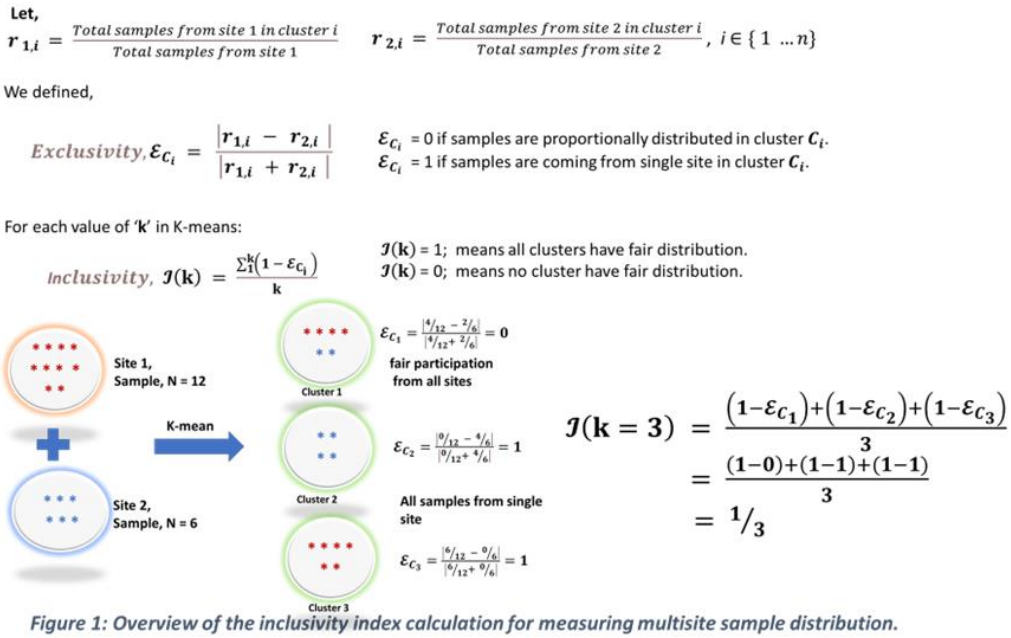


Figure 1: Overview of the inclusivity index calculation for measuring multisite sample distribution.

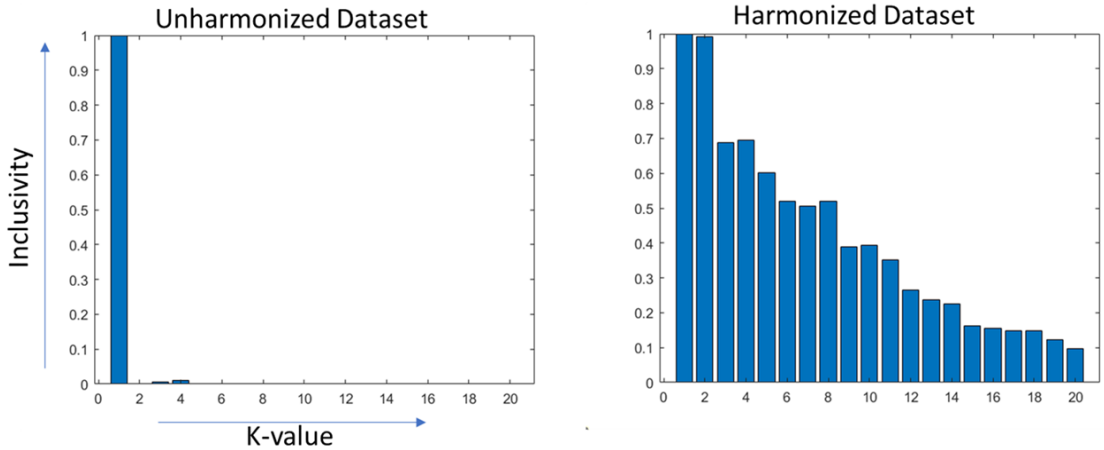


Figure 2: Unharmonized and harmonized inclusivity index for a range of number of clusters, k=1:20. The harmonized index results showed that harmonization increases the cluster inclusivity values. However, these values decrease as the number of clusters increases.

Disclosures: **B. Bostami:** None. **F. Espinoza:** None. **V. Calhoun:** None. **V. Vergara:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.13

Topic: I.07. Data Analysis and Statistics

Support: NIH grants 1U01NS108923, R21EY032381, and 1R01NS118091
NSF Faculty Early Career Development (CAREER) Award (1944415).

Title: Integrated organic electronic devices for functional characterization of human cortical microcircuits

Authors: *A. HASSAN[1], Z. ZHAO[1], J. J. FERRERO[1], C. CEA[1], P. JASTRZEBSKA-PERFECT[1], J. MYERS[2], P. ASMAN[3], N. F. INCE[4], G. M. MCKHANN II[1], A. VISWANATHAN[4], S. A. SHETH[4], D. KHODAGHOLY[1], J. GELINAS[1];
[1]Columbia Univ., New York, NY; [2]Baylor Col. of Med., Houston, TX; [3]Univ. of Houston, University of Houston, TX; [4]Univ. of Houston, Houston, TX

Abstract: Recording from the human brain at the spatiotemporal resolution of action potentials provides critical insight into mechanisms of higher cognitive functions and neuropsychiatric disease that is challenging to derive from animal models. Here, we employ organic materials and conformable electronics to create an integrated neural interface device compatible with minimally invasive neurosurgical procedures and geared toward chronic implantation on the surface of the human brain. We developed an organic mixed-conducting particulate composite material (MCP) to establish a scalable and biocompatible interface between soft and hard electronics. MCP enabled integration with conducting polymer-based electrode arrays (NeuroGrids) and creation of neural interface devices that can be placed on the surface of the human brain through small craniotomies and burr holes. NeuroGrids recorded both action potentials and local field potentials from superficial cortical neurons of human subjects without penetrating the brain surface (n = 64 channels per array). Data generated with these devices enabled identification and characterization of individual, spatially distributed human cortical neurons in the absence of any tissue penetration (n = 229 single-units; n = 7 subjects). Putative single-units were effectively clustered, and found to possess features characteristic of pyramidal cells and interneurons (85 pyramidal cells, 144 interneurons), as well as identifiable microcircuit interactions. Human neurons exhibited consistent phase modulation by oscillatory activity such as spindle oscillations during anesthesia and beta oscillations during alertness and a variety of population coupling responses. When action potential waveforms were detected across multiple channels, deliberate elimination of neighboring channels (mimicking access to only a single electrode) was associated with loss of detection or decreased isolation distance, increased L-ratio, and increased contamination rate. These results suggest that MCP- and NeuroGrid-based neural interface devices are capable of acquiring neurophysiological signals at the resolution of

individual neurons from the surface of the human brain. Therefore, we establish parameters to optimize the yield and quality of single-unit activity from the cortical surface, enhancing the ability to investigate human neural network mechanisms without breaching the tissue interface and increasing the information that can be safely derived from neurophysiological monitoring.

Disclosures: **A. Hassan:** None. **Z. Zhao:** None. **J.J. Ferrero:** None. **C. Cea:** None. **P. Jastrzebska-Perfect:** None. **J. Myers:** None. **P. Asman:** None. **N.F. Ince:** None. **G.M. McKhann II:** None. **A. Viswanathan:** None. **S.A. Sheth:** None. **D. Khodagholy:** None. **J. Gelinas:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.14

Topic: I.07. Data Analysis and Statistics

Support: NIH DP5OD012109-01
NIH 1U01MH121766
NIH R01MH112746
NIH 5R01MH112189
NIH 5R01MH108590
NIAAA 2P50AA012870-11
Brain and Behavior Research Foundation Young Investigator Award

Title: Qunex: an integrative platform for reproducible neuroimaging analytics

Authors: *J. JI[1], J. DEMŠAR[2], C. FONTENEAU[1], Z. TAMAYO[1], L. PAN[1], A. KRALJIč[2], A. MATKOVIč[2], N. PURG[2], M. HELMER[3], S. WARRINGTON[4], M. P. HARMS[5], S. SOTIROPOULOS[4], J. D. MURRAY[1], A. ANTICEVIC[1], G. REPOVŠ[2];
[1]Yale Univ., New Haven, CT; [2]Univ. of Ljubljana, Ljubljana, Slovenia; [3]Manifest Technologies, New Haven, CT; [4]Univ. of Nottingham, Nottingham, United Kingdom; [5]Dept. of Psychiatry, Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Neuroimaging technology has experienced explosive growth and has transformed the study of neural mechanisms across health and disease. However, given the diversity of sophisticated tools for handling neuroimaging data, the field faces challenges in method integration. Specifically, researchers often have to rely on siloed approaches which limit reproducibility, with idiosyncratic data organization and limited software interoperability. To address these challenges, we have developed Quantitative Neuroimaging Environment & Toolbox (QuNex), a platform for consistent end-to-end processing and analytics. QuNex is engineered for reproducible deployment of custom workflows, from onboarding raw data to generating analytic features, in a single “turnkey” command. The platform enables inter-operable integration of multi-modal, community-developed neuroimaging software through an extension

framework with a software development kit (SDK) for seamless integration of community tools. QuNex supports multiple forms of input neural and behavioral data as well as popular community-developed tools including FSL FreeSurfer, HCP, PALM, and XTRACT. Additionally, QuNex includes a well-defined framework for informing the future integration of externally developed tools, and is publicly available as a container that contains all required dependencies for easy distribution, portability, and execution. Critically, it supports high-throughput, parallel processing in high-performance compute environments, either locally or in the cloud. We show that QuNex has successfully processed over 10,000 scans across neuroimaging consortia including multiple clinical datasets. Moreover, QuNex enables integration of human and non-human workflows via a cohesive translational platform. Collectively, this effort stands to significantly impact neuroimaging method integration across acquisition approaches, pipelines, datasets, computational environments, and species. Reliable standardized processing of neuroimaging data is a necessity for reproducible results in cognitive neuroimaging. Building on this platform will enable more rapid, scalable, and reproducible impact of neuroimaging technology across health and disease.

Disclosures: **J. Ji:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anticevic A, Murray JD, Ji JL: Systems and Methods for Neuro-Behavioral Relationships in Dimensional Geometric Embedding (N-BRIDGE), PCT International Application No. PCT/US2119/022110, filed March 13. F. Consulting Fees (e.g., advisory boards); Neumora (previously BlackThorn Therapeutics). **J. Demšar:** F. Consulting Fees (e.g., advisory boards); Neumora (previously BlackThorn Therapeutics), Manifest Technologies. **C. Fonteneau:** F. Consulting Fees (e.g., advisory boards); Neumora (previously BlackThorn Therapeutics), Manifest Technologies. **Z. Tamayo:** F. Consulting Fees (e.g., advisory boards); Neumora (previously BlackThorn Therapeutics), Manifest Technologies. **L. Pan:** None. **A. Kraljič:** F. Consulting Fees (e.g., advisory boards); Neumora (formerly BlackThorn Therapeutics). **A. Matkovič:** F. Consulting Fees (e.g., advisory boards); Neumora (previously BlackThorn Therapeutics). **N. Purg:** None. **M. Helmer:** A. Employment/Salary (full or part-time):; Manifest Technologies. **S. Warrington:** None. **M.P. Harms:** None. **S. Sotiropoulos:** None. **J.D. Murray:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neumora (formerly BlackThorn Therapeutics), Manifest Technologies, Murray JD, Anticevic A, Martin, WJ:Methods and tools for detecting, diagnosing, predicting, prognosticating, or treating a neurobehavioral phenotype in a subject, U.S. Application No. 16/149,903 filed. F. Consulting Fees (e.g., advisory boards); Neumora (formerly BlackThorn Therapeutics), Manifest Technologies. **A. Anticevic:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neumora (formerly BlackThorn Therapeutics), Manifest Technologies, Anticevic A, Murray JD, Ji JL: Systems and Methods for Neuro-Behavioral Relationships in Dimensional Geometric Embedding (N-BRIDGE), PCT International Application No. PCT/US2119/022110, filed March 13, Murray JD, Anticevic A, Martin, WJ:Methods and tools for detecting, diagnosing, predicting, prognosticating, or treating a neurobehavioral phenotype in a subject, U.S. Application No. 16/149,903 filed. F. Consulting Fees (e.g., advisory boards); Neumora (formerly BlackThorn Therapeutics), Manifest Technologies. **G. Repovš:** F. Consulting Fees (e.g., advisory boards); Neumora (formerly BlackThorn Therapeutics), Manifest Technologies.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.15

Topic: I.07. Data Analysis and Statistics

Support: NIH K00MH122372

Title: Preliminary empirical effect size guidelines for typical fMRI studies

Authors: *S. NOBLE[1], M. ROSENBLATT[4], L. TEJAVIBULYA[2], J. YE[2], R. JIANG[1], M. ROLISON[3], H. PETERSON[1], J. DADASHKARIMI[5], C. HORIEN[2], A. S. GREENE[2], D. SCHEINOST[1];
[1]Radiology & Biomed. Imaging, [2]Interdepartmental Neurosci. Program, [3]Child Study Ctr., Yale Sch. of Med., New Haven, CT; [4]Biomed. Engin., [5]Computer Sci., Yale Univ., New Haven, CT

Abstract: At the turn of the century, functional Magnetic Resonance Imaging (fMRI) exploded in popularity and transformed our understanding of the human brain. However, recent work has exposed an endemic lack of statistical power (i.e., ability to detect effects of interest) in fMRI studies, leading to findings that do not replicate or only uncover a small "tip of the iceberg" of true effects. This is partly because researchers are often unsure what range of effect sizes to expect for their studies, which is critical for planning well-powered studies. Existing databases fill a critical need but do not yet provide effect summaries that are readily interpretable for standard power analyses. Here, we provide a preliminary, interpretable overview regarding the range of effect sizes that may be expected for typical fMRI studies.
We estimated effects from 6 large openly available datasets (n>400: SLIM; n>1000: HCP-Young Adult, HBN, IMAGEN; n>10,000: UKB, ABCD) that spanned a range of typical task-based activation and functional connectivity study designs (e.g., task-versus-rest contrast, correlation with phenotype, phenotype group contrast, etc.). Effect sizes for each univariate feature (voxel or edge) were estimated via Cohen's d to facilitate comparison across designs and interpretation for power analyses.
As expected for between- versus within-subject designs, brain-behavior correlations showed the smallest effect sizes (i.e., 97% of effects were below d=0.2 and none were above d=0.8) and task-based contrasts showed the largest (i.e., 52% of effects were below d=0.2 and 4% were above d=0.8). However, effect sizes were typically below medium across contexts (i.e., 80-99.9% of effects), even for fairly robust task-based designs. Given sampling variability, true population effects are expected to be smaller still.
Altogether, effects are generally expected to be small, and it may be advisable to plan accordingly. Since power depends on effect size, power will likely remain low for typical study designs, particularly using typical sample sizes (i.e., n<50) and inferential procedures (e.g., mass univariate inference), although within-subject designs can be used to produce substantially larger effects. Furthermore, effects were also widespread throughout the brain across study designs, pointing towards structured low-dimensional signals that are not captured by typical inferential procedures. We hope this empirical evidence helps not only inform current study planning, but

also ignite motivation for multivariate methods that capture effects occurring in concert across the image or connectome.

Disclosures: **S. Noble:** None. **M. Rosenblatt:** None. **L. Tejavibulya:** None. **J. Ye:** None. **R. Jiang:** None. **M. Rolison:** None. **H. Peterson:** None. **J. Dadashkarimi:** None. **C. Horien:** None. **A.S. Greene:** None. **D. Scheinost:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.16

Topic: I.07. Data Analysis and Statistics

Title: Linear discriminant in machine learning with application to face recognition and unknown rejection

Authors: *H. C. YUAN[1], M. V. CHAO[2];
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Abstract: Machine Learning is progressively important in neuroscience to process and analyze large amounts of data. Machine learning helps to understand structure in the data and to help build a model that predicts outputs from input data. This poster investigates the use of the linear discriminant in Machine Learning with the Olivetti face database as an example of how this can be applied to face recognition and unknown face rejection. Artist Georgia O'Keeffe's famous advice is "making your unknown known is the important thing - and keeping the unknown always beyond you," (In letter to S. Anderson, October 1923). In face recognition, it would be prudent to keep the unknown always beyond to potentially reject it should it not match any faces in a certain database as in the case of secure entry into a building or meeting. Linear discriminant analysis assumes that all classes are linearly separable and multiple linear discrimination functions representing several hyperplanes in the feature space are created to distinguish the classes. The classic machine learning approach to face recognition is to estimate the class densities, assigning the face to the class with the highest posterior probability. In contrast, linear discriminant is a way to project a dataset onto a lower-dimensional space and find the area that maximizes the separation between multiple classes. The classifier performance for face recognition is deemed as good if the known test face is correctly classified. If the known test face is misclassified by the face recognition classifier, then the misclassification is tallied as a classification error. An unknown face presented to the face recognition classifier could still classify the unknown face erroneously as a known face because both the unknown face and known face might both have very similar features. Distance thresholds as used in k-nearest neighbor or Euclidean based classifiers could classify a single presentation of an unknown face as an unknown should the distance threshold not be high enough to declare as a known face, but may not be consistent to reject the unknown. Unknown face rejection is investigated in this

poster using the Olivetti face dataset with linear discriminant analysis as the classifier trained on known faces and multi-look presentation of an unknown face for determining unknown rejection. Unknown rejection performance is computed and compared using single-look presentation processing of an unknown face to the classifier, and multi-look presentation processing with up to three input unknown faces. Unknown rejection is determined by the inconsistency of classification among the multiple unknown presentations of the same unknown face.

Disclosures: H.C. Yuan: None. **M.V. Chao:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.17

Topic: I.07. Data Analysis and Statistics

Support: NIH K25DA048179

Title: Influence of fMRI preprocessing on dynamic functional network connectivity and meta-state parameters

Authors: *B. JARRAHI;
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Abstract: Due to the nature of BOLD signals and inherent presence of artifacts in fMRI, images generally require preprocessing before meaningful statistical inferences are made. Little is known about the effects of preprocessing choices on emergent analysis techniques notably dynamic functional network connectivity (dFNC). Here, we tested the hypothesis of whether physiological noise correction and spatial smoothing kernel size would influence the dynamics of functional connectivity. By introducing a higher-dimensional state space, the meta-state approach allows complex states to overlap in time, thus enabled us to estimate effects of preprocessing on different measures of neural dynamism. We collected BOLD fMRI data from 22 healthy subjects on a 3.0 T scanner and created two copies of images. One copy was corrected for physiological noise prior to preprocessing using RETROICOR, while the other copy was not. Both copies were preprocessed using SPM12b. Preprocessing pipeline included motion and slice time correction, and spatial normalization into MNI. To identify the effects of spatial smoothing on network dynamics, Gaussian kernels with FWHM sizes of 4, 8, and 12 mm were applied. Group ICA with 75-IC was performed using GIFT toolbox. dFNC was computed using a sliding window approach with k-means clustering. Meta-state dynamics method was performed by reducing the number of windowed FNC correlations using k-means, PCA and ICA. Results revealed that denoising and spatial smoothing induced significant changes (FDR-corrected p of 0.05) in time-varying connectivity patterns across a wide range of networks including the default-mode, sensorimotor, and cognitive networks. These effects were particularly pronounced (with regard to significance and extent) on the dynamic state with highest number of occurrences

implying probable robust effect on the static FNC. Further, meta-state analyses indicated significant changes in (i) the number of changes of meta-states, i.e., how often does a subject switch between distinct meta-states, (ii) the number of distinct meta-states, i.e., how many unique distance vectors are present in an individual and (iii) the total distance travelled through the meta-state space between raw and denoised data or between different spatial smoothing conditions. Our preliminary results suggest significant effects of physiological denoising and spatial smoothing on the dynamics of functional connectivity and their consequences on meta-state parameters. If confirmed with larger sample sizes, these results provide further indication of the importance of evaluating variance associated with preprocessing steps on analysis outcomes.

Disclosures: B. Jarrahi: None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.18

Topic: I.07. Data Analysis and Statistics

Title: Optimizing functional MRI design and analysis for studies of working memory

Authors: *A. ABDUJABBOROV, K. K. SREENIVASAN;
New York Univ. Abu Dhabi, New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates

Abstract: Functional MRI is commonly used to study the neural basis of working memory (WM) in humans. These studies often utilize tasks with long memory delays (~10s) to isolate neural activity evoked by different phases of WM (e.g., maintenance). Traditional fMRI analyses of WM are rendered suboptimal by two key features of these tasks: they involve compound trials whose epochs (stimulus, delay, response) are (1) necessarily temporally contiguous and (2) deterministic in order. The low-pass temporal filter imposed by the hemodynamic response function (HRF) increases both the volatility of individual estimates and the risk that observed activity is attributed to the wrong epoch, reducing estimation power and accuracy. Unfortunately, many standard solutions to this problem (e.g., increasing the time between epochs) are unfeasible. This issue is further compounded for analyses that rely on single-trial estimates of neural activity, such as multi-voxel pattern analysis (MVPA). To determine the optimal approach for estimating WM activity, we compared several methods designed to isolate activity from different task epochs using realistic simulations of fMRI activity. These methods fall into three categories: task design (e.g., the duration of the memory delay); HRF estimation (e.g., using a separate run to estimate individual HRFs); and analytic approach (e.g., modifying the standard general linear model [GLM] approach for estimating epoch activity). There were three key findings from our simulations. (1) The optimal approach involved combining a task with variable delay durations with the estimation of subject- and voxel-specific HRFs from a predetermined library (HRF library approach). (2) The optimal analytic approach for single-trial estimates was Least Squares Separate (LSS), which uses a separate GLM to model each event. However, LSS

was outperformed by Least Square Unitary (LSU), which obtains run-wise rather than trial-wise estimates. (3) The optimal methods remained relatively robust at shorter memory delays, opening the possibility of using shorter trials with fewer psychological confounds. To validate our simulation results, we applied these methods to existing datasets, and confirmed that LSU significantly increased MVPA classification accuracy, although LSS and the HRF library approach did not provide substantial benefits over standard approaches. These results provide important guidelines to optimize fMRI estimates of neural activity evoked by different phases of WM. Importantly, these guidelines can be applied generally to studies that involve multi-epoch tasks.

Disclosures: A. Abdujabborov: None. **K.K. Sreenivasan:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.19

Topic: I.07. Data Analysis and Statistics

Support: NBRC Flagship program, Department of Biotechnology, Government of India, Award ID: BT/MED-III/NBRC/Flagship/Flagship2019
NBRC Core funda

Title: Concurrent separation of phase-locked and non-phase-locked activity

Authors: S. SINGHAL[1], P. GHOSH[4], N. KUMAR[2], ***A. BANERJEE**[3];
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Abstract: Brain dynamics recorded via electroencephalography (EEG) is conceptualized as a sum of two components, "phase-locked" and "non-phase-locked" to the stimulus. Phase-locked activity is studied as Event Related Potential (ERP), which is both time and phase-locked to the stimulus. Whereas non-phase-locked activity is considered time-locked but not phase-locked to the stimulus. Both activities are understood to be stemming from different neuronal mechanisms and hence accurately characterizing them is of immense importance in neuroscientific studies. Here, we discuss the drawbacks of currently used methods to separate the phase-locked and non-phase-locked activity and propose a new method named concurrent phaser method (CPM) that decomposes the two components simultaneously. First, we demonstrate that single-trial separation of phase-locked (PL) and non-phase-locked power (NPL) is an ill-posed problem. Second, using simulations where ground truth validation is possible, we elucidate the drawbacks of the widely used averaging method and efficacy of the proposed CPM. Using two experimental datasets, audio oddball EEG data and auditory steady-state responses (ASSR) we show how the empirical signal-to-noise estimates warrant the usage of CPM to separate phase-locked and non-

phase-locked activity. Most probable estimates of single-trial phase-locked and non-phase-locked power are also proposed. CPM guided single-trial estimates showed a significantly higher Pearson correlation between simulated (ground-truth) and estimated power, 0.82, 0.73 ($p<0.0001$) for PL and NPL components respectively. In comparison, averaging method estimates yielded Pearson correlation of 0.36 ($p<0.0001$) for NPL and 0.35 correlation ($p<0.0001$) for PL component.

Disclosures: **S. Singhal:** None. **P. Ghosh:** None. **N. Kumar:** None. **A. Banerjee:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.20

Title: WITHDRAWN

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.21

Topic: I.07. Data Analysis and Statistics

Support: CBIR15MIG004

Title: Robust Clustering of ICA components related to the Anticipatory Postural Control Task

Authors: *V. SHENOY HANDIRU, E. S. SUVISESHAMUTHU, G. H. YUE, D. ALLEXANDRE;
Kessler Fndn., West Orange, NJ

Abstract: EEG studies have an inherent challenge in that the recorded brain activity is often corrupted due to the noisy artifacts from non-cortical sources. Therefore, Independent Component Analysis—a blind source separation method—is recommended to separate the cortical sources from other sources such as muscle contractions from the neck and jaw muscles, those making eyeblinks, head movement and heartbeat, etc. The resulting sources across datasets are then clustered using a traditional clustering algorithm i.e., *k*-means for group-level analysis. However, it is known that the *k*-means algorithm does not guarantee convergence to the global optimum. The clustering results, therefore, heavily rely on the initial *k* number of random seeds selected with the Forgy method, which are regarded as cluster centroids in the first iteration. To address this issue, we propose a robust approach to source clustering based on *repeated k*-means.

We demonstrate the robustness of our approach on the EEG dataset collected from 17 individuals with Traumatic Brain Injury and 15 age-matched healthy individuals while they are performing the anticipatory postural control task. Participants stood on the balance platform (NeuroCom Inc) and were subjected to unpredictable anterior/posterior sinusoidal perturbations, while brain (64 channels EEG from Brain Products) activities were continuously recorded. We followed the pre-processing procedure mentioned in (Handiru et al. 2021) and the Extended Infomax algorithm to deduce the independent components (IC). The cortical sources corresponding to these ICs were identified using a dipole fitting model. These source dipoles across subjects were clustered using the proposed repeated *k*-means algorithm. The number of clusters is selected per the thumb rule based on the average number of brain-related ICs per subject. The *k*-means algorithm was executed $N_{\text{iteration}}$ times with N_{cluster} random initial seeds in each iteration. In the end, the resulting $N_{\text{iteration}} \times N_{\text{cluster}}$ cluster centroid positions were supplied to the *k*-means to determine the "robust" cluster centroids. The results from the repeated *k*-means concur with those from the state-of-the-art approach, namely the global *k*-means (Likas et al. 2003) which is two times slower than the proposed approach. Thus, the repeated *k*-means is a computationally efficient expedient to mitigate the reliance on the clustering results offered by *k*-means based on the initial seeds generated by a pseudorandom process. Aside from EEG source clustering, the proposed method can be applied to clustering problem, in general, that is ubiquitous in many scientific domains.

Disclosures: V. Shenoy handiru: None. **E.S. Suviseshamuthu:** None. **G.H. Yue:** None. **D. Allexandre:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.22

Topic: I.07. Data Analysis and Statistics

Support: NICT CRCNS 21701

Title: Effects of head movements on EEG while wearing VR goggles

Authors: *T. KAGAWA[1], H. KAMBARA[2], M. MIYAKOSHI[3], S. SAETIA[4], H. KIM[3], H. TANAKA[5], J. R. IVERSEN[3], N. YOSHIMURA[4];
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Abstract: VR goggles have been used as a tool to present visual stimuli in neuroscience research. Since the activities in the virtual space involve head movements, it is difficult to assess neural activity while wearing VR goggles. High density EEG recording and advanced signal processing techniques are one of the possible methodologies to evaluate the neural activity during movement, while the contact of the electrodes and cables with the headband of VR googles may induce non-negligible motion artifacts. In this study, we evaluated the effects of

head movements on steady-state visual evoked potential (SSVEP) and visual mismatch negativity (VMN) for visual stimuli presented by VR goggles. 64-ch EEG electrodes were attached to the scalp of human participants, and a VR goggles were placed on the EEG electrodes and cables. The participants were asked to keep watching a flashing visual target. In the SSVEP task, a red target flashing at 5 Hz was presented. In the VMN task, a visual target flashing at 1 Hz was presented, where 80 % of the target was red and 20 % was green. To evaluate the effects of head movements, two conditions of target movement (stationary target and moving target) were conducted. In the moving target condition, the target moved on the circular trajectory at 0.2 Hz. In addition, the target rapidly moved to the left or right every 10 second to evaluate the effects of rapid head movements. The measured EEG data were bandpass filtered and decomposed into independent components (ICs) using independent component analysis. For the data in the SSVEP task, the power spectrum densities were calculated by the Welch method. For the data in the VMS task, the event-related potential (ERP) of presenting the green and red targets was evaluated. The experiment results showed that the SSVEP and VMN were observed in both the stationary and moving target conditions. The power spectrum density of the occipital ICs in the SSVEP task showed a peak around 5 Hz, and ERPs associated with the green target in the VMS task were observed in the occipital and frontal ICs. In both SSVEP and VMN, signal intensities were attenuated under the moving target condition, which might result from contamination of EMG and artifacts due to electrodes and cables.

Disclosures: **T. Kagawa:** None. **H. Kambara:** None. **M. Miyakoshi:** None. **S. Saetia:** None. **H. Kim:** None. **H. Tanaka:** None. **J.R. Iversen:** None. **N. Yoshimura:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.23

Topic: I.07. Data Analysis and Statistics

Support: NSF IIS 1636893
NSF IIS 1912270
NSF OAC 1916518
NIH NIBIB 1R01EB029272
NIH NIBIB R01EB030896
NIH NIMH 1R01MH126699
NSF BCS 1734853

Title: Improving structural brain connectomes through informed forward modeling

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Abstract: Accurate mapping of the structural brain connectomes is fundamental to understanding the role of white matter in health and disease. Diffusion-weighted magnetic resonance imaging (dMRI) and fiber tractography provide the only way to map brain connectome in living human brains. Several studies have shown technical gaps in robustly mapping brain connectomes. Biases can be due to limits in the available tractography algorithms and brain segmentation methods. The lack of connectome evaluation methods is evident from the recent findings.

The present work focuses on developing methods for the statistical evaluation of brain connectomes. We present a new method that builds on LiFE and COMMIT2 methods to reduce a candidate tractography to an optimized one by identifying the brain connections that best predict the measured dMRI signal. Whereas in the early LiFE model, individual streamlines were removed independently, our model removes streamlines while keeping track of their grouping into white matter bundles. We used sparse group and lasso regularizations, which requires finding a parameter (λ) for the trade-off between better fitting the signal with individual streamlines while maintaining the bundle's cohesion. Previous methods using group regularization to evaluate connectomes set fixed λs, identifying the optimal λ by searching a large set of values, and refitting the model. We propose an efficient approach to selecting the optimal λ value without refitting the whole model.

We performed experiments to test the complexity and efficacy of the approach using two datasets: simulated and real datasets. The simulated data were generated using Phantomas, with simple bundles and isotropic factors. In addition, we used data from the Human Connectome Project (HCP), with tractography preprocessed using the Brainlife platform and the RACE-Track pipeline.

Results show that our approach can identify the optimal λ in a reliable amount of time. The entire λ optimization process for 100 different λ took only 17 min on a standard desktop computer, while it takes 4x more time than COMMIT 2 to select the optimal λ. In addition, the model's mean squared error is 0.0036 for the HCP dataset and 3.89e-5 for the simulated dataset. This is 14.78x less than COMMIT 2 (0.0544). The reduction in error is due precisely to the optimized selection of λ.

We present improvements over the state-of-the-art tractography filtering methods. Future research leveraging our new method will allow using different LiFE model optimization approaches to identify the best solutions with the most robust structures of the human connectome anatomy by testing different λ values and white matter bundles group sets.

Disclosures: **A.S. Heinsfeld:** None. **D.J. McDonald:** None. **F. Pestilli:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.24

Topic: I.07. Data Analysis and Statistics

Support: NIH/NIBIB (P41-EB018783)
NIH/NIBIB (R01-EB026439)
NIH/NINDS (U24-NS109103)
NIH/NINDS (U01-NS108916)
McDonnell Center for Systems Neuroscience
Fondazione Neurone

Title: A Novel Oscillation Detection Method Considering 1/f Noise and Auto-Correlation of Neurophysiological Signal

Authors: *H. CHO[1,2], P. BRUNNER[1,2];
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Abstract: Detecting temporal and spectral features of neural oscillations is essential to understanding dynamic brain function.Traditionally, the presence and frequency of neural oscillations are determined by identifying peaks over 1/f noise within the power spectrum. However, this approach solely operates within the frequency domain and thus can neither accurately determine the oscillation's onset/offset time, nor properly distinguish between the fundamental frequency of a non-sinusoidal oscillation and its harmonics.To overcome these limitations, we propose a novel method based on principle criteria to identify neural oscillations.1. Oscillations (peaks over 1/f noise) must be present in the time and frequency domain.2. Oscillations must exhibit at least two full cycles.3. Oscillations must share the same periodicity as the original time-series' autocorrelation.Non-sinusoidal signals are known to generate harmonics, significantly increasing the false-positive detection rate —the confounding factor that is addressed by the third criteria in our method. We evaluated our proposed method by verifying its performance on simulated sinusoidal and non-sinusoidal oscillatory bursts convolved with 1/f noise. Our results demonstrate that our proposed method outperforms the conventional techniques in accurately detecting oscillations. We also observed the sensitivity of our method to be a function of signal-to-noise ratio (SNR) that is negatively influenced by sub-optimal SNR.We further assessed our method by testing it on electrocorticographic (ECoG, N=8) and electroencephalographic (EEG, N=7) signals recorded during the pre-stimulus period of an auditory reaction time task. Our method detected auditory alpha and pre-motor beta oscillations in ECoG signals; occipital alpha and pre-motor beta oscillations in EEG signals; and accurately determined the offset of these oscillations to correspond with the onset of the auditory stimuli. In summary, our novel method demonstrates high precision and specificity in detecting neural oscillations in time and frequency domains.

Disclosures: H. Cho: None. **P. Brunner:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.25

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant R24MH120037
RF1MH126700
R01EB023297
The Swartz Foundation

Title: Hed: tagging the nature of events in time series data using hierarchical event descriptors

Authors: *S. MAKEIG[1], D. TRUONG[2], M. DENISSEN[4], A. DELORME[3], K. A. ROBBINS[5]; [1]Univ. of California San Diego, La Jolla, CA; [2]Electrical and Computer Engin., [3]Inst. for Neural Computation, UCSD, La Jolla, CA; [4]Univ. of Salzburg, Salzburg, Austria; [5]Computer Sci., Univ. of Texas at San Antonio, San Antonio, TX

Abstract: Although open standards for archiving and sharing neuroimaging data have now been developed, most notably the Brain Imaging Data Structure (BIDS) effort, only one system has been developed for describing the nature of events recorded in time series data, the Hierarchical Event Descriptors (HED) system proposed first by Nima Bigdely-Shamlo a dozen years ago. Now in its third generation, the HED system and software architecture is ready for widespread application, in particular to complete the BIDS annotation of time series neuroimaging data. For this reason the BIDS steering committee has explicitly accepted HED tags into the BIDS system, and the BIDS validator software now calls the HED validator when HED tags are included in a BIDS formatted dataset. Use of HED in archived and shared data makes possible search across archived datasets for any class of marked events, thereby speeding analysis of single datasets and making possible efficient meta- and mega-analysis of collections of datasets using machine learning or other modern statistical methods.

Disclosures: S. Makeig: None. **D. Truong:** None. **M. Denissen:** None. **A. Delorme:** None. **K.A. Robbins:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.26

Topic: I.07. Data Analysis and Statistics

Title: Bias-free fractional anisotropy measurement in MR-diffusion tensor imaging using region-of-interest methodology

Authors: *Y. SEO;
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Abstract: Bias-free quantification of fractional anisotropy (FA) in diffusion tensor imaging (DTI) requires adequate signal-to-noise ratio (SNR) in various brain structures, which

necessitates clinically impractical long image acquisition times. It has been previously reported that bias-free FA can be obtained with number of signal averages (NSA)=2 or 3 in low FA regions of the brain in the native brain space using region-of-interest (ROI)-based methodology. It is highly desirable to apply the ROI-based approach to DTI normalized to a standard space and to benefit from ROI-based analysis in various low FA regions with NSA=1. The purpose of this study is to investigate the ROI-averaged image processing method which can obtain bias-free values on DTI metrics with only one or a few NSAs in the standard brain space. A total of fifteen DTI data sets were acquired from a normal adult male at 3 T. DTI parameters were acquisition voxel size $2\times2\times2$ mm^3, b=1000 and 30 gradient directions. Fifteen acquisitions were averaged to minimize bias in the very high SNR DTI data set and the FA and mean diffusivity (MD) values derived from this data set were used to be the "gold standard" for our hardware-software platform. DTI data sets with NSA=1 were co-registered and averaged with affine transformation for the correction of eddy current distortions and head motion artifacts using FSL. These fifteen acquisitions were grouped to construct images with different NSAs: (i) seven tensor data sets each with NSA=4; (ii) eight data sets each with NSA=3; (iii) thirteen data sets each with NSA=2; and (iv) fifteen independent image sets each with NSA=1. Using SPM12, all images were normalized into the MNI standard brain space. Using software written in IDL8.4, a single observer manually placed ROIs on low FA regions. ROI-averaged FA and MD values were compared to the conventional voxel-based ones. Equivalence tests were conducted using the voxel-based metrics in the native space as the reference value. The 90% confidence intervals of error relative to the reference values for both ROI-averaged and voxel-based FA and MD in terms of NSA were obtained (equivalence tolerance = 0.05)**.** NSA requirement for bias-free FA and MD estimation in the caudate nucleus, globus pallidus, putamen and Thalamus lateral dorsal on our hardware-software platform was only one in the standard space, compared to at least NSA=3 in the native space using ROI-based analysis. ROI-averaged analysis allowed bias-free FA and MD measurements in DTI data sets with fewer NSA values in the standard space using ROI-based method. This approach will allow reliably FA and MD quantification in various brain structures previously difficult to study.

Disclosures: **Y. Seo:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.27

Topic: I.07. Data Analysis and Statistics

Support: Brain and Spinal Cord Injury Research Trust Bridge Funds, Center for Respiratory Research and Rehabilitation (CRRR) and the Trauma, University of Florida (SV)

Title: Fasb: an integrated processing pipeline for functional analysis of simultaneous spinal cord-brain fmri

Authors: *S. VAHDAT[1], C. LANDELLE[2], O. LUNGU[2], B. DE LEENER[3], J. DOYON[2], F. BANIASAD[1];
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Abstract: **Background:** Simultaneous functional magnetic resonance imaging (fMRI) of the spinal cord and brain provides an unprecedented opportunity for studying the functions of ascending sensory and descending motor pathways in humans (Vahdat et al., 2015, 2020). However, the image acquisition parameters and processing pipeline for simultaneous spinal cord-brain fMRI are less well established. Here, we propose an optimized image acquisition protocol including necessary anatomical and functional images, as well as an integrated processing pipeline including a novel approach for automatic modeling and handling of spinal voxels with low temporal signal to noise ratio (tSNR).
Method: We collected BOLD fMRI data covering the whole brain and the cervical cord (C1-T1 levels) using simultaneous multi-slice (SMS) EPI sequence on a 3T Prisma Siemens scanner (slice thickness: 4mm, resolution:1.6x1.6 mm^2, TR:1.85 s). A MEDIC $T2^*$w image was acquired with similar slice angle and thickness as EPI data (resolution 0.8x0.8 mm^2). A T1w image was acquired for registration to the template (PAM50). During functional scans, 15 participants performed a manual grip force control task using their right hand in a block-design paradigm. We developed and validated a new processing pipeline for analysis of spinal fMRI data. The novel aspects of our pipeline include: slice-wise centerline alignment to $T2^*$w image using the tSNR map to minimize registration errors, independent component analysis (ICA) of spinal cord data to automatically identify non-neuronal related regressors, and automatic tSNR threshold selection based on MAP estimation of two Gaussian distributions to remove the effects of subject-specific low-tSNR voxels at the group level.
Result: Our results show 1) significant activation clusters ($p < 0.05$, corrected using GRF) at the ipsilateral ventral horn in C6-C7 cervical level corresponding to motoneurons innervating hand muscles, as well as bilateral activations at C3-C4 level corresponding to the propriospinal pathway for hand muscles using our proposed pipeline, 2) the proposed automatic ICA component selection algorithm significantly improved results (no activation cluster without ICA), and 3) the proposed voxel-wise tSNR-based regressors significantly improved the group-level results (only one activation cluster detected without this correction).
Conclusion: Overall, our proposed acquisition protocol and processing pipeline result in stronger activations at the spinal cord during manual grip force task. Our validated methods will provide the necessary spatial resolution and SNR for studying the function of spinal cord-brain pathways in humans in vivo.

Disclosures: **S. Vahdat:** None. **C. Landelle:** None. **O. Lungu:** None. **B. De Leener:** None. **J. Doyon:** None. **F. Baniasad:** None.

Poster

751. Advances in Human Neuroimaging Data Analysis and Statistics

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 751.28

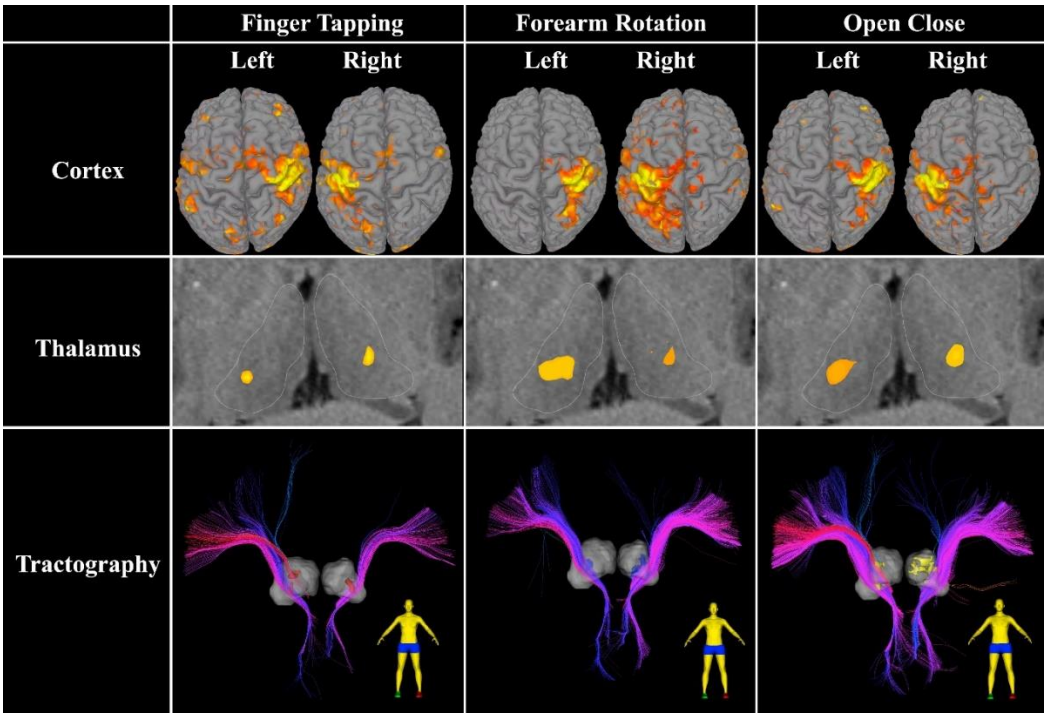
Topic: I.07. Data Analysis and Statistics

Support: The Winston and Maxine Wallin Neuroscience Discovery Fund (awarded to Rémi Patriat)
NIBIB P41 EB027061
P30 NS076408
S10 OD025256
NIH/NINDS P50NS123109

Title: Subject-specific identification of motor thalamus using task fMRI at 7Tesla: a proof of concept

Authors: *R. PATRIAT, T. PALNITKAR, H. BRAUN, O. SOLOMON, N. HAREL; Radiology / CMRR, Univ. of Minnesota, Minneapolis, MN

Abstract: Background: Deep brain stimulation (DBS) relies on the accurate placement of an electrode within a target, which, in the case of the ventral intermediate nucleus of the thalamus cannot be reliably seen on standard clinical magnetic resonance images (MRI). This has led clinicians to use templates that often do not adequately represent the anatomy of individual patients. Functional (f)MRI can detect brain activity in response to a task in individuals but it suffers from poor signal sensitivity in the center of the brain where DBS targets are located. Thus, researchers acquire lower resolution data and rely on processing techniques (e.g. excessive spatial smoothing and group averaging), which, should not or cannot be utilized in individualized applications and when the structure of interest is small. Objective: The goal of this project is to identify the subject-specific motor territory of the thalamus using 7Tesla (7T) fMRI.Methods: Three healthy volunteers were scanned using a 7T MRI scanner. 7T MRI offers many advantages including an increase in signal strength, which can be used to acquire higher resolution images with less noise in a timely manner. fMRI motor tasks consisted in finger tapping, forearm rotation and fist opening and closing. Each fMRI scan consisted in four 39.6s task blocks separated by 9.6s resting blocks. During task blocks, each individual was instructed to perform one task unilaterally. Four 3.5min (roughly) fMRI scan were acquired for each task (12 scans total; about 14min of data per task). The images were acquired using 1.25mm isotropic voxels covering the whole brain with a TR of 1.2s. Other scans included high resolution T1, diffusion and field maps.Results: All three motor tasks resulted in clusters in the thalamus in each volunteer and required roughly seven minutes of data. Additionally, tractography validated the functional relevance of these clusters by showing that the clusters were connected to the motor cortex (Fig. 1). Conclusion: These results show the potential of 7T fMRI to pre-operatively localize the motor portion of the thalamus and aid DBS targeting.



Disclosures: **R. Patriat:** F. Consulting Fees (e.g., advisory boards); Surgical Information Sciences. **T. Palnitkar:** None. **H. Braun:** None. **O. Solomon:** None. **N. Harel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Surgical Information Sciences. F. Consulting Fees (e.g., advisory boards); Surgical Information Sciences.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.01

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant 3OT2OD025307-01S4
NIH Grant R01 HL126747
NIH Grant R01 NS121372

Title: Selective IR neural inhibition can be reproduced by simple inexpensive resistive heating-based cuff

Authors: *J. ZHUO[1], C. E. WEIDRICK[2], Y. LIU[1], M. A. MOFFITT[1], E. D. JANSEN[4], H. J. CHIEL[3], M. W. JENKINS[1];
[1]Biomed. Engin., [2]Nutr., [3]Biol., Case Western Reserve Univ., Cleveland, OH; [4]Biomed. Engin., Vanderbilt Univ., Nashville, TN

Abstract: *Objective.* Small-diameter afferent axons carry various sensory signals that are critical for the homeostasis of vital physiological conditions. Infrared (IR) neural inhibition (INI) can selectively heat block small-diameter axons, which has potential for translational applications such as pain management. Previous work suggested that IR-heating-induced acceleration of voltage-gated potassium channel kinetics is the dominant mechanism for INI. Therefore, we hypothesized that other heating methods, such as resistive heating (RH) with a heating cuff, could reproduce the selective inhibition effect by INI. *Method.* We tested this hypothesis *in vitro* using pleural-abdominal connective nerves of *Aplysia californica* (n=6). A thermocouple was co-located with the IR optical fiber and heating cuff to measure temperature elevation (ΔT) on the nerve surface during the heating period. For each nerve, both heating modalities were applied at a range of power levels covering a similar ΔT range. We also deduced the ΔT at the axon region of the nerve by simulating the INI and RH scenarios with the COMSOL Multiphysics® and mesh-based Monte Carlo simulation (MMC) of light propagation. We recorded stimulated compound action potentials (CAPs), which were segmented into subpopulations (fast large-diameter vs. slow small-diameter) based on their conduction velocities. We calculated normalized inhibition strength (NIS) based on the reduction of rectified area under the curve of the CAPs when different ΔT was tested. The size selectivity was quantified by the NIS of each subpopulation. *Results.* INI and RH showed a similar selective inhibition effect on CAP subcomponents for slow-conducting axons. This was confirmed by the inhibition probability vs. ΔT dose-response curve based on approximately two-thousand CAPs. The measured nerve surface ΔT for a 50% probability of inhibition of the small-diameter axons was 9.3 °C for INI and 10.0 °C for RH. Simulation of the heating process revealed that the average ΔT in the axon region of the nerve was identical (9.4 °C for both INI and RH). The inhibition selectivity of the two heating modalities was similar. Together, the results suggested that size selectivity on small-diameter axons is an inherent property of heat-induced neural block. In addition, to achieve the same ΔT, RH only required half of the total electrical power. *Conclusion.* The results demonstrate that selective INI can be reproduced by other heating modalities such as resistive heating using a simple and cheap heating cuff. Resistive heating has great potential for longitudinal studies and translational applications because of its high energy efficiency and simple design.

Disclosures: J. Zhuo: None. **C.E. Weidrick:** None. **Y. Liu:** None. **M.A. Moffitt:** None. **E.D. Jansen:** None. **H.J. Chiel:** None. **M.W. Jenkins:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.02

Topic: I.08. Methods to Modulate Neural Activity

Support: National Institutes of Health (DC 01089)
Fondation Bertarelli (Translational Neuroscience and Neuro-Engineering)
National Institute on Deafness and Other Communication Disorders (R01

DC015824)
Fondation Bertarelli (Bertarelli Endowed Professorship)
U.S. Department of Defense (CDMRP - VR170089)
BRAIN Initiative (NS110575)
Novo Nordisk Fonden (0064289)

Title: Magnetic Stimulation of the Cochlear Nerve: Enabling Next-Generation Cochlear Implants

Authors: *J.-I. LEE[1], R. SEIST[2], S. MCINTURFF[2], D. LEE[2], M. BROWN[2], K. M. STANKOVIC[2], S. FRIED[1];
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Abstract: Cochlear implants (CIs) provide sound and speech sensations for patients with severe to profound hearing loss by electrically stimulating the auditory nerve. While most CI users achieve some degree of open-set word recognition under quiet conditions, hearing that utilizes complex neural coding (e.g., appreciating music) has proved elusive, probably because of the inability of CIs to create narrow regions of spectral activation. Several novel approaches have recently shown promise for improving spatial selectivity, but substantial design differences from conventional CIs will necessitate much additional safety and efficacy testing before clinical viability is established. Outside the cochlea, magnetic stimulation from small coils (micro-coils) has been shown to confine activation more narrowly than that from conventional micro-electrodes, raising the possibility that coil-based stimulation of the cochlea could improve the spectral resolution of CIs. To explore this, we delivered magnetic stimulation from micro-coils to multiple locations of the cochlea and measured the spread of activation utilizing a multi-electrode array inserted into the inferior colliculus; responses to magnetic stimulation were compared to analogous experiments with conventional micro-electrodes as well as to responses when presenting auditory monotones. Encouragingly, the extent of activation with micro-coils was ~60% narrower compared to electric stimulation and largely similar to the spread arising from acoustic stimulation. The dynamic range of coils was more than three times larger than that of electrodes, further supporting a smaller spread of activation. While much additional testing is required, these results support the notion that magnetic micro-coil CIs can produce a larger number of independent spectral channels and may therefore improve auditory outcomes. Further, because coil-based devices are structurally similar to existing CIs, fewer impediments to clinical translational are likely to arise.

Disclosures: J. Lee: None. **R. Seist:** None. **S. McInturff:** None. **D. Lee:** None. **M. Brown:** None. **K.M. Stankovic:** None. **S. Fried:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.03

Topic: I.08. Methods to Modulate Neural Activity

Support: Samsung Electronics (PHO021239)

Title: Exercise using exoskeletal hip-assist robot improved physical function and walking efficiency in older adults

Authors: *S.-H. LEE[1], J. KIM[1], H. CHUN[1], E. KIM[2], E. CHUNG[2], H.-J. LEE[4], D. KIM[4], Y.-H. KIM[1,3];
[1]Samsung Med. Ctr., Samsung Med. Ctr., Seoul, Korea, Republic of; [2]Sungkyunkwan Univ., [3]Sungkyunkwan Univ., Seoul, Korea, Republic of; [4]Samsung Electronics, Samsung Electronics, Suwon, Korea, Republic of

Abstract: Robotic technology has developed rapidly in recent years and several robotic devices have been applied in the process to improve physical, sensory, intellectual, psychological, and social functioning levels of people with disabilities and elderly people. The purpose of this study was to investigate the effect of exercise using the newly developed wearable robotic hip exoskeleton, the EX1, on physical function and walking efficiency in older adults. We designated four parallel experimental conditions and randomly assigned participants into four groups: Group A (overground walking exercise without EX1), Group B (overground walking exercise using resistance mode of EX1), Group C (stair ascent exercise using assistance mode of EX1), and Group D (inclined treadmill walking exercise using assistance mode of EX1). A total of 60 community-dwelling elderly persons participated in 10 exercise intervention sessions for 4 weeks, and all participants were assessed at 2 time points: before and after exercise. Physical functions were measured by the 10-Meter Walk Test for self-selected velocity (10MWT-SSV), Short Physical Performance Battery (SPPB), Berg Balance Scale (BBS), Timed Up and Go (TUG), Functional Reach Test (FRT), Geriatric Depression Scale-Short Form (GDS-SF), and muscle strength of trunk and lower extremity. Cardiopulmonary metabolic energy efficiency was measured using a portable telemetric gas analyzer system, K5. In 10MWT-SSV and TUG, a significant increase was observed in Groups B, C, and D ($p < 0.01$, $p < 0.05$), but not in Group A. In SPPB and FRT, there was a statistically significant improvement only in Group D ($p < 0.05$, $p < 0.01$), and GDS-SF decreased significantly after exercise with EX1 in Groups B and D ($p < 0.05$). Trunk and lower limb muscle strength was more increased in the exercise groups with EX1 than without EX1, especially in Group B, which performed exercise using the resistance mode of EX1. Furthermore, the net metabolic energy costs and energy expenditure measurement during walking significantly improved in the exercise groups C and D ($p < 0.05$), which performed stair ascent and inclined treadmill walking exercise using the assistance mode of EX1. The findings in this study provide evidence supporting application of EX1 in physical activity and exercise is effective to improve age-related declines in physical function and walking efficiency among older adults. In addition, personalized exercise programs using different modes and training environments with EX1 can be applied to enhance physical performance and walking efficiency in the elderly.

Disclosures: **S. Lee:** None. **J. Kim:** None. **H. Chun:** None. **E. Kim:** None. **E. Chung:** None. **H. Lee:** None. **D. Kim:** None. **Y. Kim:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.04

Topic: I.08. Methods to Modulate Neural Activity

Support: Marie Skłodowska-Curie grant agreement No 861423

Title: A membrane-targeted polyconjugated compound engineered for photostimulation and optoporation

Authors: *M. E. PFEFFER[1,3], J. JASNOOR[1,3], M. L. DIFRANCESCO[1,4], E. COLOMBO[1,4], A. MARCHESI[5], F. VACCA[1], L. MARAGLIANO[1,6], L. BEVERINA[7], P. BALDELLI[3,4], G. LANZANI[8,2], F. BENFENATI[1,3,4];
[1]Ctr. for Synaptic Neurosci. and Technol., Italian Inst. of Technol., Genova, Italy; [2]Ctr. for Nano Sci. Technol., Italian Inst. of Technol., Milan, Italy; [3]Dept. of Exptl. Med., Univ. of Genova, Genova, Italy; [4]Irccs, Ospedale Policlinico San Martino, Genova, Italy; [5]Dept. di Medicina Sperimentale e Clinica, Univ. Politecnica delle Marche, Torrette di Ancona, Italy; [6]Dept. of Life and Envrn. Sci., Univ. Politecnica delle Marche, Ancona, Italy; [7]Dept. di Scienza dei Materiali, Univ. degli Studi di Milano Bicocca, Milan, Italy; [8]Dept. di Fisica, Politecnico di Milano, Milan, Italy

Abstract: Light-driven modulation of neuronal activity at high spatio-temporal resolution is becoming of high interest in neuroscience opening up to diverse applications. Our efforts are dedicated to accomplishing light-controlled modulation of passive neuronal properties without the need of genetic modification. We engineered a membrane-targeted polyconjugated compound (BV-1) that undergoes a charge transfer upon light stimulation. Our findings using molecular dynamics simulations and confocal imaging show that BV-1 spontaneously partitions into the lipid bilayer when added to the extracellular medium of primary neurons. In whole-cell recordings of primary hippocampal neurons, no modulation of neuronal activity is observed in the dark. In contrast, millisecond pulses of light in the cyan region of the spectrum induce a progressive decrease in membrane resistance and an increasing inward current matched to an irreversible depolarization. High-speed atomic force microscopy imaging on planar lipid bilayers incubated with our compound suggests that the underlying mechanism is the light-driven pore formation in the cellular membrane. Indeed, live confocal imaging experiments and electrophysiological recordings revealed the entry of sodium into primary neurons upon light stimulation. BV-1 affects the passive neuronal properties and impairs voltage-activated ion currents, affecting the shape of generated action potentials. Within seven days after initial incubation, BV-1 is partially internalized, and light-driven membrane depolarization is consequently reduced, indicating that the effect is due to the presence of the compound at the plasma membrane level. This work provides the first proof of concept study, prompting us to take advantage of BV-1 for its unique light-controlled properties and perform patch-clamp experiments in a light-controlled perforated configuration. The main advantage of BV-1 is the possibility of modulating membrane perforation using light as a trigger and with significantly

faster kinetics compared to conventional antibiotics used for the perforated-patch electrophysiological technique.

Disclosures: **M.E. Pfeffer:** None. **J. Jasnoor:** None. **M.L. DiFrancesco:** None. **E. Colombo:** None. **A. Marchesi:** None. **F. Vacca:** None. **L. Maragliano:** None. **L. Beverina:** None. **P. Baldelli:** None. **G. Lanzani:** None. **F. Benfenati:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.05

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH/NINDS (1U24NS113647)
USC Neurorestoration Center

Title: A miniaturized coil for studying transcranial magnetic stimulation in rodents

Authors: ***W. JIANG**, R. ISENHART, Z. LU, H. XU, D. J. LEE, C. Y. LIU, D. SONG; USC, USC, Los Angeles, CA

Abstract: Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique widely used in clinical and experimental settings. Animal model is an indispensable tool for understanding the underlying mechanisms of TMS since it allows invasive electrophysiological investigations to the effects of TMS at the single neuron level. However, most commercially available coils are designed for human studies, which have large geometric sizes and electromagnetic fields that cause non-focal stimulation in small animals. To address this issue, we designed, fabricated, and tested a miniaturized TMS coil for small animal studies. This coil (5 mm outer diameter) was composed of a C-shaped iron powder core and 30 turns of insulated copper wires. The magnetic field and the induced electric field were measured via a search-coil magnetometer and a dipole probe. The coil was able to generate a maximum magnetic and electric field at 473 mT and 5.2 V/m. Finite element modeling was performed to compare those measurements with simulation. A 3D head model derived from magnetic resonance imaging (MRI) data was used to characterize the electric field in the rodent brain. To evaluate the neural responses of repetitive TMS (rTMS), high frequency subthreshold rTMS (10 Hz, 3 min) was delivered to the sensorimotor cortex of anesthetized rats (n=10). Microelectrodes were implanted in the primary motor (M1) and somatosensory (S1) cortices to record local field potentials (LFPs) and single unit activities before and after rTMS. Results show that 10 Hz rTMS consistently alters the LFP frequency bands (two-tailed t-test, $p < 0.05$) and increases the mean firing rates of single unit activities (paired t-test, $p<0.01$) in both regions. S1 neurons show larger increases of mean firing rates compared to M1 neurons. This experimental paradigm makes it possible to examine the effects of TMS on both single neuron and neuronal population levels. It

provides a powerful tool for studying the neurobiological mechanisms of TMS and optimizing therapeutic strategies for treating neurological and neuropsychiatric disorders.

Disclosures: **W. Jiang:** None. **R. Isenhart:** None. **Z. Lu:** None. **H. Xu:** None. **D.J. Lee:** None. **C.Y. Liu:** None. **D. Song:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.06

Topic: I.08. Methods to Modulate Neural Activity

Support: NSF Grant 1631329

Title: Update on our user-friendly, universal closed-loop phase-locked stimulation controller based on oscillatory episodes in the LFP

Authors: *J. DITTERICH;
Ctr. for Neurosci., Univ. of California, Davis, CA

Abstract: Synchronized oscillatory activity has been proposed to play important roles in modulating functional connectivity between populations of neurons and in memory storage/retrieval processes. Testing these hypotheses requires techniques that allow manipulation of the timing relationship between neural activity in different brain areas. Closed-loop phase-locked stimulation is such a technique. We have recently published a user-friendly, universal, robust algorithm for the detection of oscillatory activity in the LFP and prediction of its phase. Oscillatory episodes are detected based on analyzing the short-time power spectrum. An adjustable zero-phase bandpass filter in combination with the Hilbert transform are used for phase estimation. Linear extrapolation based on a Bayesian frequency estimate is used for phase prediction.
Here we present an update on our real-time implementation of this algorithm on an embedded device, which serves as a user-friendly, universal, standalone closed-loop phase-locked stimulation controller. The device is provided with an analog LFP signal, which is sampled at 1 kHz, and outputs a digital control signal for gating a stimulator. It can therefore be used with virtually any recording system and any stimulator. The algorithm was optimized for real-time implementation by performing the bandpass filtering in the frequency domain instead of the time domain, which reduces the number of required spectral transformations, and by replacing one of the time-consuming robust linear regressions with a standard linear regression after artifact rejection, which did not impact the overall detection and prediction performance. The embedded device features an FPGA, which is used for the time-critical input and output operations as well as a coprocessor for the spectral transformations, and a dual-core ARM processor running a real-time Linux operating system, which handles the remaining aspects of the algorithm and the user interface. Only a few milliseconds are needed between retrieving the last LFP sample of an

analysis window and scheduling the time intervals, when the stimulator will be activated. The only primary parameters that have to be specified by the user are the range of frequencies, within which oscillations are to be tracked, and the phase range, during which the stimulator should be active. Other parameters, like frequency-dependent detection thresholds for the presence of oscillatory activity and filter parameters, are adjusted automatically by the algorithm, which makes the device easy to use.

Disclosures: J. Ditterich: None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.07

Topic: I.08. Methods to Modulate Neural Activity

Support: R00MH120279
29878

Title: Material Engineering Toolset for Neurological Interfaces

Authors: *S. RAO;
UMass Amherst, Amherst, MA

Abstract: Effective engineering toolset can provide methodological assistance to link behavioral output to molecular-, cellular- and circuit-level neurological events and to reveal the neural mechanism underlying neurological and psychiatric disorders for the development of therapeutic approaches. We aim to develop a toolset platform with minimal invasiveness to biological tissue, functional longevity, widespread coverage of neural circuits, the capability to manipulate neurons at multiple scales, ranging from individual synapse to broad neural circuits, and the specificity to identify targeted neural populations. This toolset platform consists of two main directions to investigate neural circuits with behavioral observations: precise interventional tools for remotely controlled neuromodulation and real-time recording techniques to monitor neural dynamics. Firstly, a magnetic toolkit for remote neuromodulation, which allows remotely controlled release of pharmacological compounds to modulate targeted neural circuits. This chemomagnetic technique combines magnetic tools and behavioral neuroscience to enable temporally precise modulation of specific neural circuits underlying motivation and social interactions. Secondly, an optical recording system to monitor neural dynamics from multiple sites across the central nervous system in freely behaving mice with simultaneous behavioral output.

Disclosures: S. Rao: None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.08

Topic: I.08. Methods to Modulate Neural Activity

Support: University of Iowa Institute for Clinical and Translational Science, StrokeNet Pilot Grant, 2022

Title: Transcutaneous magnetic stimulation of the cervicothoracic spine: effect of stimulation site location on spinal motor evoked potentials

Authors: L. ZHU, S. G. NOPOULOS, K. M. ANDERSON, ***S. L. DEJONG**;
Physical Therapy and Rehabil. Sci., Univ. of Iowa, Iowa City, IA

Abstract: Transcutaneous magnetic spinal stimulation (TMSS) has the potential to become a comfortable, safe and effective neuromodulatory intervention to improve recovery in people with neural injury. Responsiveness of upper limb muscles to TMSS over the cervicothoracic spine, however, has not been fully characterized. For example, few studies have examined the effect of stimulation site location on TMSS-induced spinal motor evoked potentials (sMEPs). The purpose of this study was to map upper limb muscle responses to TMSS over the cervicothoracic spine. Seven healthy adults participated (3 male, age 44.2 ± 24.4 years). Surface electromyography electrodes recorded sMEPs from bilateral biceps brachii (BB), triceps brachii, wrist flexors, wrist extensors, abductor digiti minimi, and first dorsal interosseous. Magnetic stimulation was delivered using a MagVenture MagPro X100 stimulator and a C-B60 figure-of-eight coil. The coil was aligned at a 45-degree angle to the spine, to induce current flow in the tissues directed rostrally and toward the left. Prior investigation showed that this current direction elicited larger sMEPs in the left upper limb than other directions tested. A 3-column x 10-row grid of stimulation sites was marked on the skin over the cervicothoracic spine, with the middle column centered over the midline and left/right columns 3 cm laterally. Rows were spaced 1 cm rostrocaudally. The grid was aligned with the left column, 6^{th} row over the left wrist extensor optimal site, which had been previously determined. Using the grid, the optimal site and resting motor threshold (rMT) of the left BB was determined. Ten consecutive stimuli were delivered at each site using intensity 120 % of the left BB rMT, interstimulus intervals > 4 seconds, and a randomized order of sites. Neuronavigation using an electromagnetic motion tracking system and custom-written software ensured consistent, accurate placement and rotation of the coil. The average of 10 peak-to-peak sMEP amplitudes was calculated for each site. Across muscles, Friedman two-way ANOVA revealed significant differences across rostrocaudal and mediolateral levels (p < 0.001), consistent with known somatotopic patterns of segmental muscle innervation. Further, specificity of muscle activation across the 30 stimulation sites demonstrated selective neural activation induced by focal TMSS over the cervicothoracic spine. These findings will further inform development of TMSS as a neuromodulatory intervention.

Disclosures: L. Zhu: None. **S.G. Nopoulos:** None. **K.M. Anderson:** None. **S.L. DeJong:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.09

Topic: I.08. Methods to Modulate Neural Activity

Title: Transcranial magnetic stimulation over the precuneus disturbed its functional connectivity with the hippocampus

Authors: *M. ABDOLLAHI[1], A. MOHARRAMIPOUR[2], S. KITAZAWA[3];
[1]Grad. Sch. of Frontier Biosci. (FBS), Osaka Univ., Suita, Japan; [2]Lab. of Consciousness, Ctr. for Brain Sci. (CBS), RIKEN, Tokyo, Japan; [3]Grad. Sch. of Medicine, Osaka University/Center for Information and Neural Networks (CiNet), Natl. Inst. of Information and Communications Technol., Suita, Osaka, Japan

Abstract: Background: In recent years, it has become recognized that transcranial static magnetic stimulation (tSMS) is a promising non-invasive tool for modulating brain activity. According to the previous studies, the tSMS seems to be able to influence the brain's neuromodulatory functions just under the magnet. Despite this, the effects of tSMS on the different brain networks remain controversial.**Methods**: The experimental group comprised sixteen healthy individuals exposed to tSMS by placing a neodymium magnet (45 mm in diameter, 1 Tesla in the center) over their precuneus for an hour. We measured their resting brain activity before and immediately after the exposure using functional fMRI. We compared the tSMS with a sham (non-magnet metal) as a control in a within-subject design. We conducted this experiment on two different days, each exposing participants to a sham or magnet.**Results**: We selected the most affected part of the brain by the tSMS (dorsal part of the precuneus) and calculated its functional connectivity with the rest of the brain. We discovered that the tSMS blocked the connections between the precuneus, right hippocampus, and parahippocampal areas, in contrast to the sham. When we looked at the less affected regions in terms of the tSMS magnetic field, the significantly attenuated connections with the hippocampus disappeared, and some marginally significant regions in the frontal area came out.**Conclusion**: Our results are highly consistent with a recent tractography study, which reported the significant connections between the precuneus and the medial temporal lobe regions, including the hippocampus (Tatsuya & Atsushi, 2021). As the precuneus, hippocampus, and parahippocampal areas are highly involved in memory formation and retrieval, our findings might implicate that the tSMS on the precuneus should somehow disturb the memory-related functions.

Disclosures: M. Abdollahi: None. **A. Moharramipour:** None. **S. Kitazawa:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.10

Topic: I.08. Methods to Modulate Neural Activity

Support: NSF Grant NeuroNex 1707352

Title: Molecular, cellular and functional effects of chemogenetic neural stimulation

Authors: E. L. CRESPO[1], F. PARYANI[2], M. KNOBLOCK[1], J. PATEL[1], V. MENON[2], ***U. HOCHGESCHWENDER**[1];
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Abstract: Chemogenetic modulation of neural populations exerts selective control over cells engineered to express an exogenous receptor that responds selectively to a small molecule. Chemogenetic approaches have steadily gained use for studies requiring circuit-wide manipulation over longer periods of time in behaving experimental animals. There are several chemogenetic platforms for manipulating neural activity. These are built from either ligand gated ion channels (i.e. PSAMs, pharmacologically selective actuator modules) or G-protein coupled receptors (i.e. DREADDs, designer receptors exclusively activated by designer drugs). An orthogonal chemogenetic approach is BL-OG (BioLuminescent-OptoGenetics), where an opsin is activated by bioluminescent light emitted from a tethered luciferase (luminopsin, LMO); light emission occurs only in the presence of a luciferin that is oxidized by the luciferase enzyme. While in both acute and long-term treatments the effects of chemogenetic activation of neurons on animal behavior are well documented, information is lacking on the molecular, cellular, and functional effects of chemogenetic stimulation technologies on the neurons expressing the actuators. We initiated in vitro studies designed to gain insight into how chemogenetic stimulation affects neurons by characterizing their electrophysiological attributes, their morphological features, and their transcriptome signatures. We cultured primary rat cortical neurons on multi electrode arrays (MEAs) for electrophysiological recordings, on 24 well plates for morphological analysis, and on 12 well plates for collection of RNA. Mature cultures of neurons expressing three representative chemogenetic actuators, hM3Dq, PSAM^4-5HT3 and LMO7 or a control plasmid (EYFP), were stimulated once daily over 5 days with their respective effectors (CNO, PSEM, CTZ, or vehicle). The data showed differences between chemogenetic platforms in how the neurons, after repeated stimulation, reacted to excitation, the degree of their dendritic arborization, and the quantity and quality of transcriptome changes. This information on how chemogenetic stimulation affects cells is important because the causality between neural activity and behavior remains obscured without knowledge about effects of stimulation modalities on genetic repertoire, morphology, and/or electrophysiological properties of neurons. Identification of key parameters significantly altered through chemogenetic stimulation will guide interpretation of past and future chemogenetic experiments and will be instructive for users and toolbuilders of chemogenetic platforms.

Disclosures: E.L. Crespo: None. **F. Paryani:** None. **M. Knoblock:** None. **J. Patel:** None. **V. Menon:** None. **U. Hochgeschwender:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.11

Topic: I.08. Methods to Modulate Neural Activity

Support: NWO VENI

Title: Magnetothermal nanoparticle technology alleviates parkinsonian-like symptoms in mice

Authors: *S. HESCHAM[1], P.-H. CHIANG[2], D. GREGUREC[3], J. MOON[4], M. CHRISTIANSEN[5], A. JAHANSHAHI[1], H. LIU[1], D. ROSENFELD[4,6], A. PRALLE[7], P. ANIKEEVA[4], Y. TEMEL[1];
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Abstract: Deep brain stimulation (DBS) has long been used to alleviate symptoms in patients suffering from psychiatric and neurological disorders. The application of DBS to modulate neural circuits is, however, afflicted by its mechanical invasiveness and the use of chronically implanted leads. Here, we further characterized a wireless alternative to DBS, called magnetothermal DBS, in freely moving mice. Magnetothermal DBS exploits hysteretic heating of magnetic nanoparticles in the presence of an alternating magnetic field. Therefore, we heat-sensitized neurons by expressing the cation channel TRPV1 in the subthalamic nucleus (STN) first in naïve and then in parkinsonian mice. We found that the delivery of magnetic nanoparticles to the STN allows remote modulation of motor behavior in mice exposed to an alternating magnetic field. Moreover, mDBS of the STN reversed the motor deficits in a mild and severe parkinsonian model. Immunohistochemical analysis revealed increased neural activity in several motor regions, suggesting a circuit-wide effect of STN mDBS. Our results indicate that mDBS is able to activate deep-brain circuits therapeutically without the need for surgical implants and connectors.

Disclosures: S. Hescham: None. **P. Chiang:** None. **D. Gregurec:** None. **J. Moon:** None. **M. Christiansen:** None. **A. Jahanshahi:** None. **H. Liu:** None. **D. Rosenfeld:** None. **A. Pralle:** None. **P. Anikeeva:** None. **Y. Temel:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.12

Topic: I.08. Methods to Modulate Neural Activity

Support: University of Iowa Institude for Clinical and Translational Science, StrokeNet Pilot Grant, 2022

Title: Transcutaneous magnetic stimulation of the cervicothoracic spine: effect of induced current direction on spinal motor evoked potentials

Authors: *L. ZHU, S. G. NOPOULOS, K. M. ANDERSON, S. L. DEJONG;
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Abstract: Spinal stimulation is an emerging strategy to modulate neural excitability and improve motor recovery after injury. Although most studies have focused on electrical stimulation, transcutaneous magnetic spinal stimulation (TMSS) is an alternative method that may produce different effects compared to electrical methods. Few studies have applied TMSS in humans, thus effects of variations in stimulation parameters are unknown. The purpose of this study was to determine how the direction of induced current influences TMSS-induced spinal motor evoked potentials (sMEPs). Nine healthy adults participated (3 male, age 40.2 ± 22.6 years). Surface electromyography electrodes were applied over wrist extensor muscles bilaterally. Magnetic stimulation was delivered using a MagVenture MagPro X100 stimulator and C-B60 figure-of-eight coil. An optimal stimulation site for the left wrist extensors was determined by moving the coil rostro-caudally along a line 3 cm to the left of midline, and the left wrist extensor resting motor threshold (rMT) was determined at that site. Additional sites were marked at the same rostro-caudal level, one in the midline and one 3 cm to the right of midline. Ten stimuli were delivered to each site at 8 induced current directions, produced by rotating the coil in 45-degree increments. The order of sites and directions were randomized. Intensity was 120% of the left wrist extensor rMT. Consecutive stimuli were separated by at least 4 seconds. Neuronavigation using an electromagnetic motion tracking system and custom-written software ensured accurate, consistent coil rotation and placement. Peak-to-peak amplitudes were determined for all sMEPs and averaged across the 10 repetitions at each site and induced current direction. Friedman 2-way ANOVA by ranks identified differences across sites and induced current directions (p < 0.001). For the left site, pairwise comparisons revealed larger sMEPs in the left wrist extensors when induced current was directed rostrally and to the left (p < .05). Conversely, for the right site, sMEPs in the right wrist extensors were larger when induced current was directed rostrally and to the right (p < 0.05). Left wrist extensor sMEPs elicited at the left site with rostral-left induced current were similar to right wrist extensor sMEPs elicited at the right site with rostral-right induced current (p > 0.9). At the midline site, smaller amplitude sMEPs were elicited from bilateral wrist extensors. In summary, the direction of induced current strongly affects responses to TMSS, and the optimal angle differs on the left versus right sides. These findings will inform further development of TMSS techniques.

Disclosures: L. Zhu: None. **S.G. Nopoulos:** None. **K.M. Anderson:** None. **S.L. DeJong:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.13

Title: WITHDRAWN

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.14

Topic: I.08. Methods to Modulate Neural Activity

Support: Connecticut State Grant

Title: A precise neuromodulatory technology for phase-dependent modulation of alpha oscillations with audio stimuli.

Authors: T. J. HARLOW[1], S. BRESSLER[2], *H. L. READ[1];
[1]Univ. of Connecticut, Storrs, CT; [2]Elemind Technologies, Inc, Cambridge, MA

Abstract: Synchronous alpha oscillations coordinate neural ensemble and brain network activity to enable the ability to detect salient stimuli, ignore irrelevant sensory events, and to maintain attention, working memory, and executive control. Intracranial recordings identify alternating inhibited and excitable neural network states corresponding to alpha oscillation peak and trough phases, respectively (Haegens et al., J. Neurosci. 2015). Accordingly, scalp electroencephalogram (EEG) studies find the sensory-evoked response potential (ERP) varies when the stimulus onset occurs during the peak versus trough phase of alpha oscillations (Haegens & Colmic, 2018). In theory, differences in the ERP could reflect a phase-dependent feedforward sensory-evoked modulation of alpha oscillations. To test this hypothesis, we employ a novel neuromodulatory technology (Schreglmann et al., Nature Comm. 2020) to track alpha oscillation phase for delivering phase-locked acoustic stimulation. Firstly, the resting alpha frequency measured at two EEG channel positions (Fz, Fpz) was on average 10.2 (1.18) Hz (N=20 subjects). Secondly, across random alpha phases, the pink-noise sound pulse (65 dB) evoked ERPs had early positive component “P50” latencies of 56 (10) ms and 63 (8) ms at the Fz and Fpz positions, respectively. Based on the frontal alpha frequency and ERP latency for each subject, we calculated the “peak” and “trough” onset phases for stimulation to allow the ERP P50 component to arrive during the “excitable” (trough) or “inhibited” (peak) phases, respectively. To probe the phase-dependent effects of audio stimulation on alpha, subjects rehearsed multiplication tables with eyes closed while ignoring the audio sound bursts. With our “individualized” audio stimulation phase-locked to alpha peak, the alpha oscillation magnitude and alpha-gamma cross-frequency coupling were decreased and the alpha oscillations following stimulation were disrupted. In contrast, with alpha trough phase-locking, the alpha oscillations continued for 2.5 cycles after simulation. These results support our hypothesis that sensory stimulation can modulate alpha in a phase-dependent manner. Across all conditions, the phase-

locking error for the frontal channel was low and on average 8.85° (5.57). These results support the feasibility to develop this novel brain-computer interface technology to modulate aberrant alpha oscillations observed in a variety of conditions including age-related memory loss, dementia and hyperarousal insomnia.

Disclosures: **T.J. Harlow:** None. **S. Bressler:** A. Employment/Salary (full or part-time):; Elemind Technologies, Inc. **H.L. Read:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Elemind Technologies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Elemind Technologies, Inc..

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.15

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01NS105691
NSF CAREER 1943906

Title: A Photovoltaic Polymer Interfaces Of Ultrasmall, Untethered Carbon Fiber Electrodes For Neuromodulation.

Authors: *K. CHEN[1,4], B. WU[1,4], D. KRAHE[1], X. CUI[1,4,2], T. D. KOZAI[1,4,3,2,5];
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Abstract: Advanced neuromodulation technologies are of great importance for treating neurological disorders as well as exploring basic neuroscience. Currently, the most prevalent neuromodulation technique focuses on electrical microstimulation, which delivers a depolarizing charge into the brain through a wired tether from an external power source. However, traditional electrical microstimulation requires large-dimension invasive microelectrodes implanted into the brain, which leads to tissue damage and neuronal apoptosis. This limits the therapeutic potential of electrical stimulation on brain injuries and neurological disorders. To address this limitation, we developed a novel stimulation technique that minimizes tissue damage and device-induced mechanical strain. Our prototype involves a free-floating 7 μm diameter carbon fiber electrode interfaced with a special photovoltaic polymer coating. The ultrasmall, flexible carbon fiber electrode reduces the risk of neuroinflammation and chronic foreign body responses. Meanwhile, in order to avoid tether-related tissue damage, this technique utilizes the photoelectric effect to create a transient electrical field for local neuronal activation. Therefore, it is not necessary to connect it to an external power source. A special organic polymer coating, poly(3-hexylthiophene) (P3HT) and [6,6]-phenyl C_{61}-butyric acid methylester (PCBM) blends, is

deposited on carbon fiber electrode to increase light conversion efficacy. With a strong photovoltaic effect, P3HT:PCBM has wide applications in solar cell and recently has been used in wafer-based *in vitro* biological stimulation. Therefore, this polymer interface allows to promote neuronal activation with lower laser power to avoid phototoxic damage and remain in the safety window. Our preliminary data show that compared to bare carbon fiber electrode, P3HT:PCBM interface leads to an increase in voltages by 379.2± 32.1% under 800 nm wavelength, 20 mW intensity two-photon laser stimulation. These preliminary data suggest this technique has a great potential of providing a promising alternative stimulation modality for future neuroscience study and clinical applications.

Disclosures: K. Chen: None. **B. Wu:** None. **D. Krahe:** None. **X. Cui:** None. **T.D. Kozai:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.16

Topic: I.08. Methods to Modulate Neural Activity

Support: R36MH130105-01

Title: Toward implementing a DREADDs-fMRI perturbation study of the anterior cingulate cortex in Nonhuman Primates

Authors: *A. K. CUSHNIE, A. M. MANEA, D. BULLOCK, J. ZIMMERMANN, S. R. HEILBRONNER;
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Abstract: The use of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), in nonhuman primates (NHPs) allows for targeted causal perturbation in a model brain that is highly homologous with the human brain. Resting state functional magnetic resonance imaging (rs-fMRI) is a non-invasive neuroimaging approach that measures blood oxygenation level - dependent (BOLD) signals in the absence of a task. Combining DREADDs with rs-fMRI allows for remote, reversible perturbation of neuronal activity accompanied by brain wide visualization of functional connectivity.
The aims of this study were to (1) *Characterize the effects of novel chemogenetic ligands on resting state functional properties **prior** to the expression of DREADDs.* (2) *Use DREADDs to **modulate** the functional connectivity of the Anterior Cingulate Cortex (ACC), as part of the salience network.*
First, we characterized the effects of chemogenetic ligands prior to DREADDs expression. Low dose clozapine (CLZ) and novel ligand deschloroclozapine (DCZ) have a high affinity for DREADDS with minimal off-target binding, as compared to Clozapine-N-Oxide, which has poor blood-brain barrier permeability and is metabolized into CLZ. Macaques (N=2) were

administered CLZ or DCZ (at 0.1 and 0.2 mg/kg) acutely before the start of each rs-fMRI session. We then assessed resting-state functional connectivity (rs-FC) by examining temporal correlations between spontaneous BOLD, as well as intrinsic neural timescales (INTs) a innate property of the brain that reflects task and variable independent temporal fluctuations in the neural signal.
Our results revealed that CLZ, but not DCZ, induced consistent changes in rs-FC and INTs prior to DREADDs expression. This was true at both doses. Moreover, rs-FC profiles become more homogeneous after chemogenetic ligand delivery. Overall, this suggests that DCZ, and especially low-dose DCZ, has a negligible impact on rs-FC and INTs and is better suited for future studies. This study highlights the need for caution when selecting chemogenetic ligands. The results presented here suggest that some chemogenetic ligands may induce alterations in brain activity *independent* of their DREADD-mediated role.
Next, we injected the bilateral ACC with AAV5-CAMK11-hM4DI - HA and AAV5-CAMK11-hM4DI-Mcherry. The ACC has widely dispersed anatomical connections and is a core node for many brain networks. Planned analysis will employ a region of interest approach, and network metrics to evaluate local and global changes in rs-FC following ACC inhibition. As well as explore ACC inhibition in the context of the Salience Network.

Disclosures: A.K. Cushnie: None. **A.M. Manea:** None. **D. Bullock:** None. **J. Zimmermann:** None. **S.R. Heilbronner:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.17

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH 1RF1MH117055
NIH 1DP2MH119425
NIH 5R01NS107472
NIH 5R61DA051530

Title: Dart.2—Optimized capture chemistry for cell-specific pharmacology

Authors: B. C. SHIELDS[1], H. YAN[1], S. S. X. LIM[1], S. C. BURWELL[1], E. FLEMING[1], C. M. CAMMARATA[1], E. KAHUNO[1], V. Z. GOLDENSHTEIN[1], I. A. WEAVER[1], T. M. HAWLEY[1], M. L. SCALABRINO[1], M. THAPA[1], P. P. VAGADIA[2], M. MCDONNELL[3], A. B. REITZ[3], G. E. SCHILTZ[2], L. L. GLICKFELD[1], C. HULL[1], G. D. FIELD[1], ***M. R. TADROSS**[1]; [1]Duke Univ., Durham, NC; [2]Northwestern Univ., Evanston, IL; [3]Fox Chase Chem. Diversity Ctr., Doylestown, PA

Abstract: Neuropharmacology is central to the treatment of brain disorders. Nevertheless, new tools are needed to untangle how canonical drug-receptor interactions are transformed by

interwoven brain cells to alter mood, anxiety, addiction, psychosis, attention, and motor coordination. **DART** (drugs acutely restricted by tethering) offers a path forward, by making it possible to deliver clinical drugs to one cell type at a time, observe ensuing behaviors and cellular dynamics, and reconstruct mechanisms from parts to the whole. DART leverages a local-dosing approach, in which clinical drugs are captured and locally accumulated onto genetically defined cells to achieve cellular specificity. This simplicity facilitates compatibility to broad pharmaceutical classes. However, the resulting cellular specificity is approximate, as governed by the pharmaceutical dose-response curve. Here we describe the DART.2 platform, comprising three advances. First, we improve cellular specificity via optimized capture, which accumulates drug to ~1,000-times the ambient concentration in minutes. Second, we improve rigor with control reagents and fluorescent tracers, providing a behavior-independent quantitative metric of target engagement. Third, we extend the approach to positive allosteric modulators, demonstrating compatibility with this clinically significant class. Four new DART.2 pharmaceuticals are showcased, enabling antagonism or positive-allosteric modulation of excitatory (AMPAR) or inhibitory ($GABA_AR$) synapses. Across four labs, we tested reagents in the mouse basal ganglia, cerebellum, retina, and visual cortex. Collectively, we find that DART.2 enables cell-specific pharmacology over large brain volumes, dosing from a distance, and safe delivery of even epileptogenic drugs. We provide a distribution platform for reagents, including click-chemistry modules for extension to diverse pharmaceuticals.

Disclosures: B.C. Shields: None. **H. Yan:** None. **S.S.X. Lim:** None. **S.C. Burwell:** None. **E. Fleming:** None. **C.M. Cammarata:** None. **E. Kahuno:** None. **V.Z. Goldenshtein:** None. **I.A. Weaver:** None. **T.M. Hawley:** None. **M.L. Scalabrino:** None. **M. Thapa:** None. **P.P. Vagadia:** None. **M. McDonnell:** None. **A.B. Reitz:** None. **G.E. Schiltz:** None. **L.L. Glickfeld:** None. **C. Hull:** None. **G.D. Field:** None. **M.R. Tadross:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.18

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant ZIAMH002955

Title: Parametric Effects of Intertrain Interval of Theta Burst Stimulation (TBS) On Changes in Motor Cortical Excitability

Authors: *H. GURA, E. FEUER, C. ABBOUD CHALHOUB, S. AWASTHI, M. NOH, B. LUBER, S. H. LISANBY, Z.-D. DENG;
Noninvasive Neuromodulation Unit, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Theta burst stimulation (TBS) is a form of transcranial magnetic stimulation (TMS) shown to modulate cortical excitability with lasting after-effects and is used as a treatment for

major depressive disorder. Standard TBS trains consist of bursts of 3 pulses at 50 Hz, applied at a frequency of 5 Hz. These trains are repeated with a specified intertrain interval (ITI) for a total of 600 pulses. Prior studies demonstrated that continuous TBS (cTBS), in which the TBS trains were delivered continuously (i.e., ITI=0 s), inhibit cortical excitability, and decrease motor evoked potential (MEP) amplitude following TBS. Intermittent TBS (iTBS), with an ITI of 8 s, was found to increase cortical excitability and MEP amplitude. Given that the cTBS and iTBS protocols differ only in the ITI, we aimed to systematically assess the effects of ITI on TBS-induced changes in motor cortical excitability. Twenty-six healthy adults (18 female, 34 ± 10.5 years old) participated in this study. Each participant underwent six TBS sessions with different ITI conditions in a pseudo-randomized order: 0 (cTBS), 2, 5, 8 (iTBS), 11, and 14 s. MEPs were measured at baseline, immediately after TBS, then at 15, 20, 25, 30, 45, and 60-minute time points. TMS was applied using a figure-eight coil (MagVenture) to the left primary motor cortex. MEPs were recorded from the contralateral first dorsal interosseous muscle. TBS was administered at 70% resting motor threshold (RMT) for 600 pulses. Single pulse TMS probes at 130% RMT were used to measure MEPs. We used a linear mixed effects model to analyze MEP changes relative to baseline across timepoints and ITI conditions. The linear model showed that there was a significant main effect of ITI ($t = 5.32$, $p < 0.001$) and of time point ($t=4.9$, $p<0.001$) on MEP amplitude. Across ITI conditions, MEPs were inhibited relative to baseline between 5- and 20- minutes post TBS, with significant inhibition occurring at 10- and 20-minute time points ($p < 0.05$). MEPs were significantly facilitated at the 60-minute time point relative to baseline ($p < 0.001$). There were no effects of age, sex, or race. This work suggests that manipulation of ITI can be a way of optimizing the plasticity effects of TBS. Optimizing these parameters could potentially enhance its neuromodulatory effect, and in turn, may enhance therapeutic response in depression.

Disclosures: **H. Gura:** None. **E. Feuer:** None. **C. Abboud Chalhoub:** None. **S. Awasthi:** None. **M. Noh:** None. **B. Luber:** None. **S.H. Lisanby:** None. **Z. Deng:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.19

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant ZIA000069
NIH, National Institute on Drug Abuse - Intramural Research Program

Title: A dual chemogenetic strategy for cell type-specific bidirectional neuromodulation

Authors: *M. A. BOEHM[1,2], M. LEVINSTEIN[1], E. A. STEIN[1], M. MICHAELIDES[1,3];
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Abstract: Chemogenetic technologies provide a valuable method for selective neuromodulation of targeted cell populations and have potential for translational and clinical applications. Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) and Pharmacologically Selective Actuator Modules (PSAMs) are two types of chemogenetic systems used to modulate brain activity. Recent studies have demonstrated the use of positron emission tomography (PET) to assess the efficacy of novel chemogenetic ligands and localize DREADD and PSAM expression. In this study, we piloted a dual chemogenetics approach with hM3Dq and PSAM4-GlyR and used [^{18}F]fluorodeoxyglucose (FDG) to measure brain activity following administration of JHU37160 (J60, DREADD agonist) or uPSEM817 (PSAM agonist). A co-injection of adeno-associated viral vectors $AAV_{2/5}$-Syn1-HA-hM3Dq and $AAV_{2/5}$-Syn1-PSAM4-GlyR was delivered into the left or right motor cortex (M1) of rats (Sprague Dawley, n = 4 female and 4 male) for targeted neuronal transduction. Animals were administered J60 (0.1 mg/kg), uPSEM817 (0.1 mg/kg), or saline (i.p.) to assess the effects of chemogenetic stimulation on awake brain activity and locomotor behavior. Treatment with J60 or uPSEM817 resulted in higher FDG uptake in the M1 AAV injection area compared to within-subject saline scans ($t = 2.9$, $p < 0.01$). However, the two drugs elicited different effects in brain regions outside of M1. J60 scans showed higher FDG uptake in areas such as the somatosensory cortex (S1), striatum, ipsilateral hippocampus, and contralateral insular cortex (IC), but lower FDG in areas including ipsilateral orbitofrontal cortex (OFC) and IC. In contrast, uPSEM817 scans showed no areas with higher uptake other than the M1 AAV site when compared to saline scans. Instead, we observed lower FDG uptake in the ipsilateral OFC, IC and cerebellum, and bilaterally in S1, striatum and hippocampus. Locomotor behavior analysis showed significantly greater distance travelled and number of rotations following uPSEM817 compared to saline ($p < 0.05$). Treatment with J60 resulted in greater average velocity ($p < 0.05$) but no significant differences in distance traveled or rotations compared to saline. Immunohistochemistry confirmed brain expression of hM3Dq and PSAM4-GlyR, and 50-60% of cells with expression showed co-expression of both receptors. This study demonstrates hM3Dq and PSAM4-GlyR can be combined *in vivo* to elicit distinct effects on brain activity and behavior in response to their respective agonists.

Disclosures: M.A. Boehm: None. **M. Levinstein:** None. **E.A. Stein:** None. **M. Michaelides:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.20

Topic: I.08. Methods to Modulate Neural Activity

Title: Development of a neurofeedback system using In-Ear EEG for eustress-distress modulation

Authors: D. INOUE[1], *K. UEDA[1], T. IBARAKI[2], Y. IMAMURA[2];
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Abstract: In recent years, neurofeedback has been increasingly used to modulate cognitive functions. Especially in the working environment, it is desirable to measure and train brain activity with a simple device that does not interfere with work. This study aims to verify whether neurofeedback using a portable In-Ear electroencephalograph (In-Ear EEG) can modulate the eustress-distress state. Three healthy men (22.0 ± 0.0 years) were recruited for the experiment. They performed an N-back task to stimulate working memory while measuring EEG from the left and right ear canals using the In-Ear EEG as a preliminary experiment for machine learning. Eustress and distress states were induced by monetary reward and punishment, and a model was created to estimate the two stress states by sparse modeling. In the neurofeedback task, the number on the screen was assigned to move to the upper right in the N-back task when the model predicted the EEG to be in the eustress state and to the upper left when it was predicted to be in the distress state. Participants were instructed to keep in mind that they should move the number to the upper right corner of the screen. To exclude external factors such as participant placebo, learning, and habituation effects from the effects of neurofeedback, a control condition was set up in which the assignment of the direction of number movement was reversed. The test and control conditions were alternated for a total of six days. We hypothesized that eustress model predictions would tend to increase in the test condition and decrease in the control condition. For some participants, eustress model predictions remained at the same level across sessions in the test condition, while the model predictions decreased in the control condition. This study is the first report of the possibility of modulating brain activity in the eustress/distress state by neurofeedback using a portable In-Ear EEG. The system should be improved in the future by increasing the model's accuracy.

Disclosures: D. Inoue: None. **K. Ueda:** None. **T. Ibaraki:** None. **Y. Imamura:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.21

Topic: I.08. Methods to Modulate Neural Activity

Support: National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Number R01NS110554

Title: Feric: a magnetogenetic technique to control the membrane currents and drive the neuronal membrane voltage

Authors: *K. MORALES WEIL, M. HERNÁNDEZ-MORALES, V. HAN, C. LIU; Univ. of California, Berkeley, Univ. of California, Berkeley, Berkeley, CA

Abstract: Magnetogenetics allows controlling the cell activity via activation of diverse ion channels using magnetic fields. This group of experimental techniques has been proposed to control neuronal excitability and understand their complex relationship with brain functions. Our

laboratory devised the magnetogenetic technique FeRIC (Ferritin-iron Redistribution to Ion Channels) that uses radiofrequency (RF) magnetic fields (180MHz, 1.6 μT) to activate ferritin-tagged ion channels via the production of ROS and oxidized lipids. Here, we used the patch-clamp technique to examine the effects of activation of the ferritin-tagged transient receptor potential channel vanilloid 4 ($TRPV4^{FeRIC}$) and the chloride permeable TMEM16A ($TMEM16A^{FeRIC}$) on the bioelectrical membrane properties of Neuro2a (N2a) cells and cultured hippocampal neurons. In N2a cells expressing $TRPV4^{FeRIC}$, stimulation with RF increases the inward membrane currents on mean amplitude, active duration time, and carried charges. This effect is blocked with the TRPV4 antagonist GSK2193847. Consistently, the activation of $TRPV4^{FeRIC}$ with RF or the agonist GSK1016790A decreases the membrane resistance (Rm) and this effect is inhibited by GSK2193847. RF stimulation does not affect the Rm in mock-transfected N2a cells or those expressing the nonconductive $TRPV4^{FeRIC}$ mutant (M680D/ΔK675). In hippocampal neurons expressing $TRPV4^{FeRIC}$, RF stimulation depolarizes the membrane potential up to a sub-threshold level. Conversely in neurons expressing $TMEM16A^{FeRIC}$, RF stimulation hyperpolarizes the membrane potential. Our results indicate that FeRIC allows controlling cells' bioelectrical properties including manipulating the neuronal excitability by either depolarizing or hyperpolarizing the membrane potential. Therefore, FeRIC can be used to control the neuron membrane voltage on subthreshold values that are key for synaptic computation and neuronal excitability. Because magnetic fields are noninvasive and have no depth limitation, FeRIC opens opportunities to understand the role of neuronal excitability in several brain functions in freely moving animal models

Disclosures: K. Morales Weil: None. **M. Hernández-Morales:** None. **V. Han:** None. **C. Liu:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.22

Topic: I.08. Methods to Modulate Neural Activity

Support: Fortalecimiento U de G 2021 to LGM

Title: Sustained deficits on sensory and motor test and differences in Morris Water Maze performance in male and female rats with lateral traumatic brain injury produced by a novel hydropneumatic fluid percussion device.

Authors: *J. C. SALAZAR-SÁNCHEZ[1], G. A. CHIPRÉS-TINAJERO[2], L. G. MEDINA-CEJA[3], J. M. ORTEGA-IBARRA[2], A. MORALES-VILLAGRAN[2];
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Abstract: Each year, about sixty-nine million individuals sustain a traumatic brain injury (TBI). In order to determine the effects and mechanisms underlying a TBI event, several models have been developed, which among others, the lateral fluid percussion-induced brain injury (FPI) model stands out as the most established and commonly used. However, such a model is perfectible, especially with regard to the control of the maximum applied pressure and its duration, which serves to delimit the severity of the injury. In this respect, complete control of brain injury severity is the most important feature of any TBI model. TBI has been classified by the Glasgow Coma Scale in severe, moderate and medium. In this work we introduced a new hydropneumatic device to induce TBI with the ability to generate the impact of an aqueous fluid in the rat brain through precise electromechanical control, which allows to induce lesions in rats, in an accurate way. In this sense, a middle TBI was caused in rats that were subsequently evaluated by a neuroscore test (five sensory and five motor tests), the evaluation was made the day before TBI and 5 hours later and at 1, 7, 14, and 21 days after TBI. Performance in the Morris Water Maze (MWM) was also evaluated before and after TBI, in which the latency to find the hidden platform and the total time spent in the MWM were assessed. The results showed a significant sustained deficit ($p<0.05$) in sensory and motor performance between the TBI group (male n=10; female n=5) versus sham (male n=6; female n=6) and intact groups (male n=3; female n=3) in both female and male rats. In addition, we observed differences in the performance of MWM in sham vs. TBI groups. This leads to the conclusion that the hydropneumatic option presented in this work is feasible and has a high level of precision and accuracy, in addition to being of a very simple handling, which make it an excellent option for laboratory work.

Disclosures: J.C. Salazar-Sánchez: None. **G.A. Chiprés-Tinajero:** None. **L.G. Medina-Ceja:** None. **J.M. Ortega-Ibarra:** None. **A. Morales-Villagran:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.23

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant R01NS109498

Title: Repetitive transcranial magnetic stimulation (rTMS) induces synaptic plasticity in human cortical slices.

Authors: *C. GALANIS[1], J. STRAEHLE[1,2,3], E. A. BALTA[1], D. H. HEILAND[2,3,4], J. BECK[2,3,5], A. VLACHOS[1,3,5,6];
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Abstract: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that modulates cortical excitability through the intact skin and skull. Despite its wide clinical use, the cellular and molecular mechanisms of rTMS-induced plasticity remain poorly understood - with most of the evidence obtained from studies performed in the rodent brain. In this study we used human neocortical access tissue (obtained as part of routine neurosurgical procedures and usually discarded), and generated acute neocortical slices within 10 minutes of tissue extraction. Using single-cell patch clamp electrophysiology, microscopy and molecular biology techniques we assessed the effects of distinct rTMS parameters on synaptic plasticity of layer 2/3 pyramidal neurons in human neocortical slices. Our results identify specific protocol parameters that affect the outcome of rTMS. Specifically, we provide the first experimental evidence that intermittent theta burst stimulation (iTBS) induces excitatory synaptic plasticity in human cortical slices. Determining the cellular and molecular mechanisms involved in rTMS-induced plasticity will enable the design of more suitable rTMS protocols tailored to the treatment of individuals.

Disclosures: C. Galanis: None. **J. Straehle:** None. **E.A. Balta:** None. **D.H. Heiland:** None. **J. Beck:** None. **A. Vlachos:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.24

Topic: I.08. Methods to Modulate Neural Activity

Support: DARPA ElectRx grant BAA 15 06

Title: Expansion and reduction of spike inactive zone along axons by sonication stops and recovers spike transmission

Authors: *Y. BABA[1], S. A. LEE[3], B. HOFFMAN[4], E. KONOFAGOU[3], E. A. LUMPKIN[2]; [2]Univ. of California Berkeley, [1]Univ. of California Berkeley, Berkeley, CA; [3]Columbia Univ., New York, NY; [4]Univ. of California, San Francisco, San Francisco, CA

Abstract: Since the discovery of reversible ultrasound-based, non-invasive inhibition of neural activity, it has become of interest to develop applications for anesthesia and pain control treatments. Although numerous ultrasound neuromodulation studies have been reported, a standard protocol for robust control of neural activity has not been developed. Here, we provide evidence for a relationship between sonication intensity and the inhibition of spikes using focused ultrasound (FUS: 3.57MHz) in two animal models: murine skin-nerve preparation and insect ventral nerve cord. Spike transmission was observed before and after one sonication (the

sonication was applied only once). The parameters of the sonication were intensity (12-63 MPa in mouse experiments; 6-40 MPa in insect), duty cycle (1-10% in 1ms in both experiments), and sonicating time (1-10 sec in mouse; 20-400 msec in insect).Experimentally, we found that 1) FUS suppresses spike transmission around the focal region, 2) myelinated axons required larger energy (the minimum affected energy in mouse: 0.19J) than unmyelinated axons (in insect: 0.004J), 3) suppression initiation occurred during and after sonication, 4) conduction velocity of suppressed neurons decreased, and 5) conductance velocity tended to return to the baseline after recovery. Although a clear relationship between sonicated energy and suppression was not observed, larger FUS energy was often needed to suppress spike transmission; even with similar sonication energy, variations in the FUS parameters themselves had influences on the suppression rate. To explain these results, we generated a computational model using NEURON. We model FUS as a gradually expanding spike-inactive zone. The model illustrates reduced spike conductance velocity and sometimes complete spike transmission block. The model also explains the reduction in the spike-inactive zone after a while, leading to spike transmission recovery. The model suggests the membrane property changes from the sonication point and propagates along the axon. These results and the model are crucial starting points for developing a standardized FUS protocol as a powerful tool in neurobiology.

Disclosures: Y. Baba: None. **S.A. Lee:** None. **B. Hoffman:** None. **E. Konofagou:** None. **E.A. Lumpkin:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.25

Topic: I.08. Methods to Modulate Neural Activity

Support: NIGMS COBRE P20GM103645

Title: Low-intensity Single Pulse Transcranial Magnetic Stimulation (TMS) Increases Detection Accuracy of Perceptual-Threshold Level Tactile Stimuli

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Abstract: Attempts to modulate behavior using non-invasive brain stimulation often utilize rhythmic protocols designed to enhance endogenous brain oscillations, e.g. beta frequency activity (15-29 Hz), which is associated with inhibited sensory perception and motor action. However, we have shown that spontaneous inhibitory beta in primary somatosensory cortex (SI) is characterized by transient ~150 ms ‘events’ (i.e. ‘bursts’). Here we attempted to design a novel transcranial magnetic stimulation (TMS) protocol to mimic the effects of endogenous SI beta events, based on their transient dynamics and model-proposed mechanism of action. Our lab

developed a modeling framework to reproduce macroscale MEG/EEG signals based on known biophysics (hnn.brown.edu; Neymotin et al. 2020), and used it to show that beta event generation in SI creates a brief window of enhanced perception (for ~25 ms), followed by supragranular $GABA_B$-mediated inhibition of perception for more than 100 ms (Sherman et al. 2016; Shin et al 2017; Law et al. 2022). Single pulses of TMS (spTMS) in rodents can evoke similar inhibitory mechanisms (Murphy et al. 2016), so we hypothesized that low-intensity spTMS could be used to invoke similar circuit dynamics as beta events to modulate perception in humans. We predicted that spTMS would *decrease* detection accuracy when delivered 100 ms before a tactile stimulus ('TMS100'), and *increase* it when delivered 25 ms after ('TMS25'). Participants (n=18) were cued to attend to the middle finger, where they received brief threshold-level finger taps (~50% detection), and reported detection. TMS pulses were delivered at 80% active motor threshold with auditory masking (Magstim Rapid^2, D70 Alpha coil). MRI-based neuronavigation targeted SI and an active control region (junction of the central sulcus and interhemispheric fissure) in separate sessions. Contrary to our hypotheses and prior reports, response accuracy to threshold-level tactile stimuli was significantly higher for both TMS100 and TMS25 compared to null TMS ($p<0.005$), yet there was no difference between TMS100 and TMS25, and no difference between sessions for any TMS conditions ($p>0.05$). Sensitivity indices (d') and false alarm rates were not significantly different across TMS conditions, or between sessions ($p>0.05$). These results show that low-intensity spTMS increases detection accuracy of threshold-level tactile stimuli, yet participants did not detect the tactile stimulus better, or respond more indiscriminately with TMS. It is possible that our TMS protocol recruits a more complex cortical response than predicted, or that the sensory or vascular response to TMS can affect tactile perception.

Disclosures: D.D. Sliva: None. **C. Kohl:** None. **D.S. Daniels:** None. **R.M. Thompson:** None. **N. Chen:** None. **S.R. Jones:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.26

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01 NS117405
NIH R01 NS088674
NIH RF1 MH114253

Title: An improved system for collecting and analyzing neural data during transcranial magnetic stimulation in non-human primates

Authors: *R. KOTHARE[1], R. HAMDAN[2], S. M. GOETZ[2], A. V. PETERCHEV[2], M. A. SOMMER[1];
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Abstract: Transcranial magnetic stimulation (TMS) is an FDA-cleared, non-invasive form of neuromodulation. While its effects in the human brain have been assessed at the macroscopic level, there is a lack of understanding of finer-scale responses on the neuronal circuit level, and this limits the rational design of therapeutic TMS protocols. We aim to quantify the direct and indirect neuronal effects of TMS through single-unit recordings in the target region of stimulation in awake macaques. Our recent work refined the instrumentation used for the neural studies and developed a data-driven model for interpreting dose-response curves calculated from the recordings.
One of the main challenges of simultaneous recording during TMS is the presence of large, electromagnetically induced artifacts that hinder the isolation of small neuronal signals. We previously developed an electrophysiology system capable of resolving action potentials shortly after TMS pulses (Mueller et al. 2014). To improve on that system, which required manual tuning of artifact cancellation and used components that are now obsolete, we developed an updated amplifier system that is more robust, automatic, and offers short recovery times after a pulse. We added electrostatic shielding to the TMS coil to reduce its capacitive coupling with the recording electronics and we developed a low-inductance input connection that mitigates the inductive TMS artifact. Additionally, we assessed the performance of three electrode materials - tungsten, platinum-tungsten, and platinum-iridium - with our system. Here, we present a new system capable of resolving neural signals within ~0.5 ms of the start of the TMS pulse.
We also developed a model for analyzing the dose-response curves found from neural recordings during TMS. We applied this data-driven model to a population of 280 macaque motor cortical neurons stimulated by single-pulse TMS to infer the thresholds, probabilities of activation, synaptic spread, and related parameters that account for the observed dose-response curves. We found that E-field thresholds are similar across neural types (putative inhibitory neurons, excitatory neurons, and axons) but that, above threshold, the proportion of neural elements activated by TMS is significantly higher for putative axons and excitatory neurons than for putative inhibitory neurons. The results also account for the latencies and magnitudes of responses to TMS in the neural population. Overall, these advances in instrumentation and models for analyzing the neural recordings will contribute to a more fine-scale understanding of the circuit response to TMS.

Disclosures: R. Kothare: None. **R. Hamdan:** None. **S.M. Goetz:** None. **A.V. Peterchev:** Other; Invention disclosures: A. V. Peterchev is an inventor on patents and patent applications related to TMS technology. **M.A. Sommer:** None.

Poster

752. Novel Techniques: TMS, Optical, and Chemogenetic

Location: SDCC Halls B-H

Time: Wednesday, November 16, 2022, 1:00 PM - 5:00 PM

Program #/Poster #: 752.27

Topic: I.08. Methods to Modulate Neural Activity

Title: Intelligent current source for synchronized synthesis of multiple carriers for classic and temporal interference stimulation

Authors: M. H. CAPSTICK[1], M. SABATHY[2], M. BROENNIMANN[2], B. RIVARA[2], T. SCHMID[3], E. NEUFELD[1], S. REGEL[2], ***N. KUSTER**[1,3];
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Abstract: Temporal interference stimulation (TIS) [Grossman et al., Cell. 2017;169(6):1029-1041.e16] is considered a promising approach for non-invasive targeted modulation of deep brain region activity. Compared to classic transcranial electric stimulation approaches (e.g., tDCS, tACS), it strongly reduces stimulation of overlaying structures and is more customizable. TIS is based on the beat frequency envelope of two sinusoidal carriers. When the number of carriers and the complexity of the signal exceeds two, solutions based on signal generators and standalone current sources become increasingly difficult to synchronize to ensure coherent, phase-controlled modulation envelopes. The bandwidth and output impedance limitations of many available devices have prevented exploration of TIS beyond a few kHz. Here, we sought to overcome these limitations and to develop a highly flexible and safe device. We synthesized all the carriers within the same field-programmable gate array (FPGA), which allows exact control of the carrier relative phases and hence the beat frequency envelopes of all possible carrier combinations. Additionally, modification of beat frequency or beat envelope timing has been much simplified. New topologies for fully differential current sources with higher voltage, wider bandwidth and high output impedance were sorted through simulation and prototyping. Integrated monitoring of current and voltage across all electrode pairs with integrated digitizers providing real-time data simplifies the experimental setup and allows real-time verification of delivered stimulation signals. Eight channels of direct-digital-synthesizer (DDS) signal generators are implemented in an FPGA and controlled by an application programming interface to allow flexible experimental execution with up to 8 channels. Each DDS channel feeds a differential current source. A new current source topology was developed cascading fully differential high performance operational amplifiers with a low phase shift, high voltage class AB buffer circuit to simultaneously achieve high output impedance, wide bandwidth, and high output voltage. A bandwidth >200 kHz with output impedances >100 kΩ at the highest frequencies were achieved with peak-to-peak output voltages of 60 V and low distortion (even when sources are connected in parallel), allowing a wider range of load impedances to be driven. Voltage and current monitoring circuits including hardware current limiters are included to improve safety and verify applied stimulation. In conclusion, a novel flexible programmable multichannel current source was developed for advanced TIS research.

Disclosures: M.H. Capstick: None. **M. Sabathy:** None. **M. Broennimann:** None. **B. Rivara:** None. **T. Schmid:** None. **E. Neufeld:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Shareholder and Board Member of TI Solutions AG. **S. Regel:** None. **N. Kuster:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Shareholder of NFT Holding AG. Other; President of the Boards of NFT Holding AG and TI Solutions AG.