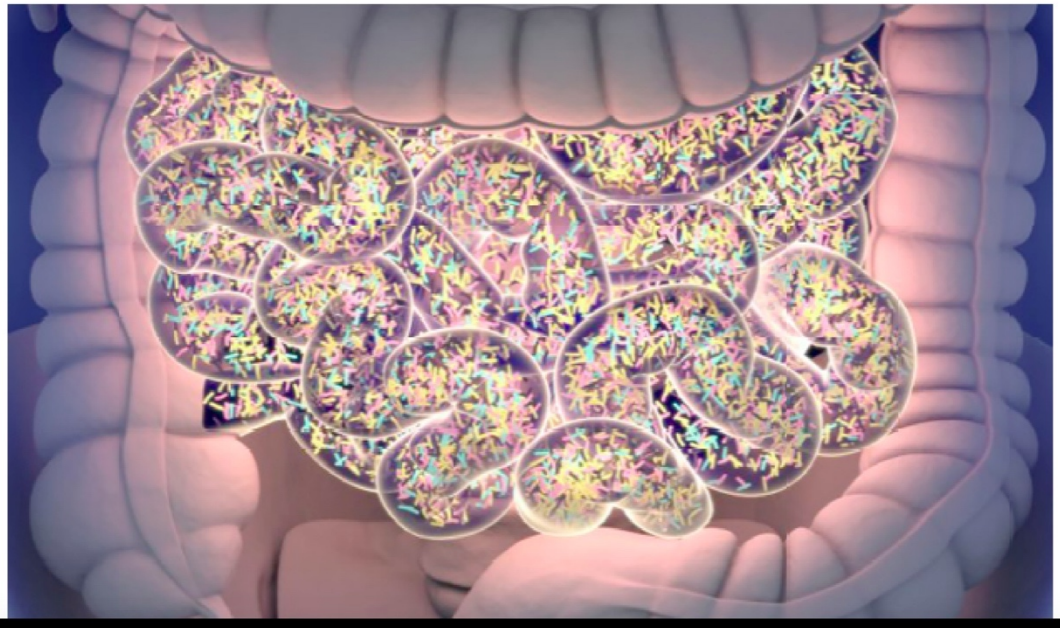
Society for Neuroscience

Oregon & Southwest Washington

ONLINE MEETING

April 15, 2021



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7:15 ***Awards and closing***

Mini-symposium

The Gut Microbiome-Nervous System Axis

Insights into the enteric nervous system: perspectives from a gut stem cell biologist

Annie Zemper, Ph.D., Assistant Professor of Biology, University of Oregon

The last 16 years of my Ph.D. career involved a long-standing commitment to examining physiological and pathophysiological processes in the GI tract. I completed my Ph.D. in Dr. Missy Wong's laboratory at Oregon Health and Science University, where I studied epithelial stem cell interactions with inflammatory macrophages in small intestine and colon and how these interactions can promote neoplastic changes in the stem cells in colitis-like states. Continuing on in a GI-related postdoc, I joined Dr. Bob Coffey's lab at Vanderbilt University Medical Center, where I identified a marker for gut stem cells and went on to show that it functions as a *bona fide* tumor suppressor. Since my lab's inception at University of Oregon, I've continued to examine how stem cells behave in both normal and diseased gastrointestinal tissue. This work as expanded to include examinations of epithelial-neuronal cross-talk and epithelial-mesenchymal interactions, which ultimately provide cues to intestinal stem cells to promote – or return to – homeostasis.

ABSTRACT: The small intestinal and colonic mucosa is in a constant state of carefully executed repair and regeneration. In addition, there are many disease states, including inflammatory disease states, which require modulation of this regenerative response to continuously heal wounded tissue. Of course, the intestinal epithelium does not function in isolation, but interacts with many components including the Enteric Nervous System (ENS). Understanding ENS and intestinal epithelial interaction requires multidisciplinary approaches to: 1. uncover cells involved, 2. Discover the mechanisms used, and 3. Determine the ultimate influence of the ENS on intestinal physiology. I will discuss the recently uncovered mechanisms by which the ENS interacts with the epithelium and the in vitro, ex vivo and in vivo techniques used to study these interactions. Finally, I will discuss how the ENS contributes to epithelial stem cell fate decision making and how the intestinal epithelium is perturbed in cases of defects in the central nervous system.

Environmental challenges, the gut microbiome, and behavioral and cognitive measures in mouse models

Jacob Raber, Ph.D., Professor of Behavioral Neuroscience, OHSU

Our research focuses on effects of genetic factors, such as apoE, and environmental factors, including irradiation, immunotherapy, a high-fat diet, environmental toxins, and other stressors, on brain structure and function in experimental mouse models of human neurological diseases. Based on what we learn in the mouse models, we try to develop tests and treatment strategies to improve brain function in humans suffering from these diseases. Routinely, we use a combination of behavioral, neuroendocrinological, pharmacological, neurochemical, immunohistochemical, cellular, and molecular approaches. Recently, as part of collaborative efforts, we started to include unbiased omics approaches to determine whether the behavioral and cognitive alterations are associated with specific pathway alterations. We developed humanized versions of the mouse object recognition and spatial navigation tests and assess whether they are sensitive to detect effects of sex and apoE4 on cognition in health and disease. These tests might be valuable in identifying biomarkers of cognitive function and susceptibility to cognitive impairments.

ABSTRACT: Increasing evidence supports a role for alterations in the gut microbiome in brain function. In humans, gut microbiomes become increasing unique with age, reflect healthy aging, and predict survival (Wilmanski et al., Nat Metabolism 3, 274, 2021). The gut microbiome can communicate with the central nervous system (CNS) via the bi-directional gut-brain axis and affect behavioral phenotypes. Our collaborative animal research with Dr. Sharpton at Oregon State University and Dr. Zemper at the University of Oregon suggests that alterations in the gut microbiome might play a role in neurodegenerative conditions like Parkinson disease (PD) and Alzheimer's disease (AD). The gut microbiome might also be important in CNS effects astronauts experience. The mouse gut microbiome is impacted by 13 days of space flight and ground-based simulated space radiation research indicate that simulated space radiation also affects the gut microbiome. Sequential three- and six-beam irradiation impacted the diversity and composition of the gut microbiome, with dose- and sex-dependent impacts and alterations to the relative abundance of several gut genera. Finally, the gut microbiome might play an important role in the ability of dietary botanical supplements to reduce detrimental effects of a Western diet and metabolic syndrome on cognitive performance. Examples of alterations in the gut microbiome in these distinct animal models will be presented. In addition, ongoing analyses to reveal general patterns when gut microbiome data across distinct studies are being compared will be discussed. Future efforts seem warranted to manipulate the gut microbiome to reveal its role in health and disease.

Microbial modulation of zebrafish behavior and brain development

Judith Eisen, Ph.D., Professor of Biology, University of Oregon

Dr. Eisen started her career at the University of Oregon in 1983 as a postdoctoral fellow in the lab of Monte Westerfield. She joined the faculty in 1985 as an assistant professor and is currently a professor in the Department of Biology and a member of the Institute of Neuroscience. She and her lab are interested in discovering how cells become committed to differentiate their specific properties during embryonic development. They have focused their attention on neurons and neural crest cells in embryonic zebrafish. She was the first person to describe individually identified vertebrate spinal motoneurons. More recently she demonstrated requirements for the enteric nervous system to regulate bacterial competition and composition within the intestinal microbiota and how changes in the microbiota positively and negatively impact intestinal health. Dr. Eisen has published over 150 scientific papers

ABSTRACT: There is growing recognition that host-associated microbes modulate intrinsically encoded developmental programs and that microbial dysbiosis is linked to human neurodevelopmental disorders. Despite this awareness, the underlying processes are generally not understood. We use zebrafish as a model to investigate how the host-associated microbial community influences brain development. We discovered that the microbiota is necessary for normal social behavior. The microbiota modulates targeting of a defined population of forebrain neurons required for social behavior by restraining their arbor complexity. We also found that the microbiota is important for normal forebrain localization of microglia, the brain's resident immune cells that remodel neuronal arbors. Altering the number of forebrain microglia affects forebrain neurite density similarly to the microbiota, suggesting the microbiota modulates neuronal arborization via a neuro-immune mechanism. Our work reveals complex interactions between a host and its associated microbes, provides evidence that microbial input is critical for development of a normal behavioral repertoire, and paves the way for studies to identify the molecular and cellular mechanisms by which hosts and commensal microbes interact to shape host neurodevelopment.

Longitudinal Study of Stool-Associated Microbial Features in Sibling Pairs with and without Autism

Maude David, Ph.D., Assistant Professor of Microbiology, Oregon State University

Dr. Maude David earned her Ph.D. at the Ecole Centrale de Lyon at the University of Lyon in France. Her laboratory studies the gut-brain axis, to understand how microbes can impact our behavior, specifically in Autism Spectrum Disorder and Anxiety. She uses a crowd-sourced approach to collect lifestyle type information, diet habits, and samples. Her team is also working on identifying bottlenecks in microbial ecology and bioinformatics, bringing novel solutions to unravel microbial molecular mechanisms by optimizing new molecular methods and improving massive sequencing data annotation.

ABSTRACT: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder associated with an array of behavioral, social, and cognitive impairments. Among many genetic and environmental factors, gut dysbiosis has emerged as a powerful contributor to ASD pathology. Few studies to date have gathered longitudinal data relating to gut microbiome composition and ASD, and none integrate closely matched (age and diet-wise) controls to appraise the interrelated impacts of gut microbiota, diet, and lifestyle variables on ASD. In this study, we recruited over 100 age-matched sibling pairs (between 2 and 8 years old) where one participant had an Autism Spectrum Disorder diagnosis and the other was developing typically. We collected stool samples over four weeks, tracked over 100 lifestyle and dietary variables, and surveyed behavior measures related to ASD symptoms. We leveraged our longitudinal design and performed differential abundance analysis on 16S V3-V4 amplicon gene sequencing to pinpoint microbial taxa that differed between typically developing children and siblings with autism over time. We also analyzed metagenomic, meta-transcriptomics and metabolomics data at the initial sampling time. Our study showed that 1/microbiome composition followed lifestyle and diet habits 2/ some biomarkers distinguishing the two cohorts *did not* associate with lifestyle or diet 3/ biomarkers associated with lower anxiety across time appeared depleted in children with less diverse gut microbial communities 4/ children with higher severity scores showed less diverse gut microbiomes.

Role of the Gut Microbiome in Effects of Dominant Human Amyloid Precursor Protein (APP) Mutations on Behavioral and Cognitive Performance in Mice

Payel Kundu[1], Ph.D.
and Natalia Shulzhenko[2], Thomas J. Sharpton[3], Jacob Raber[1]

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Alzheimer's disease (AD) is the most common form of dementia. Early intervention before pathology becomes advanced is critical. Amyloid precursor protein (APP) mutations and the E4 variant of apolipoprotein E (apoE) are both genetic risk factors for AD. The dominant APP^{NL-G-F} mutation increases total Amyloid Beta (Aβ) production, increases the Aβ42/Aβ40 ratio, and reduces degradation of Aβ. Pior work links the gut microbiome to the pathogenesis of AD. To advance determination of potential causality, we transferred the gut microbiome of APP^{NL-G-F} and APP^{NL-G-F}/apoE4 mice, and assessed whether fecal transplants are sufficient to induce AD-pertinent behavioral phenotypes. To do so, we evaluated whether behavior and cognition tests can be applied to gnotobiotic mice in a biosafety cabinet. We finalized testing the first of three cohorts of mice and will share the data at the meeting. After colonization, behavioral and cognitive performance measures are in the same range as we see for testing outside a safety cabinet. Based on preliminary data and analysis of only the first cohort, we found that the gut microbiome affected performance on a novel object recognition task as well as a spatial Y-maze task. These preliminary results indicate that behavioral and cognitive testing in a biosafety cabinet is feasible and that the gut microbiome may be causally linked to the cognitive impairments in AD. This work could enhance our understanding of the gut-brain axis and its role in behavioral and cognitive performance and ultimately facilitate early diagnosis and the developments of novel therapeutic strategies for AD.

SESSION I

An eye on neurogenesis: Exploring how retinal progenitors transition from proliferation to differentiation in the developing zebrafish visual system

Kara Cerveny, Ph.D., Professor of Biology, Reed College

Kara Cerveny is an Associate Professor of Biology at Reed College. She earned a BS in Biology from Duke University, a Ph.D. in Biochemistry, Cellular, and Molecular Biology from Johns Hopkins School of Medicine, and conducted research as a post-doctoral fellow at the University College London, before joining the Reed Biology faculty in the fall of 2012. The research in Kara's lab focuses on how cells transition from proliferation to differentiation in the developing zebrafish visual system and is supported by the NIH National Eye Institute and the MJ Murdock Trust. Kara has a passion for sharing the beauty of biology and is always happy to share movies and images of developing zebrafish with any who would like to tour her lab.

ABSTRACT: In zebrafish, visual system growth and development is a life-long process. Specialized stem cell niches established early in eye and brain development support life-long growth of each retina and corresponding optic tectal lobe. Coordinated growth of these tissues ensures that accurate retinotopic mapping is maintained as new neurons are added. Studies of adult fishes provide evidence that tectal cell survival, proliferation, and differentiation is correlated with retinal innervation, raising the possibility that retinal axons provide crucial information for control of stem and progenitor cell behaviors in the optic tectum. To explore how retinal innervation influences optic tectum growth in larval zebrafish, we examined brains lacking innervation from (i) both eyes as a result of the *lakritz* mutation and (ii) one eye as a result of physical eye removal, and compared them with wild-type larvae with two eyes. Our data show elevated cell death counts in non-innervated or denervated optic tecta lobes no earlier than 9 days post-fertilization (dpf). In addition, we observed fewer *sox2*+ stem/progenitor cells and a smaller proportion of proliferating progenitors in optic tecta lacking innervation. This difference in the number of proliferating cells is maintained, albeit at a lower level of significance, when light-evoked retinal activity is blocked. Although the identity of the cue from the optic nerve remains elusive, we have found that Wnt/B-catenin pathway activity is activated in optic tecta in an innervation-dependent manner, raising the possibility that Wnt, transported along the optic nerve, serves as a trophic cue for tectal stem cells.

Comparing Response Times Between HSAN2 and Typical Participants

Chris Koch
George Fox University

Hereditary sensory and autonomic neuropathy type II (HSAN2) is a rare genetic disorder that primarily affects sensory neurons associated with pain, temperature, and touch. Given that HSAN2 is a rare disorder and affects tactile perception, there is essentially no research examining response times (RTs) using non-touch experimental tasks. RTs reflect several stages including processing of the sensory information, deciding how to respond, and making the response. In this study, a Stroop task was modified to differentiate between movement time and the other stages of processing. Specifically, participants were instructed to press a key upon viewing a fixation which would initiate the presentation of the color-word stimulus. They were to keep the key depressed until they were ready to respond by making a second key press corresponding to the color of the font. One participant was diagnosed with HSAN2. The RTs for that participant were compared to a control participant matched on sex, age, gpa, and mother's education level. Both the decision and movement times were significantly longer for the HSAN2 participant. Additionally, the decision and movement times for the HSAN2 individual were consistent for both color congruent and color incongruent conditions. The control participant, however, showed similar decision times across conditions but significantly slower movement times for the incongruent condition. These findings suggest that processing associated with the sensory information, decision making, and responding may be delayed in HSAN2. Further, the results of the control participant suggest that interference in the color-word Stroop task may occur during the actual response.

A Non-Human Primate Model of Neonatal Encephalopathy to Evaluate Novel Translational Therapeutics

Meredith Kelleher[1], Sudeshna Tripathy[1], Stacey Ellery[2], Rod Snow[3], David Walker[4], Larry Sherman[1]

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Intrapartum hypoxia-ischemia is associated with 30-60% of cases of hypoxic-ischemic or neonatal encephalopathy (HIE/NE), often resulting in cerebral palsy. Infants that receive current treatments (e.g., hypothermia) may still develop adverse neurologic outcomes. Novel therapies have been shown to reduce injury and improve functional outcomes in rodent and sheep models of HIE. However, further preclinical studies are required in order to translate these therapies in humans. The aim of this study was to characterize an HIE model in rhesus macaques using a comprehensive range of translational neonatal assessments.

A laparotomy was performed on pregnant rhesus monkeys (n=10) at ~155d gestation (term=167d). The uterus was exteriorized, a small incision made and the umbilical cord occluded for 10-15min using a vascular clamp. Fetal blood was sampled through an umbilical catheter for blood gas analysis, and fetal heart rate monitored by ultrasound. After the occlusion period, neonates were resuscitated and received respiratory support and total parenteral nutrition for a period of four days. Neonatal assessments included neurological exams; electroencephalography; auditory testing; retinal imaging and electroretinography; and magnetic resonance imaging/spectroscopy. Post-mortem tissues were collected and evaluated immunohistochemically to assess brain injury.

Infants (occlusion time 10-12min) demonstrated neurological signs of mild to moderate HIE with evidence of retinal hemorrhaging and auditory impairment. One infant exhibited clinical seizures, with cerebral lesions attributed to stroke visible on MRI. Marked immune infiltration was observed in the brains of infants, including Iba-1+/CD-45+ cerebral and cerebellar lesions, and extensive loss of Purkinje cells.

Symptoms observed in neonatal rhesus monkeys after umbilical cord occlusion closely recapitulate human cases of HIE. The neonatal testing protocols developed in this study allow for comprehensive characterization of neurological and sensory impairments that are associated with HIE. Utilizing clinically-relevant assessments and imaging techniques in a translational monkey model will enable future preclinical testing of novel therapeutic and diagnostic strategies for HIE.

Brain Volumetrics Across the Lifespan of the Rhesus Macaque

Steven Dash[a], Byung Park[b], Chris D. Kroenke[a,c,d], Henryk F. Urbanski[a,d], Steven G. Kohama[a*]

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The rhesus macaque is a long-lived primate with a brain structure similar to humans. MRI studies have shown atrophy in temporal and frontal lobe structures in aging humans that accelerates in later age and is exacerbated with dementia. However, rhesus macaques do not show neuron loss with age, similar to normative aging in humans, but prior MRI studies of volumetric changes have been equivocal. Moreover, the lack of subjects across the complete age range makes it difficult to identify changing volumetric trajectories. The current study included structural T1 weighted MRI scans of 66 animals, 34 females (aged 6-31 years) and 32 males (aged 5-27 years). Analysis included 35 regions of interest (ROIs) normalized to intracranial volume. We analyzed volumetric data by age and sex to capture all possible differences. There were few differences between sexes. We found several changes expected in the aging brain including enlargement of the lateral ventricles and a decrease in the volume of the frontal cortex. A number of the white matter structures measured showed an inverted-U-shape with a peak in middle age and late age decrease (frontal WM, occipital WM, corpus callosum [genu, body and splenium], and the internal capsule). Several sub-cortical structures also showed age-related decreases including the caudate, putamen, hypothalamus, and thalamus. In contrast, we saw increases to the volume of the hippocampus (and dentate gyrus), amygdala, and globus pallidus. Overall, it appears that the rhesus macaque shows a pattern of changes similar to normative clinical aging, in the absence of overt neurodegeneration.

Centella asiatica and *Withania somnifera* improve resilience in a *Drosophila melanogaster* model of aging

Christine McClure, ND, MS.[1,2], McClure CK[1,2], Kretzschmar D[1,3], Lak P[4], Caruso M[2], Alcazar-Magana A[1,5,6], Brandes MS[1,2], Cabey KA[7], Speers AB[1,2], Wright KM[1,2,7], Maier C[1,5,6], Stevens JF[1,4,6], Soumyanath A.[1,2]

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Introduction: *Centella asiatica* (CA) and *Withania somnifera* (WS) are traditional "rasayana" herbs reputed to promote resilience to neurological changes that can occur during aging. Their efficacy was explored here in a *Drosophila melanogaster* (DM) fruit fly model.
Methods: Botanical raw material was authenticated and analyzed using thin layer chromatography and liquid chromatography coupled to mass spectrometry. DM were fed either a water extract of CA (CAW; 10 mg/ml), a CAW fraction (A1; 1.15 mg/ml), or caffeoylquinic acid (CQA) or triterpenoid (TT) constituents of A1. Some DM received a water extract of WS (WSW; 0.5 mg/g or 5.0 mg/g). Phototaxis experiments were used to measure locomotion and reaction times.
Results: CAW and A1 significantly improved phototaxis in both female and male DM aged between 4-weeks and 6-weeks-old. However, only female, but not male, 4-week-old DM fed CQA or TT performed significantly better than controls. WSW (0.5 mg/g but not 5 mg/g) significantly improved phototaxis in 6-week-old female DM but significantly decreased phototaxis in both male and female 4-week-old DM compared to controls.
Conclusions: CAW improves phototaxis scores as indices of locomotion performance and reaction deficits that occur during normal aging and at younger ages. Both TTs and CQAs contribute to CAW's activity in female DM. WSW (0.5 mg/g) may be beneficial for locomotion and reaction times in 6 week and older female DM but may not be beneficial when used in younger ages or in a higher dose. The active compounds of WSW are under investigation.

CANNABIDIOL VAPOR INHALATION EFFECTS IN MEMORY, SOCIAL INTERACTION AND INSTRUMENTAL BEHAVIOR OF FEMALE RATS

Rivera-Garcia Maria T, Wilson-Poe Adrianne R
Dow Neurobiology Labs - Legacy Research Institute

Recent legislative changes in the United States has rapidly expanded the legal market for cannabidiol (CBD), the second most abundant phytocannabinoid produced by the plant. The majority of preclinical studies have analyzed the effects of synthetic cannabinoid injection in male rodents. Because of important sex differences in cannabinoid responses, it is imperative to study CBD's effects in females, particularly using routes of administration that resemble cannabis human consumption. In female Long Evans rats (6-7 weeks old) we studied the impact of acute (30 min) and chronic (30 min, twice/day for 20 days) CBD vapor inhalation or vehicle (Propylene Glycol and Vegetable Glycerin-PGVG) in rats' social interaction and cognitive performance in the Novel Object Recognition test. Our results show that neither acute nor chronic CBD vapor exposure induced changes in social interaction, and only acute CBD inhalation impaired rats' cognitive function compared to PG/VG treatment. In a different set of experiments, we evaluated CBD's reinforcing properties under three different fixed ratio schedules (FR1, FR2 and FR4) and one progressive ratio (PR) session. Rats showed significantly higher instrumental responses for PG/VG than CBD vapor in FR-1 and PR schedules. Opposite to previous findings in males, we found that CBD impairs female rats performance in the NOR test, and thus, further research using additional cognitive paradigms is needed. CBD vapor lacks of reinforcing effects while future studies to understand PG/VG rewarding mechanisms are warranted.

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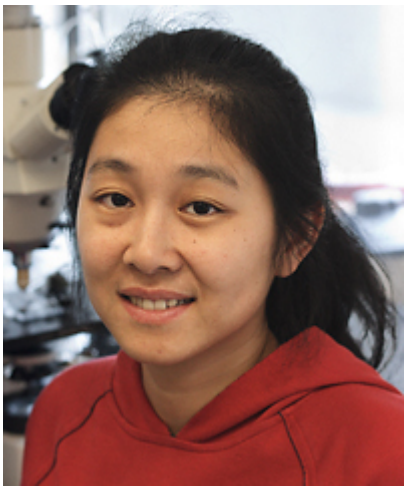
SESSION II

Understanding functional architecture and neuromodulation of brain circuits using connectomic and novel imaging approaches

Tianyi Mao, Ph.D., Vollum Institute, OHSU



After earning her B.S. in Biological Science and Biotechnology at Tsinghua University in Beijing, China in 1997, Mao received her Ph.D. in Neuroscience from the Johns Hopkins University School of Medicine in 2005. She did postdoctoral research at the Cold Spring Harbor Laboratory and then at the Howard Hughes Medical Institute's Janelia Farm Research Campus. Mao was appointed as an assistant scientist at the Vollum Institute in September 2010 and was promoted to scientist in 2017.

ABSTRACT: My laboratory is interested in elucidating brain circuit mechanisms underlying animal behaviors, such as sensori-motor interactions and motor control, and understanding how these circuits are changed and modulated by disease, brain state and behavioral context. This talk will first focus on using whole brain imaging combined with novel computational algorithms to establish connectomic maps at the mesoscopic scales (~300 μm) between the mouse cortex, thalamus, and striatum. Connections across these brain structures are essential for motor control, affective pain sensation, decision making, and reward. Novel structural principles governing the neuronal connectivity will be discussed. The second part of the talk will address how to use the structural connectomic maps to facilitate our understanding of circuit function. Utilizing the connectome we established, we uncovered circuit mechanisms of how opioid differentially modulate individual circuit components in the cortico-thalamo-striatal loop. Using a novel imaging modality that we recent developed, we obtained live imaging of intracellular signaling pathway of cAMP/PKA which is downstream of opioids in the aforementioned circuits and further confirmed the action sites for distinct opioid receptor families in cell type-specific and subregion-specific manners, which might shed light on how opioid's effects on pain and reward are shaped by the relative selectivity of different opioid drugs to specific circuit components.

Our work highlights the necessity and importance of establishing whole brain wiring diagram, as well as illustrates how to the thalamo-cortico-striatal wiring diagram to deepen our understanding of the circuit functions.

INVESTIGATING THE ROLE OF CELL MIGRATION INDUCING AND HYALURONAN BINDING PROTEIN (CEMIP) IN CENTRAL NERVOUS SYSTEM DISEASE

Alec Peters, Peter Pham and Larry Sherman

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The extracellular matrix glycosaminoglycan hyaluronan (HA) is an active signaling molecule in the healthy and diseased central nervous system (CNS). HA signaling properties vary based on its size, associated molecules, and the receptors it interacts with. In chronic demyelinated lesions such as those observed in Multiple Sclerosis (MS) and animal models of MS, there is increased HA synthesis coinciding with elevated hyaluronidase activity. The resulting HA fragments inhibit the differentiation of oligodendrocyte progenitor cells into myelinating oligodendrocytes, impairing remyelination. it is unclear which hyaluronidase is responsible for the production of inhibitory HA fragments in chronic lesions. Cell migration-inducing and hyaluronan binding protein (CEMIP) digests extracellular HA, is elevated in experimental autoimmune encephalomyelitis, a model of MS, and delays oligodendrocyte progenitor differentiation *in vitro*. Additionally, CEMIP activity is inhibited by selective small molecules shown to enhance remyelination in a mouse model of inflammatory demyelination. Mechanisms of CEMIP-induced delay of OPC differentiation are currently under investigation. Our current results suggest that CEMIP is the hyaluronidase producing inhibitory HA fragments in chronic MS lesions, and suggest that it could be a target for therapies designed to enhance remyelination and improve outcomes in MS patients.

Expression and Distribution of Aquaporin-1 in Extremely Aged Rhesus Brain

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The brains of old rhesus macaques display low levels of Alzheimer's disease biomarkers, but no neuronal loss, and can thus be considered a model of normative brain aging. Aquaporin-1 (AQP1), a membrane-bound water channel found in the choroid plexus, white matter, and perivascular astrocytic end feet, increases clinically with neurodegeneration, but has not been studied in the aged macaque brain. Hence, we examined AQP1 in the rhesus temporal lobe from: 1. Cross-sectional aging study from the ONPRC (6-33 years), and 2. NIA Longitudinal Caloric Restriction (CR) study, including extremely old animals (22-44 years). Formalin-fixed coronal sections were immunohistochemically-labeled for AQP1 and characterized in terms of phenotype, distribution pattern and intensity of labelling. In study 1, positive staining was found in white matter and the glial limitans across age, matching astrocyte distribution. AQP1 density, number of stained cells, and phenotypic diversity increased with age, in the cortex, dentate hilus and CA subregions. Circular "bushy" cells often bordered vessels, while dense, fibrous cells were found in white matter regions. In older animals, we found numerous large fibrous cells in the deep cortical layers. In study 2, there was a further increase of AQP1 in hippocampal and cortical regions with advanced age. We also noted a decrease of stain intensity in white matter of the temporal cortex of the oldest animals. CR treatment had no apparent effect on AQP1 expression across age. These data present a progressive upregulation of AQP1 in the macaque brain, which was further exacerbated with extreme age. The AQP1 response may represent an adaptive/maladaptive astrocytic response to age-related changes.

Ibuprofen induces differences in NMDA and AMPA receptor functions between males and females

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Characteristics of Alzheimer's disease include memory deficits and amyloid plaques. Interactions between amyloid and N-methyl D-aspartate receptors (NMDAR) appear to contribute to declines in synaptic plasticity. Our lab discovered that the 5xFAD mouse model of amyloid overexpression showed hyperactive NMDAR responses at 4 months of age, which could lead to excitotoxicity or increased amyloid interactions. Previously, our lab determined that ibuprofen (IBU), a non-steroidal anti-inflammatory drug (NSAID) can decrease NMDAR expression in male mice, so we treated 5xFAD mice with ibuprofen for 2 months, in order to try to reduce the increased synaptic NMDAR responses and improve spatial memory.

At 2 months of age, hemizygous 5xFAD or wildtype (WT) mice were fed either regular chow or chow with 375 ppm of ibuprofen. At 4 months of age, mice underwent testing in the Morris water maze (MWM) and then were used for electrophysiology. The MWM involved acclimation (2 days), place & probe trials (4 days), reversal trials (1 day) and cued trials (1 day). For electrophysiology, mice were transcardially perfused with calcium-free cold artificial cerebral spinal fluid (aCSF). Brain slices (300μm) in normal aCSF were placed on a multielectrode probe (MED64) to examine the Schaffer collateral to CA1 synapses in the hippocampus. The field excitatory post synaptic potential (fEPSP) was analyzed in a drug study with the use of AMPA (DNQX), GluN2A (PEAQX), GluN2B (Ro25-6981) and all NMDA receptors (AP5) antagonists. Following equilibration, an input (fiber volley)/output (fEPSP) curve was generated and analyzed by comparison of linear curve fit.

All groups showed improved performance across place trials ($p=.04-<.0001$) except female WT IBU fed mice, but there was no significant effect of treatment or genotype on long term memory or reversal trials with the hidden platform. IBU did improve performance in probe trials in hemizygous females and IBU-fed mice overall showed more perseveration in reversal probe trials. Based on curve fit differences for electrophysiology, both male and female 5xFAD showed increased I/O responses for NMDAR and GluN2A ($p=.007-<.0001$). IBU increased responses for NMDAR, GluN2A and AMPAR in both WT ($p<.0001$) and 5xFAD ($p=.02-.0009$) females, but decreased responses to GluN2B and AMPAR in 5xFAD males ($p=.045-.0002$) and had no effect on WT males ($p=.35-.94$). Overall, IBU improved memory in 5xFAD females, potentially by further increasing glutamatergic signaling in the hippocampus, but reduced cognitive flexibility. In addition, it appeared that IBU had opposite effects on NMDARs and AMPARs in females versus males.

AMYLOIDOSIS IN THE PREFRONTAL CORTEX OF OLD RHESUS MACAQUES RESEMBLES THAT OF HUMANS, SHOWING EXTRACELLULAR PLAQUES AND CEREBRAL AMYLOID ANGIOPATHY

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Cerebral amyloid angiopathy (CAA) is a common cerebrovascular disorder that occurs in a subset of elderly humans, and is characterized by depositions of amyloid beta peptides in cerebral blood vessels. Further, clinical CAA has been shown to directly correlate with instances of Alzheimer's disease as well as cognitive decline (Arvanitakis et al. 2011), and the prefrontal cortex (PFC) has been identified as being one of the first brain regions to be affected by CAA (Thal et al. 2020).

The aged rhesus macaque shows CAA and is an excellent behavioral and physiological model for clinical aging. Our goal was to see if CAA levels further increased between old and the oldest-old macaques (n = 20; mean= 31.8 years, range = 22.4-44.1 years; old to oldest-old). Brain sections were immunostained for β–amyloid (4G8; BioLegend) and CAA was stereologically quantified in the anterior cingulate (ACg), a functionally relevant region of the macaque PFC. CAA (% coverage) was found to increase with age in the ACg, and positively correlated with extracellular plaque load. However, neither plaque load nor CAA correlated with neuronal number in the ACg, as neuronal number remained constant across age (Stonebarger et al. 2020). So it seems CAA is not associated with overt neurodegeneration in the macaque, but may be related to other age-related vascular changes. These data help characterize the nonhuman primate as a model of normative brain aging and validate the use of the aged rhesus macaque as an appropriate model for observing the consequences of naturally occurring amyloidosis.

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POSTERS

Cell-type contribution and mechanisms of glycine transporter 1-mediated seizure suppression

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Background: Glycine, is a major inhibitory neurotransmitter in the CNS and important regulator of hippocampal excitability. Glycine augmentation via inhibition of glycine transporter 1 (GlyT1) emerges as a therapeutic strategy for epilepsy treatment. This study aimed to explore the cellular contribution of GlyT1 inhibition on seizure suppression.

Methods: Two mouse lines with conditional forebrain-selective deletion of GlyT1 in neurons (CamKIIα-GlyT1 KO) or in neurons plus astrocytes (Emx1-GlyT1 KO) and AAV-based viral GlyT1 knockdown approaches were used to evaluate cell-specific effects of GlyT1-inhibiton in acute and chronic seizure models - pentylenetetrazole (PTZ) threshold model and intrahippocampal kainic acid (IHKA) epilepsy model. EEG monitory and analysis was used to seizure evaluation. Pharmacological glycine receptor agonist (taurine), and NMDA receptor inhibitor (kynurenic acid) and GlyT1 inhibitors were used for mechanistic evaluation.

Results: (i) Seizure burden was significantly lower in epileptic Emx1-GlyT1 KOs vs WTs, no seizure reduction seen in CAMkII-GlyT1 KOs; similarly, (ii) Emx1-GlyT1 KOs showed an increased PTZ-seizure thresholds vs WTs, but no increase in CamKIIα-KOs; (iii) Astrocytic Gfa2-GlyT1 viral knockdown of hippocampal GlyT1 significantly delayed the progression of seizures vs control virus; (iv) Single- and repeated-treatment of taurine (300 mg/kg, i.p.) significantly reduced seizure burden in epileptic WT mice, this effect was not seen in epileptic Emx1-GlyT1 KOs; (v) Pretreatment of taurine (300 mg/kg, i.p) increased PTZ-seizure threshold in WTs but not in Emx1-GlyT1 KOs.

Conclusion: Our findings suggest a key role of astrocytic GlyT1 on seizure suppression and activation of glycine receptor contributes to GlyT1-mediated seizure suppression.

Adenosine kinase isoforms in cellular proliferation

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Aims: The adenosinergic signaling pathway is revealed participating in cancer pathology and adenosine metabolic enzyme, adenosine kinase (ADK) is dysregulated in cancers with disturbance of its two isoforms – ADK long (ADK-L) and short (ADK-S) isoforms. This study aimed to characterize ADK isoform actions on cellular biology.

Methods: We used a retroviral approach to establish in vitro system model of cultured baby hamster kidney (BHK) cell-lines that have selective expression patterns of isoforms with a subcellular refined manner. The xCELLigence real-time cell analysis and MTT assay were employed with a combination of immunocytochemistry to determine proliferation and morphological changes of BHK cell-lines. Pharmacological ADK inhibitors were used to differentiate isoform-specific actions of ADK in BHK cell-lines.

Results: (i) Immunocytochemistry and Western blot confirmed that our engineered BHK cell lines have distinct expression patterns of ADK isoforms - the endogenous ADK isoforms were knocked out in BHK-AK2 cells, and exogenous human ADK-L or ADK-S were introduced into BHK-AK/L and BHK-AK/S cells; (ii) Deletion of ADK in BHK-AK2 resulted in significant lower proliferation rate vs BHK-WT cells; whereas the presence of ADK isoforms in BHK-AK/S and BHK-AK/L cells led to different proliferation rates vs BHK-AK/L cells; (iv) ADK inhibitor 5-iodotubercidin suppressed proliferation of BHK cells with a predominant effect on ADK-S isoform, i.e., in BHK-WT and ADK-AK/S; conversely, a novel ADK inhibitor NSC-B showed an ADK-L referent effect in the suppression of BHK cell growth.

Conclusion: We established a cellular platform for the development of ADK inhibitors as a potential therapeutic antitumor application.

NW NOGGIN: AXONS AND ARPILLERAS – ADDRESSING TRAUMA AND SUPPORTING COMMUNITY ACROSS DISCIPLINES AND NATIONAL BOUNDARIES

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"No happiness or pain, no more forgetting" — Gabriela Mistral

Science needs investment and diverse perspectives. Integrating arts in STEM (STEAM) encourages more people to get involved. Nonprofit NW Noggin (nwnoggin.org) organizes undergraduates and graduates to collaborate, build community networks and inspire people about neuroscience and art. Volunteers benefit from work across disciplines and institutions, serve as "near peer" role models, gain skill explaining research, and think creatively about careers. We've met over 45,000 academic priority K-12 students, homeless youth, incarcerated youth and members of the public since 2012!

Extreme inequality defines the United States, with devastating brain, health and social consequences, as more people struggle to access food, water, education, public transit, healthcare and housing. Concentrated wealth isolates those with extravagant resources from the broader community. Isolation is worsened by degrading rhetoric from political leaders and pundits who protect privileges, often by dehumanizing others. Inequality can also lead to the violation of human rights, and violence.

Valparaíso, Chile, home to both a long history of neuroscience research and astonishing art traditions, is currently targeted by a repressive and authoritarian government, whose leader, billionaire Sebastian Piñera, has declared "war" (guerra) on those protesting injustice. Noggin partnered with Chilean artist/educator Cecilia Araneda to teach how the art of "arpilleras," the sewing of embroidery and patchwork to depict aspects of life, has helped many express traumatic experiences and contribute to the memory of significant national violations of human rights.

We participated in a public radio interview and displayed arpilleras and human brains at Street 14 Café during an "Art Walk" in Astoria, Oregon, and discussed neuroscience research on stress, trauma, memory, dehumanized perception, resilience and recovery. We then presented and crafted our own arpilleras at p:ear, a critical community center for support of Portland Oregon youth who lack access to safe, stable housing, while answering questions about behavior and the brain. NW Noggin is p:ear's Community Partner awardee in 2020.

Building excitement and awareness of discoveries, educational options and careers through arts-integrated outreach across institutional, international and generational lines trains new scientists to collaborate, engages more communities, and increases awareness and support for investment in brain research and the arts.

Metabolomic Investigation Into the Cognitive-Enhancing Effects of Centella Asiatica in a 5xfad Mouse Model of β-Amyloid Accumulation

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Centella asiatica (CAW) is an herb used in Ayurvedic and traditional Chinese medicine for its beneficial effects on brain health and cognition. Our group has previously shown that a water extract of *Centella asiatica* (CAW) elicits cognitive-enhancing effects in animal models of aging and Alzheimer's disease (AD). A recently published study by our group demonstrated a dose related effect of CAW in the 5xFAD mouse model of β-amyloid (Aβ) accumulation. Here we endeavor to elucidate the mechanisms underlying the effects of CAW in the brain by conducting a metabolomic analysis of cortical tissue from these 5xFAD mice treated with increasing concentrations of CAW. Tissue was collected from 8-month-old male and female 5xFAD and wild-type (WT) mice treated with CAW at 0, 200, 500, or 1000 mg/kg for 5 weeks and ultra-high-performance liquid chromatography coupled to high-resolution mass spectrometry metabolomics analyses were performed. We assessed relative levels of 120 metabolites in these samples. Our analyses revealed differences in pathway enrichment due to sex, genotype and CAW treatment. We found that pathways related to nicotinate and nicotinamide metabolism, purine metabolism, and glycerophospholipid metabolism were significantly altered by CAW administration. These results are in line with some of our previous findings, using other analytical techniques, regarding specific mechanisms of action of CAW and provide new information about other potential mechanisms of action of CAW in the brain.

Stress-induced changes in parvalbumin, c-Fos, and perineuronal nets in limbic circuitry of the rat brain using two stress models

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The response to stress is variable depending on factors including type, duration, and controllability of stress. We examined two stress models. Male rats had either a single prolonged stress followed by no isolation (physical restraint 2h, forced swim 20 min, exposure to ether <5 min; SPS-no iso;), or an SPS followed by 7d isolation (full SPS). The second model was escapable/inescapable stress (ES/IS) in which tail shocks were terminated by rotating a wheel or yoked controls. We examined parvalbumin (PV), their surrounding perineuronal nets (PNNs), and c-Fos in the medial prefrontal cortex (mPFC), hippocampus, and amygdala (AMY). PNNs were measured with *Wisteria floribunda* agglutinin (WFA). **Model 1:** Compared with home cage controls, in the mPFC, SPS-no iso increased, and full SPS decreased, c-Fos, and full SPS increased PV. In the CA1, SPS-no iso and full SPS decreased PV. In the CA3, SPS-no iso increased WFA. In the DG, SPS-no iso increased c-Fos, whereas full SPS decreased c-Fos. Both SPS treatments decreased PV, and full SPS increased WFA. In the BLA, SPS-no iso increased whereas full SPS decreased c-Fos. Both stressors decreased PV, and full SPS decreased WFA. **Model 2:** Compared with naïve controls, in the mPFC, both ES and IS increased c-Fos and decreased PV, whereas in the DG, c-Fos ES decreased and IS increased c-Fos, and both increased WFA. Ongoing work is examining changes in the hippocampus and BLA. Understanding neuronal changes with stress may allow for development of new therapeutic targets for stress-related disorders.

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Investigating a Potential Mechanism of Noise-Induced Synaptopathy

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Poster presentation preferred

Noise is the most common cause of preventable hearing loss, affecting 31 million Americans. A less-studied subcategory of noise-induced hearing loss is known as hidden hearing loss, in which the synapses connecting inner ear hair cells to afferent ganglion neurons are damaged (termed synaptopathy). This damage is suspected to be caused by excess glutamate release in the synaptic cleft. However, the exact mechanism of synaptopathy remains unknown, and there is currently no FDA approved treatment. Here we investigate a potential mechanism of noise-induced synaptopathy. We hypothesize that excess glutamate release following noise damage will cause AMPA receptors lacking the GluA2 subunit to leak excess calcium into the ganglion cell, and that heterogenous distribution of this GluA2 subunit will be negatively correlated with calcium entry and damage to the ganglion cell. This hypothesis was tested by using noise to damage hair cells in the zebrafish lateral line – an established vertebrate model for studying noise-induced hearing loss. Following noise damage, GluA2 and GluA4 subunit distribution and intracellular calcium levels were determined. Synaptic integrity and ganglion cell death were also assessed at different time points after noise exposure. This research can shed light on the suspected mechanism of AMPA-receptor mediated synaptopathy following acoustic trauma, thus uncovering a potential pharmacological target. Given the absence of an FDA approved treatment and the inefficacy of hearing aids in mitigating hidden hearing loss, our research has the potential to fill a health care gap for a currently untreatable condition.

Novelty-induced prediction error during memory reconsolidation

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Memories are established and strengthened by a memory maintenance process called reconsolidation. Memory-updating mechanisms exploit reconsolidation during a specific window known as the reconsolidation time window that can be opened when there is a prediction error. When there is a mismatch between what is expected and what is received, a prediction error signals for incorporation of new information by alerting, reorienting, and implementing a shift in attention to accommodate the new information. We have shown that prediction error alone prior to extinction is not sufficient to diminish a cocaine self-administration memory. Propranolol, a beta-adrenergic antagonist, has shown promising therapeutic effects for impairing fear memory reconsolidation. We hypothesized that propranolol, in addition to a prediction error, may disrupt the persistence of a strong cocaine self-administration memory. Rats were trained for 2 hr sessions for 14 days on a fixed-ratio 1 (FR1) schedule and given a 30 min memory retrieval on a cocaine-reinforced FR1 or variable ratio 5 (VR5) schedule- the latter given to induce prediction error. Propranolol was administered (10 mg/kg, i.p.) 30 minutes before or immediately after memory retrieval, and cocaine seeking was measured during a 30-min cue reinstatement one day later. The FR1 retrieval followed by propranolol decreased lever pressing during cue reinstatement, and propranolol with a VR5 retrieval did not decrease cocaine seeking, suggesting that a VR5 retrieval blocks memory updating. It is possible that the blockade of noradrenergic activity prevents the increase in arousal that is caused by prediction error, blocking the ability to accommodate new information.

Support: Alcohol and Drug Abuse Research Program (ADARP) award, Washington State University, Pullman

PARVALBUMIN, PERINEURONAL NETS, AND CUE INDUCED REINSTATEMENT AFTER LONG-ACCESS COCAINE SELF-ADMINISTRATION IN RATS

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The medial prefrontal cortex (mPFC) is involved in the reinstatement of cocaine-seeking behaviors in rodents and relapse in humans. Parvalbumin (PV) inhibitory interneurons, which tightly regulate the pyramidal output of the mPFC, are often surrounded by perineuronal net (PNN), which regulate plasticity of PV interneurons and contribute to learning and memory. Here we used a long-access model of cocaine addiction to investigate changes in prelimbic mPFC PV and PNN intensity after extinction and cue reinstatement. We also examined the impact of a short (1 - 2 day) vs. long (30 - 31 day) withdrawal period on PV and PNN levels. The longer withdrawal period is known to increase reinstatement in rodents and drug craving in humans. Extinction decreased PV intensity relative to saline controls but increased PNN intensity. Cue reinstatement had no effect on PV intensity but increased PNN intensity. The long, but not short, withdrawal period increased both PV and PNN intensity. We then determined if we could prevent the increase in cocaine cue-induced reinstatement by degrading PNNs. PNN degradation did not prevent an increase in reinstatement between the early and late withdrawal times. However, reinstatement was decreased for PNN-degraded rats compared to saline controls at both early and late withdrawal times. These findings suggest that PNNs alter PV interneuron function in a manner sensitive to various phases of cocaine addiction, and removing PNNs prevents cocaine cue-induced reinstatement after both short- and long-term withdrawal.

Prolonged treatment with *Centella asiatica* improves memory, reduces Aβ pathology and activates NRF2-regulated antioxidant response pathway in 5xFAD mice.

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Background: The medicinal herb *Centella asiatica* has been long been used for its neuroprotective and cognitive enhancing effects. We have previously shown that two weeks of treatment with a water extract of *Centella asiatica* (CAW) improves cognition and activates the endogenous antioxidant response pathway without altering amyloid-β (Aβ) plaque burden.

Objective: Here, we assess the effect of long-term treatment of CAW in the 5xFAD mouse model of Aβ accumulation.

Methods: Four month old 5xFAD mice were treated with CAW in their drinking water (2g/L) for three months at which point they underwent cognitive testing as well as analysis of Aβ plaque levels and antioxidant and synaptic gene expression. In order to confirm the involvement of the antioxidant regulatory transcription factor NRF2 on the effects of CAW on synaptic plasticity, neurons isolated from 5xFAD mice were also treated with CAW and the targeted inhibitor ML385.

Results: Three months of treatment with CAW improved spatial and contextual memory as well as executive function in 5xFAD mice. This improvement was accompanied by increased antioxidant gene expression and a decrease in Aβ plaque burden relative to untreated 5xFAD animals. In isolated neurons treatment with ML385 blocked the effects of CAW on dendritic arborization and synaptic gene expression.

Conclusion: These results suggest that prolonged CAW exposure could be beneficial in Alzheimer's Disease and that these effects likely involve NRF2 activation. Moreover, these findings suggest that targeting NRF2 itself may be a relevant therapeutic strategy for improving synaptic plasticity and cognitive function in Alzheimer's Disease.

BEHAVIORAL AND HISTOLOGICAL EFFECTS OF VAPORIZED FULL-SPECTRUM CBD EXTRACT

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Abstract: One of the most common ways of cannabinoid delivery used by the population is through vaping (inhaling cannabis oil vapor). The majority of preclinical studies about vaping uses propylene glycol, vegetable glycerol, or a combination of both (PGVG) as their control, despite being linked to increased lung inflammation after chronic exposure. The use of full-spectrum CBD extract (hemp oil which contains CBD and other cannabinoids and compounds) in vaping products is widely popular, but studies of its effects in animals or humans is lacking. In the current study, we aim to compare the behavioral and histological effects of hemp oil and PGVG, focusing the effects on female as CBD is widely used for pain relief for its anti-inflammatory properties, and women are disproportionately affected by chronic pain. Female Long Evans rats were treated with either saline or morphine (10mg/kg) and was exposed to either PGVG or hemp oil vapor twice daily for 30 minutes for 2 days. We observed the effects of full-spectrum CBD extract through the cannabinoid-induced tetrad test and a morphine dose-response test. There was no overall significant difference between PGVG vapor and hemp oil vapor; that is, full-spectrum hemp oil did not produce significant tetrad or morphine interaction results. This suggests that hemp oil could be used as an innocuous vehicle in preclinical studies of inhaled vaporized cannabis since it produced comparable behavioral effects to PGVG and did not produce histopathology.

Maternal Western-Style Diet increases pre-weaning hippocampal volume and alters in prosocial engagement and idiosyncratic behavior in Japanese macaques

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The chronic complications associated with obesity place a heavy burden on our public health system. Oxidative stress induced by obesity and the overconsumption of obesogenic diets, such as the Western-Style Diet (WSD), lead to hypertrophic environments throughout the body. These hypertrophic environments stimulate the production of inflammatory cytokines and increase the overall systemic inflammatory profile. During pregnancy, these changes are reflected in the placental inflammatory profile. It is well established that changes to the placental immune milieu are associated with alterations to fetal neurodevelopment and postnatal behavioral outcomes. Epidemiological studies have found associations between the prevalence of neuropsychiatric diagnoses such as Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) in children of obese mothers when compared non-obese mothers. Using an established non-human primate model (macaca fuscatta) of maternal western-style diet (mWSD), we assessed differences in offspring behavioral phenotypes during the Novel Peer Introductions (NPI, n= 39) at six months of age. Results show that mWSD offspring display decreased social engagement behavior (*initiated proximity,p = .02; affiliative contact,p = .048)* and increased idiosyncratic behavior *(p=.03).* Structural MRI results show differences in hippocampal volume may underlie behavioral observations, where mWSD offspring exhibit increased hippocampal volumes at four *(left, p=.032; right, p=.018)* and six *(left, p=.002; right, p=.01)* months. Both behavioral and volumetric results suggest mWSD macaque offspring display phenotypes similar to those described in individuals diagnosed with an ASD. These findings support and expand on previous hypotheses that mWSD alters postnatal behavioral outcomes.

APOE ISOFORM-DEPENDENT EFFECTS OF AGE AND SEX ON FEAR MEMORY EXTINCTION

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Apolipoprotein E (E) is involved in cholesterol metabolism. In humans, there are three major isoforms; E2, E3, and E4. Compared to E3, E4 is a risk factor for cardiovascular disease, age-related cognitive decline, and Alzheimer's Disease (AD). Compared to E3, E2 reduces AD risk but is associated with more severe post-traumatic stress disorder symptoms, which may be linked to impaired extinction of traumatic fear memories. We hypothesized that age and sex play a role in apoE isoform-dependent effects on fear memories. To test this hypothesis, we studied fear memories in human apoE targeted replacement mice expressing human apoE under control of the mouse apoE promoter, aged 5 or 12 months. Fear memory was assessed using contextual fear conditioning, in which animals received an aversive stimulus in an environment (fear learning) and are placed back in the same environment on subsequent days without the aversive stimulus to assess extinction of the contextual fear memory. During the contextual fear memory trials, young E2 males did not show successful fear memory extinction, while young E2 females did freeze significantly less across extinction trials. This trend is reversed in the aged E2 males, which significantly extinguish fear memory while aged E2 females do not. These interactions of age and sex on fear memory extinction were not observed in the E3 and E4 genotypes. Thus, the effects of age and sex on contextual fear memory extinction are uniquely seen in E2 mice and support the potential role of apoE in fear-related disorders.

Utilizing Open Source Data Repositories for Developing Researchers

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Due to COVID-19, there is a growing interest in open access resources for conducting neuroscience research due to limited in-lab research. Open source data repositories such as Cambridge Centre for Aging and Neuroscience (CAM-CAN) provide opportunities for training and conducting neuroscience research using a variety of tools, including functional magnetic imaging (fMRI). This project described the feasibility of utilizing fMRI databases and open source image analysis tools to conduct a replication and extension study. The CAM-CAN database was identified as a source of fMRI image files from a cross section of adults (N=700). The database contains interview and questionnaire demographic data, imaging data, and timing files for the trials for each of the tasks available to researchers. Image analysis training consisted of completing training modules in the FMRIB Software Library (FSL) from the University of Oxford along with mentorship by a collaborator. Image analysis was conducted using FSL. Following analysis training and file acquisition, images from samples of young (n=100) and older (n=100) adults from the CAM-CAN database were analyzed to assess significant differences in regional activation during a task. Utilizing the CAM-CAN database and FSL tutorial training modules was a feasible approach to testing research questions using open source materials during the COVID-19 pandemic. The benefits of this approach included the ability to continue research training remotely, obtain training in new research methods, and participate in open access research and collaboration. Lessons learned and suggestions for implementing remote training and collaboration will be addressed.

PORTLAND STATE UNIVERSITY NEUROSCIENCE CLUB: NAVIGATING NEUROSCIENCE EDUCATION & OUTREACH DURING THE COVID-19 PANDEMIC

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The Portland State University (PSU) Neuroscience Club is a community of service-minded students that focuses on providing quality neuroscience education to individuals with otherwise little neuroscience exposure. During the COVID-19 pandemic, we were presented with challenges that made it difficult to continue connecting with our peers. To navigate these challenges, we have worked to develop innovative ways to continue providing PSU students a neuroscience community.

After transitioning to a virtual format for our meetings, we looked for potential benefits of an online platform. These benefits have included being able to recruit neuroscientist/neurologist guest speakers from across the country, as well as collaborating with Neuroscience Clubs from different universities. We have also worked hard to create a sense of community for our members by hosting social and outreach events. Our weekly meetings range from journal clubs to medical school/graduate school panels to virtual game nights.

Our club has also strived to make a bigger impact on the PSU community by leading an initiative to develop an interdisciplinary Neuroscience minor. This initiative was well-received, and PSU could have this minor as early as Fall 2021. Our impact has also extended to our members, with 55% reporting that our club has influenced their decision to pursue a career in neuroscience, and 72% reporting that our club has helped them learn about neuroscience beyond the classroom. Overall, we have served our community by providing meaningful exposure to neuroscience and a place to connect with peers.

The role of CSPG sulfation during sympathetic nerve regeneration following myocardial infarction

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Sympathetic denervation of the heart following Myocardial Infarction (MI) predicts risk of sudden cardiac death. The cardiac scar is enriched with chondroitin sulfate proteoglycans (CSPGs), which inhibit axon regeneration into the infarcted myocardium. Previous work demonstrated that blocking CSPG signaling restores sympathetic axon outgrowth into the CSPG laden cardiac scar, decreasing arrhythmia susceptibility. Axon outgrowth inhibition by CSPGs is thought to depend on the sulfation status of the glycosaminoglycans (GAGs) attached to the core protein. In the central nervous system, it has been shown that tandem sulfation of CSPGs at the 4th (4S) and 6th (6S) positions of n-acetyl-galactosamine which comprise GAGs is thought to be a primary negative regulator of axon outgrowth. Despite this, it is unknown whether CSPG sulfation prevents sympathetic nerve regeneration in the heart after MI. Our data suggest that CSPG sulfation plays a critical role in preventing sympathetic axon outgrowth in the heart after MI. We show that sympathetic axon outgrowth across purified CSPGs is restored in-vitro by removing 4S-CSPGs with the enzyme Arylsulfatase-B (ARSB). Using an ex-vivo approach to study sympathetic growth inhibition following MI, we co-cultured cardiac scar tissue with sympathetic ganglia. Removing 4S-CSPGs from the cardiac scar with ARSB restored axon outgrowth to control levels despite the presence of scar tissue. We examined levels of the enzymes responsible for adding and removing sulfation to CSPG-GAGs by western blot to determine if they were altered in the left ventricle after MI. We found that CHST11 (4-sulfotranserase) was downregulated, CHST15 (4S dependent 6-sulfotransferase) was upregulated, and ARSB (4-sulfatase) was downregulated after MI. Increased CHST15 combined with decreased ARSB suggest a mechanism for production and maintenance of sulfated CSPGs in the cardiac scar.

The complex interactions of maternal metabolic and inflammatory state on offspring central and peripheral inflammatory outcomes

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Obesity is an epidemic that effects 40% of adults in the US. About one-third of pregnant women are classified as obese. Previous research suggests that children born to obese mothers are at increased risk for developing neurodevelopmental and neuropsychiatric disorders. The mechanisms behind this increased risk are poorly understood. Increased exposure to inflammation in-utero induced by maternal obesity is a proposed mechanism for neurodevelopmental alterations in offspring. Utilizing a non-human primate model of maternal obesity, we hypothesized that maternal consumption of an obesogenic diet will predict offspring peripheral (e.g. cytokines and chemokines) and central (microglia density) inflammatory outcomes through measures of maternal metabolic and inflammatory state (e.g. adiposity, insulin response, and maternal peripheral inflammatory measures). To understand the complex interactions of metabolic state and inflammation we employed structural equation modeling (SEM). Latent variables were created for maternal chemokines, and offspring cytokine and chemokines. Model results showed that neither maternal pre-pregnant adiposity (β=0.433, p=0.251) or maternal 3rd trimester insulin area under the curve (IAUC) (β=-0.364, p=0.150) predicted offspring peripheral cytokine or chemokine levels. However, maternal chemokines were associated with offspring chemokine (β=0.292, p<0.05) and cytokine (β=-0.390, p<0.05) measures. In contrast, maternal diet had an indirect effect on offspring amygdala microglia cell counts through both maternal adiposity (β=0.536, p<0.05) and 3rd trimester IAUC (β=-0.487, p<0.05) but was not influenced by maternal inflammatory state. In summary, these data suggest that maternal metabolic state appears to predict offspring amygdala microglial counts while maternal inflammatory state influences offspring peripheral inflammatory outcomes.

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Probing the Role of *Drosophila* Thrombospondin in Larval NMJ Formation

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Thrombospondin (TSP) is an extracellular matrix glycoprotein that plays a role in synaptogenesis at glutamatergic synapses in the mammalian brain. While there are 5 TSP genes in humans, there is a single homologous gene in *Drosophila melanogaster* (D-TSP) and there is conservation in the protein domains involved in TSP's function in synaptogenesis. It has not been investigated if D-TSP plays a role in synaptogenesis in *D. melanogaster*. Here we determined if D-TSP modulates synaptogenesis and locomotor behavior in the *D. melanogaster* larval NMJ. We hypothesized that D-TSP would be necessary for normal NMJ formation and locomotor behavior. We used the GAL4-UAS system to knock down D-TSP in neurons, muscle, or both, and quantified features of the NMJ structure and locomotor behavior in larvae with normal or decreased D-TSP expression. Our preliminary results suggest an increase in NMJ complexity when TSP is knocked down either in neurons or in neurons and muscle together. A polygon area analysis of the NMJ innervation shows no differences in the TSP knock downs. Some NMJs also seem to have a clumping phenotype that we plan to characterize further. The NMJ complexity changes are not associated with changes in zones occupancy, which is a measure of how far away from their point of origin the larva moved. We are in the process of validating the knockdowns of D-TSP by RT-qPCR. We will also normalize our morphological data by the muscle area. Next, we will quantify other larval behaviors, including head-turning, body contractions and rolling.

Effects of diazepam on hippocampal neural stem cell proliferation, neurogenesis and memory after traumatic brain injury

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Adult neurogenesis persists throughout the life of most mammals, including humans, and has important roles in learning and memory as well as mood regulation. Accordingly, the hippocampus, a brain region critical for memory, increases its generation of new neurons in response to physiological stimuli such as exercise and learning and memory. Following brain insults such as stroke and traumatic brain injury (TBI), neurogenesis also increases within the hippocampus but does so robustly. Although this increase may represent a restorative response, we previously showed that the neurons generated after TBI mislocate within the hippocampal circuitry and have abnormal dendritic morphologies, questioning the functional role of post-traumatic neurogenesis. We subsequently showed that the GABA-A agonist, diazepam, attenuates increases in post-traumatic neurogenesis and normalizes the dendrites of new neurons. To determine whether this type of modulation improves or worsens neurogenesis-dependent memory, we administered diazepam or vehicle to C57Bl/6J wild-type male and female mice for one week immediately following a controlled cortical impact (CCI) injury or sham injury. Mice were allowed to recover for one month and are currently undergoing reversal water maze testing. To determine whether diazepam attenuates post-traumatic neurogenesis through the inhibition of neural stem cell (NSC) proliferation as shown after experimental stroke, the percent of proliferating hippocampal NSCs are being quantified between mice that received diazepam or vehicle immediately after CCI or sham injury. Results from our studies will provide insights into how post-traumatic neurogenesis is modulated by diazepam and determine whether this type of modulation improves or worsens memory.

Estrogen Differentially Regulates Protein Abundance in Exosomes Released from Immortalized Kisspeptin Neurons *in Vitro*

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Estrogen (E2) is essential for multiple physiological effects in females, ensuring maximum reproductive fitness and maintaining skeletal homeostasis. E2 can stimulate cancellous bone formation via activation of estrogen receptor alpha (ERα), an effect mediated directly at bone. A recent landmark study (Herber et al., *Nat Commun* 2019) demonstrated bone density increases in female mice harboring ERα deletions in arcuate Kisspeptin (Kiss-1) neurons, with bone from transgenic females showing higher osteoblast function and increased expression of *sp7* and *runx2,* positing a neural-bone regulatory axis altered by E2 acting in brain. Our laboratory uses immortalized Kiss-1 cell lines, KTaR-1 (representing arcuate Kiss-1 neurons) and KTaV-3 (AVPV Kiss-1) as models to explore roles of Kiss-1 in physiological regulatory contexts. We determined that factors in media of KTaR-1 cells can affect osteoblast function *in vitro*, including increases in *sp7* and *runx2* expression, and formation of bone matrix (evaluated by Alizarin Red assay). Exposure of canine osteosarcoma cells to KTaR-1 conditioned media led to increased *sp7* expression in an E2-dependent manner, and E2-deprivation of these neurons stimulated secretion of osteogenic factors. In this study, we used LCMS-MS proteomic analysis to determine contents of exosomes isolated from Kiss-1 neurons under varying E2 exposures *in vitro*. Results reveal ~150-170 proteins up-regulated by E2 and ~200-220 proteins downregulated by E2 in exosomes of KTaR-1 and KTaV-3 Kiss-1 neurons. E2-regulated Kiss-1 exosomal proteins include candidates involved in bone remodeling (pentraxin, osteonectin, osteoclast-stimulating factor-1) and synaptic plasticity and signaling (annexins, semaphorins, connexins). Current work explores effects of exposure to purified exosomes on morphology and expression in GnRH neurons and osteoblasts. Initial results suggest that exosomes may represent additional intercellular communication pathways utilized by Kiss-1 neurons to elicit changes in brain and bone.

Kisspeptin Neurons from Female Mice Express Receptors for Gonadotropin-releasing Hormone (GnRH) under Specific Estrogen Exposure Conditions: A Potential Model for Positive Feedback Required for GnRH Preovulatory Surges?

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In female animals, ovarian estradiol (E2) acts as both negative feedback inhibition of GnRH secretion, as well as positive feedback stimulation at ovulation. Both E2-regulated mechanisms work via stimulation or repression of distinct neuronal populations of Kisspeptin (KP)-synthesizing neurons. While AVPV KP neurons are found to increase *kiss1* expression during the preovulatory surge, mechanisms required for potentiation of GnRH surge release remain unclear. Two KP-secreting cell lines demonstrating increased *kiss1* expression under high E2 (KTaV-3), or *kiss1* suppression under low E2 (KTaR-1), were used to probe GnRH receptor (GnRHR) expression levels under different E2 conditions.

KTaV-3/KTaR-1 cells were treated with E2 (5-100pM) and/or progesterone (20nM) for varying durations (4-96h), either constitutively or via modulating levels approximating changes found during the murine estrous cycle. Following RNA isolation, cDNAs were probed with *gnrhr* primers. Results reveal *gnrhr* expression, normally absent, is induced in KTaV-3 cells only following 50-100pM E2 for 18-24h. These conditions also increased *dlx3* expression, a transcription factor required for GnRHR in pituitary. In KTaR-1 cells, *gnrhr* expression was observed only following E2 decreases, while *dlx3* is constitutively elevated. While reciprocal GnRH-Kisspeptin connections have not yet been observed *in vivo*, results suggest Kisspeptin neurons may respond to GnRH release only under particular E2 conditions, by differentially modulating GnRH receptivity at AVPV and/or Arcuate nuclei. We are exploring temporal GnRHR induction parameters in KP cells, and if GnRH exposure of KP neurons *in vitro* elicits expression and signaling changes in a time- and E2-dependent manner, providing increased understanding of positive and negative feedback mechanisms required for normal neuroendocrine regulation of reproduction.

A VIRAL NON-HUMAN PRIMATE MODEL OF LOCALIZED DEMYELINATION

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Multiple Sclerosis (MS) is an autoimmune inflammatory demyelinating disease that affects the central nervous system (CNS). Patients with MS have deficits in motor, sensory and cognitive function. Histopathologically, MS lesions are characterized by multifocal demyelination, inflammatory infiltrates, damaged axons and loss of oligodendrocytes. To understanding MS pathogenesis and develop effective treatments, researchers have developed a wide range of models replicating various features of the disease. We have characterized one such model, Japanese macaque encephalomyelitis (JME), characterized by multiple foci of demyelination and axon damage[1]. Like MS patients, animals with JME demonstrate oligoclonal banding in their cerebrospinal fluid, have myelin-reactive T cells, and have clinical and imaging features consistent with multi-focal inflammatory demyelinating disease[1-4]. JME lesions are enriched with Japanese macaque rhadinovirus (JMRV), a novel primate herpesvirus linked to JME pathogenesis[5]. JME can be induced in animals from lineages with a history of JME following intracranial JMRV infection (manuscript in preparation). Here, we examined the patterns of demyelination and axonopathy following MRI-guided virus injection of JMRV or vehicle (as a control) into the corpus callosum of Japanese macaques from susceptible lineages. We find that all animals injected with JMRV had highly reproducible lesions with regards to location and size as assessed by MRI. Using immunohistochemistry, we observed evidence of demyelination and axonal damage in the JMRV injected tissues. This induced model is therefore able to reproduce the first stage of MS pathological changes and is useful for screening remyelination-promoting drugs.

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KEYNOTE

How genes and bacteria shape the risk of neuroinflammatory disease: The example of Multiple Sclerosis

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Sergio E. Baranzini is Distinguished Professor of Neurology at the University of California San Francisco (UCSF). He earned his PhD in human molecular genetics (1997) from the University of Buenos Aires, Argentina. His lab at UCSF uses a multi-disciplinary approach to science and it is composed by experimental and computational researchers. Dr. Baranzini leads the iMSMS, an international consortium to study the effect of bacterial populations (microbiota) on MS susceptibility and progression. In addition, he is the principal investigator of SPOKE, a large multi-disciplinary bioinformatics approach to gather, integrate and analyze all biomedical data, currently supported by NIH and NSF.

ABSTRACT: Multiple sclerosis is an autoimmune disease of the central nervous system. Ample evidence suggests that both genetics and environmental factors contribute to its pathogenesis. While a fairly complete picture of the genetic risk factors is currently available, much less is known about the role played by environmental factors. The gut microbiota is emerging as an interesting player given its role in regulating both innate and adaptive immune responses during health and disease. Growing evidence of microbiome alterations in multiple human autoimmune diseases and specifically of microbial regulation of immune responses in experimental autoimmune encephalomyelitis (EAE) led us to investigate changes in intestinal microbiota as a potential pathogenenic mechanism in MS. Current work from the international MS microbiome study (iMSMS) will be discussed. Finally, evidence will be presented that specific human gut bacteria regulate adaptive autoimmune responses, suggesting therapeutic targeting of the microbiota as a novel treatment for MS.

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