Society for Neuroscience

Oregon & Southwest Washington

MEETING

March 8-9, 2024 - Edgefield Winery

TABLE OF CONTENTS

SCHEDULE

Friday, March 8

Mini-symposium on Neuroinflammation and the Aging Brain

1:00 pm ***Mini-symposium Keynote****: Fate Mapping of Peripherally Derived Macrophages After Traumatic Brain Injury*
Susanna Rosi
Departments of Physical Therapy Rehabilitation Science and Neurological Surgery, University of California, San Francisco

1:40 pm *Environmental challenges, immune and neuroinflammatory measures, and behavioral and cognitive measures in animal models*
Jacob Raber
Department of Behavioral Neuroscience, OHSU

2:05 pm *Thrombin generation: gate keeper or grim reaper of the blood-brain barrier*
Owen McCarty
Department of Biomedical Engineering, OHSU

2:30 pm *The influence of maternal nutrition, metabolic state and inflammation on child risk for psychiatric disorders*
Elinor Sullivan
Departments of Psychiatry and Behavioral Neuroscience, OHSU

2:55 pm *Understanding the role of microglial cells in motor neuron vulnerability in Amyotrophic Lateral Sclerosis (ALS)*
Bahareh Ajami
Departments of Molecular Microbiology and Immunology and Behavioral Neuroscience, OHSU

3:20 pm Break

3:40 pm *Ferroptosis drives microglial cell death following white matter injury in the aging brain*
Philip Adeniyi
Department of Pediatrics, OHSU

4:05 pm *Will chronic inhibition of dual leucine zipper kinase (DLK) be neuroprotective and restore neuronal function in aged demyelination?*
Katie Emberley
Department of Neurology, Jungers Center for Neurosciences Research, OHSU

4:20 pm *Elevated expression of α5-integrin by myeloid cells in motor areas provides a potential target for therapeutics in ALS*
Audie Chiot
Departments of Molecular Microbiology and Immunology and Behavioral Neuroscience, OHSU

4:35 pm *Role of peripheral inflammation in driving central nervous system inflammatory signature in pathogenesis of Alzheimer's Disease*
Paula Sanchez Molina
Department of Molecular Microbiology and Immunology, OHSU

4:50 pm **Poster Session I and Networking Social Hour**

Elias M. Wisdom, OHSU
Jay C. Adams, Oregon State University
Kaitlyn Kim, Oregon State University
Rachel Morrill, OHSU
Ibrahim A. Abou-Seada, Oregon State University
Benjamin Bui, Legacy Research Institute
Mariel Kristine Micael, Vollum Institute
Will Liguore, Oregon National Primate Research Center
Kaylee Ha, OHSU
Noah Kolarsky, OHSU

6:00 pm **DINNER**

6:45 pm **Meeting Keynote:** *Determinants and mechanisms of neuroinflammation-induced memory deficits in aging*
Ruth M. Barrientos
Institute for Behavioral Medicine Research, Department of Psychiatry and Behavioral Health, Ohio State University College of Medicine

Saturday, March 9

7:00 am **BREAKFAST**

8:00 am *Las neuronas son bacanes: Interdisciplinary neuroscience in Valparaiso Chile*
William S. Griesar and Jeff Leake
Department of Psychology, Portland State University

8:30 am *The mouse olfactory bulb tracks breathing rhythms and place*
Matt Smear
Departments of Neuroscience and Psychology, University of Oregon

9:00 am *Effects of amyloid beta peptides on platelet hemostatic function and procoagulant platelet generation*
Yiheng Zhang
Department of Biomedical Engineering, OHSU

9:15 am *T cell receptor-based cell therapy for central nervous system injury*
Taitea Dykstra
OHSU

9:30 am *Effects of TFEB gene therapy on hippocampal-dependent learning and molecular signaling in obese female and male 5xFAD mice*
Danielle Osborne
Legacy Research Institute

9:45 am *Structural insight into heteromeric assembly in epithelial sodium channels*
Isabelle Baconguis
Vollum Institute, OHSU

10:15 am **Poster Session II**

Kadi Rae Smith, Portland State University
Natalie Robison, Portland State University
Emilee Brnusak, Portland State University
Connor Hilts, OHSU
Benjamin Zimmerman, Helfgott Institute
Brooke Rogers, OHSU
Olivia Monestime, OHSU
Joshua Karpf, Oregon National Primate Research Center
Opal Stayer-Wilburn, Oregon National Primate Research Center
Anahit Grigorian, Oregon National Primate Research Center

11:15 am *Electrophysiological characterization of immortalized ovine hypothalamic kisspeptin neurons*
Anna Nielson
Oregon State University

11:30 am *Assessing the role of inattention, response latency, and perseveration in predicting behavioral flexibility in rhesus macaques*
Daniel Smith
Oregon National Primate Research Center

11:45 am *Impact of ketamine and novelty on cue-induced reinstatement of cocaine self-administration in rats*
Angela Gonzalez
Washington State University

12:00 pm *Changes in cerebral morphology and microstructure associated with advancing age in rhesus macaques*
Alison Weiss
Oregon National Primate Research Center

12:15 pm *Molecular mechanisms of maternal care in a mouthbrooding cichlid fish*
Suzy Renn
Biology Department, Reed College

12:45 pm **LUNCH**

1:15 p.m. Awards and Adjournment

Mini-Symposium Keynote Speaker

Dr. Susanna Rosi (*Altos Labs and Departments of Physical Therapy Rehabilitation Science and Neurological Surgery at the University of California San Francisco*) was born and raised under the Tuscan sun. Susanna did her undergraduate and graduate studies at the University of Florence where she studied inflammation, aging and Alzheimer's disease. She then moved from Tuscany to Tucson to complete a post doc at the University of Arizona. She started her academic career at UCSF where she quickly rose to the rank of professor and became the Lewis and Ruth Cozen Chair Professor in the Departments of Physical Therapy Rehabilitation Science and Neurological Surgery, and founding Principal Investigator at Altos Labs. Her work is focused on understanding how immune cells relate to cognitive outputs in the context of aging, traumatic brain injury, cancer therapy, and space radiation. She is the recipient of several NCI, NIA, NINDS awards, has been a NASA investigator for over 10 years, and the recipient of the 2021 J.W. Osborne Award for "fundamental discovery on normal tissue radiation responses" from the Radiation Research Society.

Fate Mapping of Peripherally Derived Macrophages After Traumatic Brain Injury

Traumatic Brain Injury (TBI) represents a critical health problem for our society, given its increasing occurrence, complex pathophysiology, challenging diagnosis, and long-term neurological disabilities. It is well established that TBI-induced neuroinflammation engages resident microglia as well as infiltrating monocytes (CCR2+) recruited from the periphery which both contribute to long lasting cognitive deficits. After brain engraftment, peripherally-derived macrophages stop expressing their signature marker CCR2, thus making discrimination from reactive microglia cells elusive. To overcome this issue, we took advantage of CCR2-creER^{T2}::Ai14D mice, where CCR2+ cells are permanently labeled even after *in situ* reprogramming. Adult CCR2-creER^{T2}::Ai14D mice were injured using the Controlled Cortical Impact (CCI) TBI model. Injury-induced cognitive deficits were measured using the Radial Arm Water Maze and infiltrated CCR2+ macrophages were traced at one week, one month and eight months post injury. We characterized localization, transcriptomic signatures and functionality of peripherally derived macrophages focusing on how these features change from sub-acute and chronic time points using flow cytometry, imaging, RNA sequencing and *in vivo* synapses phagocytosis assays. We show for the first time long-lasting engraftment of peripherally-derived macrophages that maintain their distinct transcriptomic signature after TBI. Our study uses the novel CCR2-creER^{T2}::Ai14D mouse model to unravel a more comprehensive understanding of the long-term role of peripherally derived macrophages in TBI-induced cognitive impairment.

Dr. Jacob Raber (*Department of Behavioral Neuroscience, Oregon Health & Science University*) earned his B.Sc. in chemistry and M.Sc. in pharmacochemistry at the Free University of Amsterdam, and his Ph.D. in Molecular Genetics and Virology at the Weizmann Institute of Science. He received further training under the guidance of Drs. Floyd Bloom at the Scripps Research Institute in La Jolla and Lennart Mucke at the Gladstone Institutes and UCSF in San Francisco. In 2001, he was recruited to Oregon Health & Science University (OHSU) in Portland, Oregon. He was an Ellison Medical Foundation New Scholar in Aging from 2002-2006. His research is devoted to characterizing effects of environmental and genetic factors on brain function, identifying affected pathways, and developing treatments to antagonize detrimental effects.

Environmental challenges, immune and neuroinflammatory measures, and behavioral and cognitive measures in animal models

In various neurological conditions, chronic increases in immune measures and neuroinflammatory markers are seen and are being considered as pharmacological targets. However, studies using genetic and pharmacological strategies to reduce increases in immune measures and neuroinflammatory markers in animal models have revealed that while in some cases this seems a valid approach to reduce behavioral and cognitive symptoms, in other cases it is not helpful and might even worsen the behavioral and cognitive symptoms. In addition, in the absence of disease, the therapeutic strategies themselves are sometimes inducing behavioral alterations and/or cognitive injury, limiting their safe long-term use when the first symptoms become evident. Further, in some conditions like in cancer in which activation of the immune system is used to fight the tumor, reducing immune measures and neuroinflammation only in brain might be hard to achieve. In this presentation, various examples are discussed to illustrate the complex interaction between immune and neuroinflammatory measures and behavioral and cognitive function.

Dr. Owen McCarty (*Biomedical Engineering Department, Oregon Health & Science University*) is a native of Rochester, New York. He received his B.S. in Chemical Engineering from SUNY Buffalo, and a Ph.D. in Chemical Engineering from Johns Hopkins University, where his research focused on the identification and characterization of tumor cell receptors for blood platelets and leukocytes. He performed his postdoctoral research on platelet cell biology in the Pharmacology Department at the University of Oxford in the group of Dr. Steve Watson. Dr. McCarty joined Oregon Health & Science University in 2005, where he holds an appointment as a Professor in the Departments of Biomedical Engineering and Cell, Developmental & Cancer Biology and the Division of Hematology & Medical Oncology in the OHSU School of Medicine. Dr. McCarty serves as the Chair of the Biomedical Engineering Department and is a fellow of the American Heart Association.

Thrombin generation: gate keeper or grim reaper of the blood-brain barrier

The coagulation cascade and immune system are intricately linked, highly regulated and respond cooperatively in response to injury and infection. Increasingly, evidence of hyper-coagulation has been associated with autoimmune disorders, including multiple sclerosis (MS). The pathophysiology of MS includes immune cell activation and recruitment to the central nervous system (CNS) where they degrade myelin sheaths, leaving neuronal axons exposed to damaging inflammatory mediators. Breakdown of the blood-brain barrier (BBB) facilitates the entry of peripheral immune cells. Evidence of thrombin activity has been identified within the CNS of MS patients and studies using animal models of experimental autoimmune encephalomyelitis (EAE), suggest increased thrombin generation and activity may play a role in the pathogenesis of MS as well as inhibit remyelination processes. Thrombin is a serine protease capable of cleaving multiple substrates, including protease activated receptors (PARs), fibrinogen, and protein C. Cleavage of all three of these substrates represent pathways through which thrombin activity may exert immuno-regulatory effects and regulate permeability of the BBB during MS and EAE. This seminar will discuss whether thrombin activity directly, through PARs, or indirectly, through fibrin formation and activation of protein C influences neuro-immune responses associated with MS and EAE pathology. We will discuss whether thrombin is a friend or foe blood brain barrier.

Dr. Elinor L. Sullivan (*Departments of Psychiatry and Behavioral Neuroscience and at the Center for Mental Health Innovation at Oregon Health and Science University, and in the Division of Neuroscience at the Oregon National Primate Research Center*) received her Ph.D. in Physiology from OHSU in 2006 and her bachelor's degree in Biology from Willamette University in 2000. She received her postdoctoral training at the University of California San Francisco and OHSU. Her research focuses on examining the influence of early environmental factors including the nutrition, metabolic state and mental health of the birthing parent on offspring neurobehavioral regulation. These studies focus on behaviors that relate to mental health and behavioral disorders including autism spectrum disorders, attention deficit/hyperactivity disorder, schizophrenia, anxiety, and depression. Dr. Sullivan's leadership roles include co-chairing the Biospecimen Working Group for the HEALthy Brain and Child Development Study and serving as a standing member of the Biobehavioral Mechanisms of Emotion, Stress and Health NIH Study Section. Dr. Sullivan is actively involved in training future scientists through her teaching and mentoring of undergraduate and graduate students and post-doctoral fellows.

Perinatal Environmental Influences on Offspring Risk for Psychiatric Disorders

In recent decades, the prevalence of pediatric neurodevelopmental disorders such as autism spectrum disorder and attention-deficit/hyperactivity disorder have risen dramatically. Mounting evidence indicates a relationship between developmental exposure to maternal obesity and poor nutrition and increased risk of neurodevelopmental disorders; however, the mechanisms for this association remain unknown. Our work, using non-human primate models, demonstrates causal effects of maternal obesity and poor nutrition on offspring brain development and behavior, specifically increased anxious behaviors and impairments in social behavior. We hypothesize that developmental exposure to maternal obesity and/or poor maternal nutrition alters child behavior and increases risk for neurodevelopmental disorders. We examine this hypothesis in a longitudinal, prospective human study. Our data support unique effects of maternal adiposity and diet on infant temperament and emotional regulation. Specifically, we find that maternal obesity increases child negative emotions (sadness and fear) and omega-3 fatty acids are protective. New evidence indicates that alterations to the maternal tryptophan-kynurenine pathway during pregnancy could be a mechanistic link between maternal obesity and child behavioral impairments and risk for psychopathology. Lastly, we find evidence that maternal prenatal inflammation may be one common pathway by which prenatal risk factors including obesity, poor nutrition, stress and depression influence offspring mental health outcomes.

Dr. Bahareh Ajami (*Department of Molecular Microbiology and Immunology, OHSU*) aims to understand how the immune system contributes to different neurodegenerative conditions. Her team harnesses the power of multiple single-cell technologies to assess immune cell phenotypes, functions and interactions on a cell-by-cell basis. Dr. Ajami received her BA from Tehran University, Magna Cum Laude in Engineering, her Master's degree from the University of Sydney and her PhD from the University of British Columbia in 2012. She was a post-doctoral fellow in cellular immunology in Dr. Larry Steinman's lab at Stanford University. She is the first author on three seminal papers published between 2007 and 2018 that report the origin and heterogeneity of brain immune cells. In 2007, she was the first to show that microglia, the brain-resident macrophages, are self-renewing locally and do not originate from bone marrow. Her study in 2018, was one the first to use single cell technology to describe microglial heterogeneity in several neurological diseases. She has received numerous honors and awards, including twice receiving the Marlene Reimer Brain Star of the Year Award for the best research in the field of neuroscience.

Understanding the role of microglial cells in motor neuron vulnerability in Amyotrophic Lateral Sclerosis (ALS)

Motor neurons are the cells affected in ALS. In most cases, group of motor neurons controlling eye movements are spared. It is unclear why some motor neurons are selectively spared in ALS. Microglia, the resident immune cells of the brain, directly interact with motor neurons and have been implicated in ALS pathogenesis. Here, we will investigate the role of microglia in selective motor neuron death in ALS with the goal of providing a potential target for novel therapeutic strategies.

Dr. Philip A. Adeniyi (Department of Pediatrics, Oregon Health & Science University) obtained his B.Sc. and M.Sc. degrees in Anatomy from the University of Ilorin, Ilorin, Nigeria. He pursued his doctoral degree in Anatomy with a major in Neurobiology at Olabisi Onabanjo University, Ago-Iwoye, Nigeria, and was supported by grants from the Company of Biologists Ltd, UK, and the International Society of Neurochemistry (ISN) during his research work at Louisiana State University (LSU). Dr. Adeniyi has received several prestigious awards including the IBRO-ARC bursary and Young-IBRO Regional Connecting awards, which enabled him to carry out his postdoctoral work at LSU. He has over seven years of experience in teaching at the university level. Dr. Adeniyi is a member of the Young Scientists Steering Committee (YSSC) of the ISN and is currently coordinating the ISN Ambassadorship program. Currently, his research at Oregon Health and Science University focuses on understanding the role of glia in white matter injury and Alzheimer's disease. Dr. Adeniyi's dedication to research and mentoring the next generation of scientists makes him a key figure in the field.

Ferroptosis drives microglial cell death following white matter injury in the aging brain

As the brain ages, recurrent white matter injury (WMI) disrupts integrity, contributing to cognitive decline in Alzheimer's and vascular dementia. We discovered a high presence of degenerative microglia in aging WMI, rich in ferritin and PLIN2-labeled lipid droplets, exhibiting lipid peroxidation and elevated TOM20 expression. These iron-enriched microglia are susceptible to senescence-related degeneration akin to ferroptosis. Distinct ferroptosis-related genes in WMI suggest its significance in AD and vascular dementia. The failure of remyelination is linked to a substantial population of aging microglia sensitive to oxidative stress induced by phagocytosis and abnormal accumulation of myelin debris. This sensitivity promotes microglial lipid peroxidation injury that promotes ferroptosis-related degeneration.

Will chronic inhibition of dual leucine zipper kinase (DLK) be neuroprotective and restore neuronal function in aged-demyelination?

Katie Emberley[1], Greg J. Duncan[1], Samantha D. Ingram[1], Ahmed Abdelhak[2], Christian Cordano[2], Ari J. Green[2], Ben Emery[1]

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Age-related remyelination failure and neuroinflammation are thought to be key drivers of neurodegeneration which underlies the accumulation of disability in demyelinating diseases. The mechanisms underlying this neurodegeneration are not completely understood, hindering the development of neuroprotective therapies. Here, we use a transgenic mouse model to experimentally induce demyelination. Tamoxifen-induced ablation of the myelin regulatory factor (*Myrf*) gene in mature oligodendrocytes using $Myrf^{fl/fl}$; Plp1-CreERT mice results in CNS-wide demyelination. We administer tamoxifen to animals at eight weeks (young) or one year (aged) of age to determine the effects of aging on remyelination and neurodegeneration. We aim to unravel the mechanisms driving neurodegeneration in the adult demyelinated central nervous system (CNS). We find the kinetics of demyelination are similar whether tamoxifen is administered in young or aged mice. However, young mice rapidly and efficiently remyelinate a vast majority of the total axons in the CNS by 20 weeks post-tamoxifen. In contrast, aged mice show incomplete remyelination with far fewer remyelinated axons at 20 weeks post-tamoxifen. Both the aged and young mice have microglial/macrophage activation during peak demyelination. However, the young microglia/macrophages become less ramified and reactive upon remyelination, whereas the aged microglia retain a foamy macrophage morphology. Congruent with these histological findings, the aged animals exhibit severe motor behavior deficits with no improvement, whereas the young mice exhibit substantial motor recovery during their remyelination phase. Assessing the effects of chronic demyelination and inflammation on the neuronal population, we find that the aged demyelinated mice display persistently elevated levels of serum neurofilament light chain indicative of axonal injury. In addition, neuronal populations such as retinal ganglion cells show elevated staining for cleaved caspase-3 in the aged demyelinated mice, which is not seen in their young counterparts. Importantly, we also find that aged mice show heightened phosphorylation of c-Jun, a transcription factor activated in response to DLK activity, which we have recently found to mediate neuronal loss in young-adult mice genetically manipulated to prevent remyelination. Together, these results suggest age-related remyelination failure may drive neurodegeneration that is in part mediated by the DLK/c-Jun pathway. This model will serve to study the possible long-term neuroprotective effects of pharmacological inhibition of the DLK/c-Jun pathway.

Elevated expression α5-integrin by myeloid cells in motor areas provides a potential target for therapeutics in ALS.

AUDE CHIOT[1#], SHANU F. ROEMER[2#], LISA RYNER[3], ALINA BOGACHUK[1], KATIE EMBERLEY[1,4], DILLON BROWNELL[1], MICHAEL LEVITEN[3], DENNIS W. DICKSON[2], LAWRENCE STEINMAN[5], BAHAREH AJAMI[1]

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Amyotrophic lateral sclerosis (ALS) is a fatal disease affecting upper and lower motor neurons and leading to progressive paralysis. While motor neurons are the main cells affected in ALS, the microglial cells, the macrophages of the central nervous system, and peripheral macrophages in the nerve react strongly to the disease and become reactive. Previous studies have shown that microglial cells influence the progression of the disease by maintaining inflammation and interacting directly and indirectly with the motor neurons. In addition, modulating microglial cells and peripheral nerve macrophage profiles have been shown to influence disease progression. In a previous study from our lab, single-cell mass cytometry (CyTOF) analysis revealed a prominent expression of α5 integrin in microglia and macrophages in a superoxide dismutase-1 G93A mouse model of ALS ($SOD1^{G93A}$). Our new analysis revealed that α5 integrin- positive microglial cells and sciatic nerve macrophages display a very inflammatory phenotype. Interestingly, in post-mortem tissues from ALS patients with various clinical ALS phenotypes and disease duration, α5 integrin was expressed in motor pathways of the central and peripheral nervous system and highly upregulated compared to controls, making it a relevant target to modulate microglial cell and macrophage inflammatory profile. In an attempt to assess the downregulation of alpha 5 as a potential therapeutic target for ALS, we administered a monoclonal antibody against α5 integrin to $SOD1^{G93A}$ mice. Targeting α5 integrin in $SOD1^{G93A}$ mice, reduced microglial cell reactivity, improved motor functions and increased survival compared to an isotype control. Together these findings in mice and humans suggest that α5 integrin is a potential therapeutic target for ALS.

Role of peripheral inflammation in driving central nervous system inflammatory signature in pathogenesis of Alzheimer's disease

Paula Sanchez-Molina[1], Dillon Brownell[1], Alina Bogachuk[1], Carlos M Soto-Faguás[2], Randy L Woltjer[3], Sally A Cowley[4], Joseph F Quinn[5], Bahareh Ajami[1]

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[5]Department of Neurology, Oregon Health and Science University, Portland, OR, USA

Alzheimer's disease (AD) impacts an estimated 6.5 million people in the United States, however, it cannot yet be prevented, slowed or cured. Although the sporadic AD form comprises around 95% of cases, animal models of familial AD are the ones used for basic and translational research. Most of these models are based on human mutations that cause amyloid-β (Aβ) pathological accumulation. However, the failure of the majority of Aβ-related clinical trials, has begged the necessity of an alternative approach to address AD. Interestingly, most of the genetic and non-genetic risk factors for developing sporadic AD are associated with inflammation. Thus, it has been demonstrated that microglia, the immune cells in the central nervous system, play a key role in the pathogenesis of AD. At the same time, epidemiological studies indicate that people with systemic inflammatory diseases have a higher incidence of developing AD. In this context, we hypothesize that a specific subset of cells in peripheral blood contributes to AD development through its communication with microglial cells in the brain parenchyma.

To address this hypothesis, we analyzed peripheral blood mononuclear cells (PBMCs) from sex- and age-matched healthy and AD subjects using mass cytometry (CyTOF) and cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq) technologies. Moreover, we used histological and *in vitro* approaches to study interactions between PBMCs and human microglial cells.

Our preliminary data show specific subsets of peripheral immune cells characterized by the upregulation of pro-inflammatory signaling pathways and cytokines in blood of AD patients. We corroborated the pathogenic component of AD blood as healthy PBMCs developed an inflammatory phenotype after stimulation with AD plasma. In addition, T cells in contact with microglia were detected in the parenchyma of AD brains by histological analysis. Finally, using microglia derived from human induced-pluripotent stem cells, we demonstrated that PBMCs from AD donors induce an AD-related transcriptomic signature in microglial cells.

Together, our data suggest that specific peripheral immune cells in AD drive microglial cells towards an inflammatory phenotype that could contribute to AD pathology.

Poster Session I

Investigating the Interactomes of ApoE and Alpha-Synuclein via In vivo Proximity Labeling, ***Elias M. Wisdom,*** OHSU

Parental Co-Exposure to Methylmercury and Inorganic Arsenic in Zebrafish (Danio rerio): Neurobehavioral Impacts on Parents and Offspring, **Jay C. Adams,** Oregon State University

Heterozygous 5xFAD Mice Have Increased Fragmented Sleep At A Very Early Age, **Kaitlyn Kim,** Oregon State University

Investigating neuroprotective effects of Centella asiatica in a Drosophila Tauopathy model **Rachel Morrill,** OHSU

Investigation of Infectious Theory of Alzheimer's Disease using HSV-1 in the 5xFAD Mouse Model, **Ibrahim A. Abou-Seada,** Oregon State University

The absence of a neurogenic response in repeated traumatic brain injury: Impairment or adaptation? **Benjamin Bui,** Legacy Research Institute

Astrocytic Mechanisms of Developmental Synapse Elimination in Drosophila, **Mariel Kristine Micael,** Vollum Institute

Quantifying perivascular spaces in aged rhesus macaques with Magnetic Resonance Imaging (MRI), **Will Liguore,** Oregon National Primate Research Center

Effects of pesticide exposure on neuronal injury in Parkinson's disease models, **Kaylee Ha,** OHSU

Ashwagandha improves cognition and attenuates depressive-like behavior 5xFAD mice, **Noah Kolarsky,** OHSU

Investigating the Interactomes of ApoE and Alpha-Synuclein via In vivo Proximity Labeling

Elias M. Wisdom[1], Vivek K. Unni[1,2], Andrew E mili[1,3]

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Among the highest risk-associated genetic variants for both Alzheimer's Disease (AD), and Dementia with Lewy Bodies (DLB) is *APOE*, which encodes the 299-residue apolipoprotein E (ApoE) involved in cholesterol and lipid transport in the brain, and implicated in many other cellular processes. There are three common isoforms of ApoE in the population: ApoE2 (5%), ApoE3 (75%), ApoE4 (20%). Despite only differing by amino acids at positions 112 and 158, genome-wide association studies have revealed a striking difference in risk for AD/DLB. ApoE2 confers a protective effect, ApoE3 is neutral, while ApoE4 elevates AD/DLB risk. Similarly, alpha-synuclein (*SNCA)* is intimately associated with DLB and Parkinson's Disease (PD) and is enriched in pathological Lewy Body deposits. While ApoE and alpha-synuclein play crucial homeostatic roles in the brain, why they are intimately associated with AD, DLB, and PD remains unclear. We hypothesize that the protein variants engage in altered molecular interaction neighborhoods, enhancing pathogenesis. To address this, I am investigating in vivo protein-protein interaction partners of risk-associated ApoE and alpha-synuclein variants via two powerful *in vivo* protein proximity labeling techniques, namely Biotinylation by Antibody Recognition (BAR) and TurboID. To date, I have used BAR to target alpha-synuclein in cultured cells, and my data demonstrate selective biotin-labeling in both the cytoplasm and nucleus. I have also created TurboID-fused versions of ApoE (2,3,4), and alpha-synuclein, under the control of cell-specific promoters for expression in astrocytes and neurons, respectively. After AAV delivery of these constructs into mouse brains, followed by *in vivo* proximity labeling, selective isolation of biotinylated proteins, and tandem mass spectrometry, I will probe the variant- and cell-specific interactomes of ApoE and alpha-synuclein. The differential protein-protein interactions I uncover through the complementary methods of BAR and TurboID will provide clinically actionable mechanistic insights into risk-conferring ApoE variants and alpha-synuclein, reveal potential novel targets for the development of much-needed new therapeutics for AD/DLB/PD.

Parental Co-Exposure to Methylmercury and Inorganic Arsenic in Zebrafish (Danio rerio): Neurobehavioral Impacts on Parents and Offspring

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Both inorganic arsenic (iAs) and methylmercury (MeHg) are known neurotoxicants. Epidemiologic studies suggest that MeHg and iAs may act synergistically, but the mechanisms are uncertain. Using a zebrafish model (Danio rerio), this study aims to investigate the neurobehavioral impacts of co-exposure to As(III) and MeHg on both parents (F0) and offspring (F1). Juvenile F0 zebrafish first began a diet with concentrations of iAs and MeHg below detection levels. At 165-dpf, half the fish were given a diet spiked with MeHg (1000 ng/g). The fish were then exposed to 0.05 mg/L or 0.5 mg/L of As(III) via water or remained unexposed, resulting in six treatment groups total [control, low As(III), high As(III), MeHg, MeHg + low As(III), MeHg + high As(III)]. Each group was spawned in clean water to create an F1 generation. Adult zebrafish behavior (F0) was assessed using predator avoidance and startle response assays (n=24 fish/treatment/assay). For the startle response assay, electric solenoids are used to create auditory stimulus while the zebrafish's response (total movement) is recorded. During the predator avoidance assay, a monitor displays a recording of a predator, and the movement and position of the zebrafish are tracked. Differences were tested by two way ANOVA & Tukey HSD post hoc test. The behavior of larval zebrafish (F1) was assessed using a larval photomotor response (LPR) assay. Embryos were grown out until 5-dpf in 96-well plates (n=48/treatment) and evaluated for the total distance moved through several light-dark cycles. Differences were assessed by comparing the area under the curve during both light & dark periods using a Kolmogorov-Smirnov test. Neurobehavioral impacts were observed in both the F0 and F1 co-exposed fish. In the F0 fish, both groups of co-exposed zebrafish exhibited significantly less total movement in response to the auditory startle stimulus, compared to controls and single-chemical exposure groups ($p<0.001$). However, during the predator avoidance assay, the percentage of time spent away from the monitor did not differ between treatment groups. In the F1 LPR assay, both groups of larvae whose parents were co-exposed exhibited increased swimming/hyperactivity compared to the control groups and single-chemical exposure groups ($p<0.01$). Hyperactivity observed in the co-exposed groups followed a dose-dependent pattern, i.e., the group exposed to MeHg + high As(III) showed increased activity compared to the group exposed to MeHg + low As(III). Behavioral assessment of F1 adults and F2 larval zebrafish and gene expression profiling of the F0 brains is underway, which will help identify the underlying mechanisms of these observed outcomes.

Heterozygous 5xFAD Mice Have Increased Fragmented Sleep At A Very Early Age

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Alzheimer's disease (AD) is an incurable brain disease that is the most common form of dementia. There is a critical need to design treatments that can intervene in early events in the development of AD in order to prevent or delay the onset of the disease. Our recent findings showed that the 5xFAD mouse model, which was believed to develop synaptic dysfunction only at 6 months of age, actually showed synaptic alterations in N-methyl-D-aspartate receptor (NMDARs) subunit responses by 0.5-1 months of age, which could lead to alterations in memory. The 5xFAD mouse model has five mutations that are linked to familial (inherited) AD, which leads to amyloid overexpression. Since our lab had seen early changes in mitochondrial health and electrophysiology results, we hypothesized that 5xFAD heterozygotes (HET) would show non-invasive behavioral alterations early in development. During sleep recordings, animals were pair-housed in their homecage with a temporary insert enabling sight, smell, and sound interactions. Previously validated, passive electric field sensors attached to homecage exteriors captured individual animal movements for 24 hours (6pm-6pm) used to score 3-stage sleep/wake: wake, non-rapid eye movement sleep (NREM), and REM sleep [cite: Kloefkorn 2020 and Kloefkorn 2022]. Sleep during the 12-hour dark cycle was scored manually in 10-second epochs in Spike2 (Cambridge Electronic Design, Inc.). Then, a custom MATLAB script calculated the following sleep measures: percentage time spent asleep, percentage of time spent in REM sleep, sleep fragmentation index, microarousal index, REM and NREM sleep bout durations, and REM sleep onset latency. T-tests were performed to assess sleep differences between genotype (N=9-10 by genotype). At 1 month of age, we found that HET animals had increased fragmented sleep compared to WT (higher sleep fragmentation index), 2-tailed t-test $p=0.0135$. This suggests that, normalized to the total amount of sleep, HET animals divided that time into more sleep events per hour relative to WT animals. In addition, HET animals tended to have shorter duration of sleep bouts relative to WT ($p=0.11$). This may help explain the sleep fragmentation result. At an early age, there appeared to be significant differences in sleep behavior in the 5xFAD heterozygous mice.

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Investigating neuroprotective effects of *Centella asiatica* in a *Drosophila* Tauopathy model

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The average life expectancy worldwide has nearly doubled over the past century and a half, leading to an increase in patients with aging-related conditions. Even normal levels of decline in physical and cognitive ability cause hardship, with pathophysiological conditions further exacerbating these challenges. Despite the growing problem of neurodegeneration, treatment options are mostly limited to addressing symptoms. More research is needed to understand the mechanisms underlying neurodegeneration and to find effective treatment options. Our lab studies Frontotemporal Dementia with Parkinsonism Linked to Chromosome 17 (FTDP-17) and Pick's Disease, which are associated with point mutations in the microtubule-binding protein Tau. We have generated transgenic lines of *Drosophila melanogaster* that express human Tau (hTau), either wildtype or carrying a disease-associated mutation (V337M in FTDP-17, K369I in Pick's Disease). I have shown that administration of the medicinal herb *Centella asiatica* (CA) leads to locomotion improvement in 14d old $hTau^{K369I}$ homozygotes of both sexes and 30d old male $hTau^{V337M}$, $hTau^{K369I}$, and $hTau^{WT}$ heterozygotes. This indicates that CA is able to ameliorate some of the changes caused by pathogenic mutations in Tau. Other research recently showed activation of innate immune pathways by pathogenic Tau. CA is known to have immunomodulatory properties. I hypothesize that our models of pathogenic Tau also involve an immune response, and that CA's anti-inflammatory activity is responsible for the observed amelioration. My early preliminary data support this hypothesis, with differential expression of the IκB homologue Cactus observed in hTau mutants compared to wildtype, as well as between CA-treated and untreated flies.

Investigation of Infectious Theory of Alzheimer's Disease using HSV-1 in the 5xFAD Mouse Model

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Alzheimer's Disease (AD) is a neurodegenerative disease that causes memory loss, cognitive decline, and is the cause of ~70% of all recorded dementia cases. AD is characterized by two main pathologies: amyloid beta (A-beta) plaques, and hyperphosphorylated tau proteins. Recent research has found the presence of some pathogens (herpes simplex virus-1 (HSV-1), and human herpesvirus-6 (HHV-6) being commonly found in the brains of post-mortem AD patients. From this data the infectious hypothesis of AD was proposed and states that a pathogen (virus, bacteria, prion, etc.) is the root cause of AD. In humans HSV-1 can commonly be reactivated from latency due to stress. In this study we used a mouse latency/reactivation model to investigate the infectious hypothesis of AD using HSV-1. 5XFAD heterozygous and wildtype mice (C57BL/6 background) were infected with neurotropic green fluorescent protein (GFP) HSV-1 Mckrae virus at 8-10 weeks of age via application to the eye. HSV-1 was allowed to enter latency and then was reactivated via heat stress at 30 and 60 days post infection (dpi). Behavioral impairments were monitored using the Morris water maze, followed by euthanization and brain dissection to observe changes in cytokine and A beta plaque levels. Behavioral results showed that reactivation of the virus accelerated memory problems at 30 dpi and cognitive flexibility deficits at 60 dpi. At 30 dpi infected and stressed mice performed significantly worse in the memory test than infected and unstressed mice ($p = 0.0425$). At 60 dpi infected and stressed mice performed significantly worse than infected, unstressed mice ($p = 0.016$) and uninfected, unstressed mice ($p = 0.014$). The hippocampus is important for spatial memory and the retrosplenial cortex is a region of the brain associated with cognitive flexibility. Although several heat-stressed groups appeared to have increased A-beta plaques in these regions, it did not reach significance. Cytokines (TNF-alpha and IL-1-beta) did show increased transcription levels following heat stress and following acute infection indicating the virus was reactivated and inflammatory processes were triggered. This study suggests that reactivation of the virus can lead to acceleration of the behavioral impairments seen in the heterozygous mice, which provides support for the infectious hypothesis of AD.

The absence of a neurogenic response in repeated traumatic brain injury: Impairment or adaptation?

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The generation and integration of new neurons (neurogenesis) persist throughout the life of humans in the hippocampus, a brain region critical for learning and memory. Hippocampal neurogenesis has many important roles in cognitive function including memory and mood regulation. Several studies also indicate that neurogenesis, which is acutely but robustly increased after traumatic brain injury (TBI), plays a key role in recovery of hippocampal function. In contrast to acute effects of TBI on neurogenesis, constitutive levels of neurogenesis decline in the months following injury. This decline is thought to be related to stem cell exhaustion or “accelerated aging”. Therefore, we asked whether the hippocampus remains capable of eliciting increases in neurogenesis after a repeated mild TBI (mTBI). Our data demonstrates that a history of a mTBI in adult male and female mice prevents increases in neurogenesis after a subsequent mTBI. Importantly, this was observed in the absence of deficits in constitutive levels of neurogenesis, suggesting a functional deficit. We then asked how a loss in the neurogenic response affects the recovery of hippocampal function after a second mTBI. Our water maze data demonstrates impairments in the neurogenesis-sensitive task, reversal water maze in mice with a second mTBI, but not mice with a single mTBI. These results are in accord with the notion that post-TBI neurogenesis is important for hippocampal recovery after injury, and further suggests that loss of the neurogenic response after a repeated mTBI may contribute to worse outcomes observed after multiple concussive-like injuries. The blunted neurogenic response after a second mTBI requires further investigation to address whether the neural stem cells have increased their quiescence, which would be reflective of an accelerated aging process, or whether the seemingly neurogenic impairment is more characteristic of an adaptive response.

Astrocytic Mechanisms of Developmental Synapse Elimination in *Drosophila*

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Neuronal remodeling is a crucial step towards healthy maturation of synapses, circuits and eventually brain function This process involves changes in neuron morphology such as pruning of dendrites, axons, or synapses, which is mediated in part by non-neuronal cells called glia. While glia are known to be required for this process, we still have not defined how glia appropriately identify and eliminate only those synapses or neurites that require pruning. Given that many neurodevelopmental and neurodegenerative disorders such as autism spectrum disorder (ASD) and Alzheimer's Disease (AD) involve a major loss of synapses, and some glial pruning mechanisms appear to be inappropriately re-activated during disease, elucidating how glia accomplish these tasks will be crucial to finding therapeutic targets to prevent or reverse this loss. *Drosophila* offers a great model to study neuronal remodeling and the glia-neuron interactions involved as they have both neurons and astrocytes, they undergo a period of synapse elimination in early adulthood comparable to the developing mammalian brain and have many genetic targeting and imaging tools. We performed a genetic screen for novel glial regulators of synapse elimination in *Drosophila* and found Croquemort (Crq), a scavenger receptor with roles in the immune system for engulfment of apoptotic cells. Thus, we sought to investigate which neuronal populations utilize astrocyte Crq to prune their synapses and to elucidate the mechanisms by which Crq mediates this process. We used high-resolution imaging and protein assay techniques to investigate which neuronal populations undergo developmental synapse elimination and how this is affected by *crq* knockdown. Preliminary data shows us that cholinergic, glutamatergic, and GABAergic neurons undergo synapse elimination during development. Further work will aim to determine whether these neuronal subtypes require Crq to prune their synapses and how neural activity affects Crq's function.

Quantifying perivascular spaces in aged rhesus macaques with Magnetic Resonance Imaging (MRI)

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A feature common to many types of dementia are enlarged perivascular spaces (PVS) that can be visualized on Magnetic Resonance Imaging (MRI) scans. MR-visible PVS are typically elongated and cylindrical in shape, observed in white matter and basal ganglia structures, and isointense to CSF. In humans, retrospective studies have indicated that numbers of MR-visible PVS increase starting in mid-life, and are seen prior to cognitive decline, suggesting that they may be an early marker of ADRD (Alzheimer's Disease and related dementias). The aging process of nonhuman primates (NHP) shares many features in common with humans including mild cognitive impairment, as well as increased white matter diffusivity and gray matter atrophy (see adjacent poster by Weiss et al.), but the presence of MR-visible PVS in aged NHPs is unexplored. To address this gap, we quantified the number and volume of MR-visible PVS in a population of 26 rhesus macaques, ranging in age from 7 to 27 years old (14F/12M). MR-visible PVS were segmented on high-resolution (0.5mm iso) T2-weighted images using an automated method for brain-wide quantification (based on approaches currently employed by co-authors Schwartz & Silbert). The resulting segmentations were used to calculate the number (count) and total volume (mm^3) of MR-visible PVS for each animal. Using Pearson Correlation, we identified significant relationships between age and MR-visible PVS number ($r(23)=0.35$, $p=0.044$), as well as volume ($r(23)=0.36$, $p=0.039$). Fourteen of the 26 animals were scanned at two timepoints, 1 year apart, (14-27y, 6F/8M), permitting us to also evaluate within-subject changes in MR-visible PVS over time. Paired-sample t-tests revealed significant increases in MR-visible PVS volume over the 1 year interval ($t(13)=2.908$, $p=0.0061$); as well as increases in number that approached significance ($t(13)=1.716$, $p=0.0550$). Analyses of hemispheric symmetry and regional burden are underway. In order to assess the accuracy/error rate of the automatic detection method, work is currently ongoing to compare the automated segmentations with manual verifications from a trained observer (co-author Rajendran). Additional work is also underway to measure cerebrospinal fluid (CSF) kinetics in these animals by tracking brain parenchymal uptake and clearance of gadoteridol following intra-cisterna magna (ICM) delivery. Together, this research will allow for the preliminary evaluation of some of the fundamental tenets of the glymphatic hypothesis: altered CSF kinetics leads to decreased glymphatic function, and MR-visible PVS are a marker of such glymphatic dysfunction.

Effects of pesticide exposure on neuronal injury in Parkinson's disease models

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Parkinson's disease (PD) is the second most common neurodegenerative disease and is characterized by loss of dopaminergic (DA) neurons. Epidemiological evidence links maneb and paraquat exposure, known neurotoxins that have synergistic effects on DA neuron loss, to an increased risk of developing PD. However, the mechanisms behind maneb-induced neurodegeneration are still unknown. We exposed a collection of ~200 inbred and fully-sequenced *Drosophila* strains to food-containing maneb and then assessed dopamine neuron viability following a brief aging period. A genome-wide association study (GWAS) nominated several genes associated with maneb-induced DA neuron loss. To explore the effects of maneb on neuronal injury further, we developed an *in vitro* mammalian model of maneb exposure using primary cortical neurons from rats. We aim to transduce the cultures using adeno-associated viruses (AAV) to overexpress/silence genes associated with maneb-induced neuron loss in flies and use a pharmacological approach to induce maneb exposure. Following this approach, we expect to see changes in neuronal metabolism, neurite branching, and neuronal injury. Although work in this area is ongoing, we hope that this will provide insight into the mechanisms behind pesticide-induced neurodegeneration as well as target potential therapeutic strategies for treating the long-term effects of pesticide exposure.

Ashwagandha improves cognition and attenuates depressive-like behavior 5xFAD mice

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Withania somnifera (WS), also known as Ashwagandha, is a traditional Ayurvedic herb used to rejuvenate the body and promote tissue health. WS is a dietary supplement notorious for its ability to improve neuropsychiatric conditions ranging from memory loss, stress, anxiety, depression and insomnia. Severe cognitive impairment and depression are common symptoms of Alzheimer's disease (AD), suggesting that WS may be of therapeutic value in that condition. Previous studies from our group with *Drosophila* have shown that an aqueous extract of WS (WSAq) enhances cognition and alleviates markers for depression. In this study, we sought to confirm these effects in a mammalian system by evaluating the effects of WSAq in the 5xFAD mouse model of β-amyloid accumulation. Six- to seven-month-old male and female 5xFAD mice were treated with WSAq in their drinking water at either 0, 0.5g/L or 2.5g/L concentrations. Age-matched non-transgenic wild type (WT) littermates that received no WSAq were also included as a control group. In the fourth week of treatment we evaluated spatial memory using the Object Location Memory (OLM) test and depressive-like symptoms using the Forced Swim (FS) test. In the OLM test 2.5g/L WSAq significantly improved performance of 5xFAD mice at the 2hr and 24hr tests. 5xFAD mice that were treated with 0.5g/L WSAq showed a similar trend towards improvement at the 2h test but was the effect was only statistically significant at the 24hr test. Both 0.5g/L and 2.5g/L WSAq significantly reduced time immobile for 5xFAD mice in the FS test. The effects of WSAq not different between sexes for either behavioral test. The results of this study suggest that WSAq improves cognitive performance and attenuates depressive-like behavior in 5xFAD mice suggesting it has potential as a therapeutic option for use in AD. Analysis of plaque pathology and gene expression is ongoing to gain information on the mechanism by which WSAq could be eliciting these effects. Future studies using a greater variety of behavioral tests are needed to determine if the cognitive-enhancing effect of the extract extends beyond spatial memory. Optimizing timing of WSAq administration and confirming these results in other AD mouse models will also be important for gauging the therapeutic potential of this promising botanical candidate.

Meeting Keynote Speaker

Dr. Ruth Barrientos (*Department of Psychiatry and Behavioral Health, Ohio State University*) earned her B.S. in Psychology at George Mason University in Fairfax, VA. She then trained jointly in behavioral neuroscience at the George Washington University in Washington, DC, and in neuroimmunology at the National Institute of Mental Health in Bethesda, MD to earn her Ph.D. She then did her post-doctoral training at the University of Colorado Boulder under the mentorship of Dr. Steven Maier and Dr. Jerry Rudy where she honed her research expertise in behavioral neuroimmunology with an emphasis on the aging brain. She spent several years in Boulder as a Research Assistant Professor before joining The Ohio State University in 2018. She is a prominent member of the Psychoneuroimmunology community, serving on the board of directors of the Psychoneuroimmunology Research Society and as associate editor of the society's flagship journal *Brain, Behavior, and Immunity*. Her research aims are 1) to uncover the vulnerabilities associated with the aging brain that makes it more susceptible to inflammatory challenges resulting in memory dysfunctions ranging from mild cognitive impairments to Alzheimer's Disease; and 2) to discover interventions to improve these vulnerabilities and prevent memory degradation.

Determinants and mechanisms of neuroinflammation-induced memory deficits in aging

The immune cells of the aging brain exist in a sensitized state making it vulnerable to exaggerated neuroinflammatory responses following various immune triggers, resulting in precipitous and long-lasting memory impairments. Dr. Barrientos will speak about her lab's research examining one such trigger: surgery. Postoperative cognitive dysfunction (POCD) is a debilitating condition affecting various cognitive functions in primarily older patients shortly after a surgical procedure and lasting months to years. Importantly, a substantial proportion of patients that experience POCD go on to develop Alzheimer's disease or other dementias. The mechanisms underlying this dysfunction are not clear and there are no cures. Dr. Barrientos will discuss her lab's findings regarding the determinants and mechanisms underlying POCD and will provide some clues regarding potential therapeutic targets.

Speaker Session I

8:00 am *Las neuronas son bacanes: Interdisciplinary neuroscience in Valparaiso Chile*
William S. Griesar and Jeff Leake
Department of Psychology, Portland State University

8:30 am *The mouse olfactory bulb tracks breathing rhythms and place*
Matt Smear
Departments of Neuroscience and Psychology, University of Oregon

9:00 am *Effects of amyloid beta peptides on platelet hemostatic function and procoagulant platelet generation*
Yiheng Zhang
Department of Biomedical Engineering, OHSU

9:15 am *T cell receptor-based cell therapy for central nervous system injury*
Taitea Dykstra
OHSU

9:30 am *Effects of TFEB gene therapy on hippocampal-dependent learning and molecular signaling in obese female and male 5xFAD mice*
Danielle Osborne
Legacy Research Institute

9:45 am *Structural insight into heteromeric assembly in epithelial sodium channels*
Isabelle Baconguis
Vollum Institute, OHSU

Las neuronas son bacanes: Interdisciplinary neuroscience in Valparaíso Chile

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Nonprofit nwnoggin.org organizes collaboration around interdisciplinary neuroscience, going places to explore brains, hear stories, make art and see where research discoveries can contribute. Portland State University in Portland, OR offers a minor in interdisciplinary neuroscience, where Noggin co-founders Dr. Bill Griesar and Jeff Leake both teach. In 2023, we reached out to artists and STEM colleagues at the Universidad de Valparaíso Chile. Along with the PSU Education Abroad Office and Academic Programs International we created Cerebrarte, the first international, homestay-based STEAM program exploring the rich art and neuroscience traditions of the Valparaíso region. We brought 17 students and two faculty to Chile from July 27 – August 28, 2023. Through visits to labs and the historic complex at Montemar, we explored how research on the giant axons of Humboldt squid contributed to our understanding of the electrical signaling that links our perceptual and cognitive experiences to the world. We met Dr. Ramón LaTorre and Dr. Juan Saez (members of the National Academy of Sciences), Dr. David Naranjo, Dr. Jesús Olivares, Dr. John Ewer and Dr. Kate Whitlock, and graduate students and postdocs for discussions about olfaction, voltage-gated channels, spider neurons and potential therapeutic compounds in boldo tea. We welcomed Kings College London neuroscientist Dr. Richard Wingate, Editor of brainfacts.org, the outreach arm of Society for Neuroscience, who spoke about his 2023 book, “The Story of the Brain in 10 ½ Cells,” with the ½ Cell referencing the giant axon. Valpo is home to exceptional research, and is a celebrated center of public art. Street art was legalized in 1990, and eye-catching murales are everywhere. Students examined art with thiscatcallededdie, explored regional museums, created engravings (grabados), and sewed arpilleras, woven depictions of challenging and sometimes traumatic experiences that allow emotional expression and create durable memories of events with artist Cecilia Araneda. We explored the neuroscience of perception, stress and trauma as it relates to personal experience (including aspects of culture shock), research, art and the 50th year since El Golpe, the US-backed coup that violently overthrew democratically elected President Salvador Allende in 1973. The program culminated in a visit to Ciencia al Tiro, a STEAM outreach nonprofit where we made pipe cleaner brain cells and took them to the streets to speak with residents of Playa Ancha sobre porque las neuronas son bacanes (why neurons are cool). Cerebrarte was an exciting, interdisciplinary, intercultural, international experience, and will occur again in 2024.

Dr. Matt Smear (*Departments of Neuroscience and Psychology, University of Oregon*) studies the neural mechanisms of olfactory function in mice. Mice have an excellent sense of smell – much of their genome encodes odorant receptors (over 1000 genes), and a large portion of their brain processes olfactory information. These neural features support a rich repertoire of olfactory behaviors. The Smear lab interrogates olfactory function with a battery of psychophysical tests, while manipulating and recording neuronal activity with genetics, electrophysiology, and imaging. From these studies, the lab will pursue general principles of how neural circuits generate behavior.

The mouse olfactory bulb tracks breathing rhythms and place

Odors carry useful navigational and episodic information, but no matter how many receptor genes are in an animal's genome, there is no receptor for time or place. To optimally orient by olfactory information, brains must unify odor-driven activity with contextual representations of self-movement and -location. Studies in other sensory modalities demonstrate that motor- and location-related signals are common in primary sensory areas. Motivated by these findings, and given the reciprocal connection between olfactory system and hippocampus, we hypothesized that the olfactory bulb encodes contextual information. To test this hypothesis, we captured the sniffing and movement of mice while recording spiking in olfactory bulb (OB), in the absence of experimenter-applied stimuli or tasks. Breathing and spiking differ between head-fixed and freely-moving states. During free movement respiration is rhythmically organized into discrete states lasting minutes, whereas these states are not apparent during head-fixation on a stationary platform. This discrete organization is likewise apparent in the "spontaneous" activity of the olfactory bulb – many individual neurons fire selectively during particular rhythmic states. In addition to these state-selective signals, we also found that allocentric position can be decoded from neuronal ensembles in OB, with comparable decoding performance to hippocampal ensembles recorded under the same conditions. Thus, even during uninstructed behavior and ambient stimuli, contextual information about behavior and place can be read out from the activity of the olfactory bulb. We propose that these contextual signals facilitate the incorporation of olfactory information into cognitive maps of environment and self.

Effects of Amyloid Beta Peptides on Platelet Hemostatic Function and Procoagulant Platelet Generation

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Alzheimer's disease (AD) is a chronic disease marked by the abnormal accumulation of fibrillar amyloid β-peptide (Aβ) plaques in nervous tissues and cerebral microvascular vasculature associated with progressive neurodegeneration and dementia. Platelets constitute a major source of amyloid precursor protein (APP) and Aβ peptides in blood; however, the platelet-mediated processes underlying amyloid fibrinogenesis and plaque formation remain elusive. Here, we employed two distinct soluble, pathogenic Aβ peptides ($A\beta_{1-40}$ and $A\beta_{1-42}$) as stimulants to activate washed human platelets, allowing us to evaluate the effects of these pathogenic Aβ peptides on platelet activation, procoagulant platelet generation, and the process of amyloid fibril formation. Upon exposure to both $A\beta_{1-40}$ and $A\beta_{1-42}$, a pronounced enhancement in platelet aggregation was observed. Following treatment with $A\beta_{1-40}$ or $A\beta_{1-42}$, purified platelets externalized phosphatidylserine (PS), as measured by flow cytometry and visualized by fluorescence microscopy. Notably, procoagulant platelets induced by $A\beta_{1-42}$ exhibited a higher quantity, accompanied by an intriguing co-localization phenomenon with amyloid fibril formation. In contrast, such co-localization was not observed with $A\beta_{1-40}$. Furthermore, fluorescence microscopy revealed distinctive features in Aβ aggregates produced by $A\beta_{1-40}$ as compared to $A\beta_{1-42}$. Additionally, utilizing flow cytometry, we found that platelets stimulated with $A\beta_{1-42}$ demonstrated a significant increase in granule secretion (e.g., P-selectin expression) and degree of integrin αIIbβ3 activation, highlighting the impact of $A\beta_{1-42}$ on platelet activation. With Western blot analysis, we found that $A\beta_{1-42}$ uniquely enhanced the phosphorylation of tyrosine kinase and protein kinase (PKC) substrates. Pretreatment of platelets with the BTK inhibitor ibrutinib effectively suppressed the generation of amyloid fibrils and procoagulant platelets. Interestingly, the utilization of the Src inhibitor PP2 appears to promote amyloid fibril production. In conclusion, our findings indicate that $A\beta_{1-42}$ selectively activates platelets, where a subsequent formation of $A\beta_{1-42}$ amyloid peptide aggregates promotes the generation of procoagulant platelets.

T cell receptor-based cell therapy for central nervous system injury

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Traumatic injuries to the central nervous system (CNS), which affect millions of people worldwide, still lack an effective treatment. Following injury, an abundance of peripheral immune cells including T cells infiltrate the CNS. An insufficient understanding of both the function and antigenic specificity of endogenous T cells at the site of injury has hampered the development of more targeted immune-mediated cellular therapies for CNS injuries. Here, using single-cell RNA sequencing (scRNA-seq), we demonstrate clonal expansion of murine spinal cord-infiltrating T cells and of T cells in human cerebrospinal fluid after spinal cord injury. We further demonstrate a neuroprotective effect of injury-associated self-reactive $CD4^+$ T cells in murine models of optic nerve injury and spinal cord injury. These injury-associated $CD4^+$ T cell clones display antigen specificity towards self-peptides associated with myelin and neuronal proteins and dampen local immune responses via regulation of myeloid cells through interferon gamma. Using mRNA-based transient T cell receptor (TCR) reconstitution to minimize long-term side effects that could be caused by self-reactive T cells, we demonstrate a therapeutic T cell strategy for CNS injury. Treatment of CNS-injured mice with this self-antigen-targeted TCR therapy improved their locomotion and tissue morphology. This approach provides a pathway for developing custom-designed T cell therapies for traumatic CNS injuries and possibly for other neurodegenerative disorders.

Effects of TFEB gene therapy on hippocampal-dependent learning and molecular signaling in obese female and male 5xFAD mice.

Adrianah Dorn, Danielle Osborne

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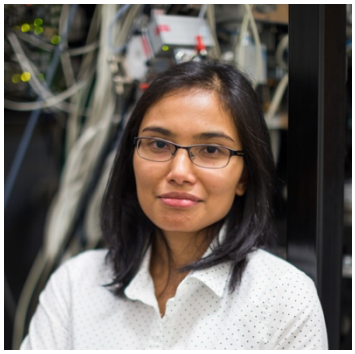
In both clinical patients and animal models of Alzheimer's disease (AD), lysosomal dysfunction is among the earliest detectible cellular changes. Major risk factors for AD include obesity and female sex; however, how those variables affect lysosomal function in the hippocampus remains poorly understood. TFEB, a major transcription factor that coordinates autophagic and lysosomal functions in the cell, has been used previously to counter AD pathology and cognitive decline in male mouse models of AD. We investigated whether TFEB gene therapy would improve behavioral and cellular outcomes in 5xFAD mice, with induced obesity and when accounting for sex differences. Female and male 5xFAD mice were placed on an obesogenic diet at 6 weeks of age, at 5 months of age we infused an AVV with mutated TFEB serine142, designed to prevent TFEB phosphorylation and enhance translocation to the nucleus. One month later, mice were behaviorally tested in Morris watermaze and tissues were collected. Female and male mice diverged greatly in their responses to TFEB therapy. TFEB therapy improved learning in non-obese 5xFAD female mice, an effect not observed in male mice; indeed, male wildtype mice treated with TFEB did more poorly than 5xFAD males. In contrast to non-obese males, obese wildtype males moderately benefitted from TFEB treatment, while the addition of obesity with 5x mutations was more than TFEB could overcome. Molecular analyses are still ongoing, but so far western blots indicate that TFEB treatment affects pAkt and mTOR signaling, with comprehensive qPCR analysis pending. The results demonstrate that females and males respond very differently to therapeutic approaches, that obesity worsens outcomes in AD and limits therapeutic interventions, and confirms that upregulating lysosomal activity early in AD progression presents a promising approach to preventing behavioral manifestations of the severe phenotype observed in 5xFAD mice.



Dr. Isabelle Baconguis (*Vollum Institute, Oregon Health & Science University*) earned her B.A. in Biochemistry from the University of Pennsylvania. Following her undergraduate studies, she remained at PENN conducting research on glutamate receptors. With her continued interest in ion channel structure-function investigations, she joined the Neuroscience Graduate Program at OHSU and Dr. Eric Gouaux's lab at the Vollum Institute. During her doctoral research at the Vollum Institute, Dr. Baconguis focused on understanding the function of acid sensing ion channels (ASICs), members of the amiloride-sensitive and Na+-selective trimeric ion channel Degenerin/ENaC superfamily. She employed a combination of x-ray crystallography and electrophysiology to advance her understanding of these channels. In 2013, Dr. Baconguis joined the Vollum Institute as its inaugural Vollum fellow. As a recipient of the NIH Director's Early Independence Award, she established a research program focused on unraveling the molecular mechanism underlying water and salt balance in mammals, initially focusing on epithelial sodium channels (ENaC). Her research program, now as an Assistant Scientist at the Vollum Institute, has since expanded to include other members of the DEG/ENaC family.

Cryo-EM analysis of human acid-sensing ion channel reveals pH-mediated conformational changes

Acid-sensing ion channels (ASICs), found in both the central and peripheral nervous systems, play crucial roles in nociception, rapid synaptic transmission, and learning and memory. Typically, these channels are activated in acidic environments. Among the seven isoforms in this family, ASIC1a stands out as it is permeable to both sodium and calcium ions. Despite the significance of ASIC1a in human diseases, a comprehensive study detailing its various conformational states has not been presented. Here we employ single-particle cryo-electron microscopy (cryo-EM) to unveil the closed, putatively open, and desensitized state structures of hASIC1a.

Poster Session II

The Neuroscience Club of Portland State University 2024, **Kadi Rae Smith,** Portland State University

Neuroscience educational interventions for mental health management within the neurodiverse population: a working model, **Kadi Rae Smith,** Portland State University

Second Language Impacts on First Language Processing, **Natalie Robison,** Portland State University

Treating attachment trauma in adolescence through neuroscience informed peer support as a novel method in coping with attachment injuries, **Emilee Brnusak,** Portland State University

Loss of postnatal retinal input perturbs late corticogenesis in the developing ferret visual cortex, **Connor Hilts,** OHSU

Evaluating the effects of Centella asiatica water extract on cerebrovascular function in mice, **Benjamin Zimmerman,** Helfgott Institute

A water extract of the plant Centella asiatica increases cortical BDNF levels in aged mice, **Brooke Rogers,** OHSU

*Centella Asiatica reduces anxiety in aged female mice, accompanied by elevated levels of GABA, and reduced levels of corticosterone in blood samples***, Olivia Monestime,** OHSU

Accounting for age and sex in the evaluation of fetal ethanol exposure effects on fetal rhesus macaque brain development, **Joshua Karpf,** Oregon National Primate Research Center

Aquaporin-1 in the prefrontal cortex of the oldest-old rhesus macaques: Astrocyte reactivity and response to amyloid, **Opal Stayer-Wilburn,** Oregon National Primate Research Center

Higher brain-wide patterns of resting state functional connectivity following chronic ethanol drinking in macaque monkeys, **Anahit Grigorian,** Oregon National Primate Research Center

The Neuroscience Club of Portland State University 2024

K. R. Smith[13], B. Bolen[123], C. Swallow[13], D. Jang[13], A. Gonzalez[13];

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The Neuroscience Club of Portland State University (PSU) cultivates a vibrant and inclusive space for interdisciplinary exploration of the brain. Our weekly events offer experiences such as research presentations, artistic journeys through neuroanatomy, expert-led mental health sessions, and community building via social activities. Neuro Club has focused on recognition and collaboration with the neurodiverse community, crafting accessible materials, dispelling common misconceptions, and promoting personal agency by cultivating a welcoming environment within academia. There is a network between club members and the greater community that is facilitated via roundtable discussions and social media initiatives. The club's impact extends beyond campus walls, as we partner with local neuroscience educational outreach nonprofit NW Noggin. We participate in local, regional, and international outreach to schools, correctional facilities, houseless shelters, and more. This partnership extends to orchestrating Nogginfest, an annual large-scale, student-run celebration of interdisciplinary neuroscience that fosters awareness and engagement with the field through art projects, music, and research presentations. It's the Northwest region's largest celebration of neuroscience. Having an impact beyond our academics is a top priority of the Neuro Club that will continue to be guided by research, social engagement, and educational initiatives of the club. The Neuro Club is also dedicated to informing political policies. In November 2023, Club officers presented to the Congressional STEAM and Neuroscience Caucuses in Washington D.C. At the US capitol, Neuro officers presented research and testimonies on the role of neuroscience engagement in offsetting economic, educational, and healthcare disparities worldwide. Neuro officers spoke in Oregon's capitol, Salem, on behalf of adopting permanent standard time, supporting the position with research on detrimental effects that daylight savings time has on the brain, and personal testimonies. These efforts to spread our love for neuroscience enable our members to uniquely connect with the needs of the local population, as well as to address overarching societal exigencies - all which inform our members in their research and collaborative efforts. This is our mission.

Neuroscience educational interventions for mental health management within the neurodiverse population: a working model

K. R. Smith[1,3], C.K. Miller[2], W.S. Griesar[1,3],J. Leake[1,3]

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[3]NW Noggin (nwnoggin.org)

Because humans are complex and multidimensional, a multitude of factors affect our mental health and wellbeing. Sociological and environmental factors, such as economic standing and cultural marginalization, hinder access to educational and medical resources. They are an inescapable part of life that must be taken into account in order to ensure sound pathological assessments, enable effective self-regulation and mental health management for neurodiverse individuals, and offset disparities in access to healthcare and education. Arbitrary attachment of social stigma to traits commonly associated with neurodivergence perpetuate harmful neuro-myths1 that have dire consequences when internalized, informing individuals' development and sense of self. The neuroscience outreach done by NW Noggin serves as a functional model for engaging communities with minimal economic resources and a greater need for social, educational, and communal services to supplement the disparities inherent to inequity. Integrated arts programming, like those employed by NW Noggin, can help bridge the gap in resources within marginalized communities, affording participants and educators the opportunity to better understand the mind and body by asking specific questions that they want to know. Neuroscience educational interventions dispel misinformation, enabling neurodiverse individuals, their practitioners, educators, social workers and family members to understand and better navigate neurodiversity. Through volunteer work and undergraduate thesis research, further inquiries are actively being pursued, via surveys, interviews, and holistic methods of fostering ongoing conversations with educators and students with a goal of determining the efficacy of neuroscience-based educational interventions in mental health management. Ongoing research on the efficacy of neuro-educational interventions in alleviating stigma surrounding neurodivergence to afford agency to those suffering from comorbid depression and anxiety.

1. From an educational approach, a neuromyth was described as "a misconception generated by a misunderstanding, a misreading, or a misquoting of facts scientifically established (by brain research) -" (OECD, 2002).

Second Language Impacts on First Language Processing

N. Robison, S. Creel, S. Elkinton, J. Kelholt, A. Lin, and C. Quam

Portland State University, Portland, Oregon, United States

Chinese and English, two of the three most widely spoken languages worldwide, differ in nearly every typological aspect. Most notably, pitch is used in distinct ways to communicate meaning. Intonational English uses pitch to denote intonation, across larger segments of speech (e.g., “it’s there?” versus “it’s there!”). Tonal Chinese uses pitch lexically, to indicate the meaning of a syllable or word, such as where the syllable /he/ means “drink” when spoken with a high, level tone, or “river” when spoken with a low rising tone. Tonal languages are generally understudied, but the present line of research probes the attrition of native, tonal language proficiency when an individual becomes more dominant (relatively more proficient) in a second, intonational language. Quam and Creel (2017) found that in native Mandarin speakers, English dominance correlated with decreased proficiency in Mandarin tones, but not in Mandarin vowels. The present study delineates between two alternative explanations for this: either attrition of both tones and vowels can be predicted by language assimilability (L1-L2 Assimilability Hypothesis), or tone is uniquely prone to attrition regardless of assimilability (Tone-Uniqueness Hypothesis). In an eye-tracked word-recognition task, participants heard a spoken Mandarin word while viewing two images, and used a mouse to select which image matched that word. The two images represent words which differ in tone only (tone trials), vowel only (vowel trials), or are completely different words (baseline trials). Vowel trials are further categorized as easy, medium, or hard difficulty based on the vowels’ assimilability into English. Both hypotheses predict best performance on the baseline trials and worst performance on the tone trials. If the attrition of tones and vowels is predicted by language assimilability, then we expect a link between English dominance and high performance on easy-vowel trials, with performance dropping as vowel-difficulty increases, so that hard-vowel performance resembles that of tone trials. By contrast, if tones are uniquely prone to attrition then we expect no gradient in performance by vowel difficulty correlated with English dominance, where the performance on all vowel trials resembles that of the baseline trials. Data collection is ongoing, with preliminary analyses (n=35) indicating that medium- and hard-vowel trials yield lower performance than tones, and easy-vowel trials yield performance similar to baseline. Insight on the interactions of two language systems in one brain may better inform clinical approaches to speech disorders and educational approaches to languages in classrooms.

Treating attachment trauma in adolescence through neuroscience informed peer support as a novel method in coping with attachment injuries

E. BRNUSAK

Portland State University, Portland, OR, USA

Attachment trauma, or attachment injuries, refers to cognitive impairments caused by an interruption to the caregiver-child bond during infancy or early childhood. A summary of literature suggests that childhood attachment injuries lead to antisocial, maladaptive relationships and neurological damage that causes executive functioning and emotional regulation problems throughout adolescence and into adulthood. Historically, research done on attachment injuries fixates on when attachment injuries occur, but little research is done to investigate how this trauma impacts these children as they go through adolescence. The aim of this study is to highlight the neuroscientific causes and societal impacts of attachment injuries, as well as ways to treat them. Attachment injuries are correlated to damage in the limbic system and the prefrontal cortex, suggesting the presence of maladaptive top-down and bottom-up processing. Additionally, the absence of parental connection at a young age may impair the development of mirror neurons critical to societal functioning. As a result of this damage, childhood attachment trauma is strongly correlated to juvenile delinquency, risky sexual behaviors, and gang activity. I propose that creating a novel organization that fosters peer support, education, and resources may ameliorate care for youths with attachment injuries.

Loss of postnatal retinal input perturbs late corticogenesis in the developing ferret visual cortex

Connor M. Hilts, Sarah E. Santiago, Christopher D. Kroenke and Anthony Paul Barnes

Oregon Health & Science University

Molecular organizing cues and activity-dependent refinements are two of the developmental mechanisms that shape visual circuitry and experiments silencing retinal input have illuminated the contribution of each to the establishment of cortical circuitry. Yet, how the loss of retinal activity affects the cellular composition and organization of visual cortex is less understood. Earlier studies have focused on how the morphology of excitatory neurons as well as the visual cortex volume, thickness, surface area, and even gyrification is impacted following neonatal enucleation. Here, we have assessed how the deprivation of retinal input occurring after neurogenesis, through bilateral enucleation on postnatal day 7 (P7), affects the distribution and density of other constituent cells of the primary visual cortex across cortical development and during maturation. We present our results tracing these spatiotemporal alterations from P20 through P38, illustrating the emergence of visual input dependent organization which display differing time-courses in both controls and enucleates. We explored altered laminar distributions of interneurons present throughout late corticogenesis as well as profound and regionalized impacts on myelination following enucleation. Specifically, our measurements of cortical thickness reveal distinct increase in layer 5/6 extent in enucleates in the absence of sulcus formation that may be associated with myelin pattern perturbation. Our findings identify specific cellular and cytoarchitectural alterations and highlight challenges that will need to be addressed in the design and development of restorative therapeutics.

Evaluating the effects of *Centella asiatica* water extract on cerebrovascular function in mice

Benjamin Zimmerman[1,2], Amala Soumyanath[2,3], Nora Gray[2,3], Martin Pike[4], Anusha Mishra[2,3]

[1]Helfgott Institute, National University of Natural Medicine, Portland, OR, USA; [2]BENFRA Botanical Dietary Supplements Research Center, Oregon Health & Science University, Portland, OR, USA; [3]Department of Neurology, Oregon Health & Science University, Portland, OR, USA; [4]Advanced Imaging Research Center, Oregon Health & Science University, Portland, OR, USA

Scientific evidence supports the reputed ability of the botanical *Centella asiatica* to promote healthy cognitive function in aging. However, the biological mechanisms mediating these beneficial effects are not well understood. Elucidating these mechanisms is critical to optimizing products derived from traditional botanicals and assessing appropriate biomarkers of target engagement and biological outcome measures in clinical trials. One potential mechanism underlying the benefit of *C. asiatica* is through acute or longer-term effects on the tone of cerebral small vessels, which could support cognition by increasing cerebral blood flow. We tested this mechanism by investigating the effects of *C. asiatica* on cerebrovascular function in mice. We treated 2-month old or 17-month old C57BL/6 mice with an aqueous extract of *C. asiatica* (CAW; 10mg/mL in drinking water) for five weeks and then assessed cerebrovascular function *in vivo* using arterial spin labeling MRI to measure resting brain perfusion and cerebrovascular reactivity to a hypercapnic challenge. Control mice received drinking water with no additives. We found that CAW treatment did not change resting perfusion but resulted in a significant increase in hypercapnia-evoked cerebrovascular reactivity compared to control animals. In the same mice, we then assessed the vasomotor response of capillaries to an oxidative stress challenge *ex vivo* using brain slice preparations. We applied 1 mM H_2O_2 and assessed the resultant change in diameter of capillaries. We found both age and treatment effects in the capillary responses to H_2O_2, with older mice showing larger constrictions than young mice, and a stronger loss of late-stage constriction in controls compared to CAW treated mice. In separate experiments, we also examined whether CAW exhibits acute vasodilatory effects *ex vivo*. However, capillaries pre-constricted with U46619 showed no significant dilation in response to CAW at 50 µg/ml or 100 µg/ml in brain slices. Overall, CAW appears to exert some beneficial effects on cerebrovascular function, which may be mediated through resilience to oxidative stress rather than acute vasodilatory effects on the cerebral microvasculature.

A water extract of the plant *Centella asiatica* increases cortical BDNF levels in aged mice

Brooke Rogers[1,2], Sam Varada[1,2], Wyatt Hack[1,2], Jon Zweig[1,2], Mikah Brandes[1,2], Amala Soumyanath[1,2], Nora Gray[1,2]

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Centella asiatica, an herb traditionally used in Ayurvedic and Chinese medicine, has been shown to improve cognitive function and brain health in humans, as well as rodent models. Previous studies from our group have found a water extract of *Centella asiatica* (CAW) administered in drinking water improves learning, memory and executive function in mouse models of aging and Alzheimer's disease yet the precise mechanism by which CAW improves cognitive function has not been fully elucidated. The neuropeptide BDNF (brain derived neurotrophic factor) is a key molecule in mediating changes in plasticity related to learning and memory. In mouse models, cognitive impairment is associated with decreased BDNF levels whereas increased BDNF levels are associated with improved cognitive performance. In this study we investigated whether the effects of CAW on cognitive performance are associated with increased BDNF levels in healthy, aged mice. Eighteen-month-old male and female C57BL6 mice were treated with either 0 or 10mg/mL CAW in their drinking water for 5 weeks. In the final two weeks of treatment, mice underwent cognitive testing, including the odor discrimination reversal learning (ODRL) test of learning and cognitive flexibility and the novel object recognition task (NORT) test of recognition memory. At the conclusion of testing, tissue was harvested and cortical BDNF levels were quantified via ELISA. CAW treatment resulted in improvements in both ODRL and NORT performance in both sexes. Cortical BDNF levels were also higher in mice treated with CAW as compared to vehicle-treated mice, with no differences observed between the sexes. These results demonstrate that CAW can improve learning, memory, and executive function in aged mice and can increase cortical BDNF levels. Future studies are needed to identify precisely how CAW administration increases BDNF and whether this increase is necessary for the cognitive enhancing effects of the extract.

***Centella Asiatica* reduces anxiety in aged female mice, accompanied by elevated levels of GABA, and reduced levels of corticosterone in blood samples**

Olivia Monestime1, Wyatt Hack1,2, Jon Zweig1,2, Mikah Brandes1, Amala Soumyanth1,2, Nora Gray1,2

[1] Department of Neurology, Oregon Health and Sciences University (OHSU), Portland, OR
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Cognitive impairment and alterations in mood are prevalent in elderly populations. The burden of anxiety disorders and sub-threshold anxiety symptoms in elderly populations is substantial, and effects daily activities, quality of life, increased health costs, and has even been associated with an increased risk of dementia. *Centella asiatica*, a botanical known in Ayurvedic medicine as Gotu Kola, has a history of usage for enhancing cognition, reducing anxiety and promoting general brain health. Prior work in our lab has shown a water extract of *Centella asiatica* (CAW) to be effective in attenuating cognitive impairment in mouse models of aging and neurodegenerative disease but we have not previously evaluated its effects on anxiety in mice. In this study, we investigated the effects of CAW on anxiety-related behaviors in aged mice as well as its effects on plasma levels of GABA and corticosterone. CAW was administered to 18-month-old C57BL6 male and female mice, at 10mg/mL in their drinking water, for a total of 5 weeks. Male and female 3 month-old and 18-month-old untreated mice were used for comparison. In the last two weeks of treatment mice underwent behavioral testing which included evaluation of anxiety using the Open Field Test. At the conclusion of behavioral testing, tissue was harvested and plasma GABA and corticosterone levels were quantified by ELISA. We found that aged female animals exhibited significantly more anxiety-related behaviors, including increased time immobile and decreased time in the center of the open field, than young animals and CAW treatment attenuated those changes in the aged female mice. In male mice, no differences in anxiety-related behavior was seen between young and old animals nor was there an effect of CAW treatment evident in aged mice. The anxiolytic effect of CAW seen in aged female mice was associated with reduced levels of corticosterone and increased GABA levels in the plasma of those animals. In contrast, in male mice no differences in corticosterone or GABA were seen regardless of age or treatment. In summary, an anxiolytic effect of CAW-treatment was observed in aged female which was associated with alterations in plasma GABA and corticosterone. These effects were not seen in male mice. Future studies, perhaps incorporating more sensitive tests of anxiety, are needed to confirm whether the results observed in this study reflect a true sex dependent anxiolytic effect of CAW.

Accounting for age and sex in the evaluation of fetal ethanol exposure effects on fetal rhesus macaque brain development

JA Karpf, VC Cuzon Carlson, EL Sullivan, JO Lo, KA Grant, CD Kroenke

Division of Neuroscience, Oregon National Primate Research Center, Beaverton, OR, 97006, USA. Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, OR, 97239, USA.

Purpose: Fetal Ethanol Exposure (FEE) causes lasting developmental perturbations that place significant burdens on human health. As early detection of FEE effects is critical for therapeutic interventions, we are interested in developing *in utero* MRI-based strategies to detect FEE-induced central nervous system (CNS) effects in a translational rhesus macaque model due to their greater similarities in CNS development to humans than other animal models. However, studies involving macaques are limited by small samples which precludes consideration of biological variables like age and sex. To address this, we compiled multi-study data from 80 *in utero* MRI-scans of control animals and re-evaluated a previous cohort of FEE fetuses in the context of this large, normative developmental dataset.

Methods: High resolution T2-weighted scans of fetal brains ranging from gestational days (G)78 to 139 were acquired using a 3T Siemens Magnetom Prisma with a 15-channel knee coil. Regional brain volumes were analyzed using atlas-based registration approaches with improved large sample atlases – G85 (N=32; 16 females), G110 (N=19; 13 females), and G135 (N=29; 15 females). Fourteen rhesus FEE fetuses (8 females) were generated from dams trained to drink 1.5mg/kg/day ethanol prior to and during the first 60 days of pregnancy. Comparisons of regional volume differences were performed using linear mixed effects (LME) modeling, which accounted for longitudinally-acquired scans in the control dataset. Significant effects of age and sex were quantified throughout the brain.

Results: Sex differences were significant in the cerebellum, brainstem, corpus callosum, caudate, ventricles, thalamus, as well as whole brain, cortical and subplate tissue ($p<0.05$). Sex differences were not observed in brain region volumes expressed as a fraction of intracranial volume (ICV) except within the subplate. A main effect of FEE treatment on both cerebellar and corpus callosum volume was observed ($p<0.05$) after ICV correction.

Conclusions: Using a large normative developmental dataset reveals brain volume sex differences and enables quantification of age-related changes in the rhesus fetal brain using LME modeling. Further, comparisons with a large normative sample recapitulated prior findings of FEE-related cerebellar volume reductions when controlling for sex related differences in head size, and uncovered volume deficits in the corpus callosum similar to those observed in the human literature.

Aquaporin-1 in the Prefrontal Cortex of the Oldest-old Rhesus Macaques: Astrocyte Reactivity and Response to Amyloid

Opal Stayer-Wilburn[a], Donald I. Brown[b], Randy L. Woltjer[c], Sathya Srinivasan[a], Douglas Rosene[d, e], Julie A. Mattison[f], Henryk F. Urbanski[a], Steven G. Kohama[a]

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Aquaporin-1 (AQP1) is a water channel protein found in many cell types, including primate brain astrocytes. Cortical AQP1 is associated with β-amyloid (Aβ) plaques in Alzheimer's disease (Pérez et al., 2007; Misawa et al., 2008) and other studies suggest co-regulation of Aβ and AQP1 (Huysseune et al. 2009; Park et al., 2020). Previously, we found an increase in AQP1 expression in prefrontal (PFC) regions of the oldest-old (>25 years old) rhesus macaques. In this study, we confirmed AQP1+ cells were astrocytes, by co-labeling with GFAP and vimentin. Moreover, we tested the interaction of AQP1 and Aβ by examining PFC sections from low, medium, and high AQP1-expressors, double-labeled for AQP1 and GFAP, vimentin, or Aβ with immuno-fluorescence. Fluorescently labeled sections were scanned at 20X magnification on Olympus VS120 slide scanner to observe distribution and possible overlap. Confocal images were taken with a Leica Stellaris8 at 40X magnification with oil immersion, to determine cellular colocalization. Section scans were qualitatively ranked for overall stain intensity of both markers, as well as proximal colocalization. We found varying levels of co-labeling across animals, some with large aberrant clusters of AQP1 associated with GFAP or vimentin^{+} reactive astrocytes. Similar to prior results (Cargill et al, 2011), GFAP in the oldest-old brains was present in all cortical layers. AQP1 staining was co-labeled with GFAP in all cases, but not all GFAP labeling contained AQP1. Vimentin typically labeled blood vessels, but vimentin+ cell bodies were only seen in clusters in regions with AQP1 labeling. Many Aβ plaques co-labeled with AQP1, concentrated in some PFC subregions (e.g. cingulate cortex), but AQP1 and Aβ labeling also existed separately in other areas. With confocal imaging, AQP1+ processes were observed to penetrate and/or surround plaques. In addition, confocal images of AQP1 and GFAP/vimentin showed that a small fraction of GFAP+ astrocytes were co-labeled with AQP1, whereas nearly all vimentin+ astrocytes were co-labeled with AQP1. AQP1 also labeled a larger extent of the astrocyte's finer processes than the cytoskeleton proteins GFAP or vimentin. AQP1 upregulation could coincide with the increase of vimentin expression in astrocytes, potentially as a reactive response to accumulating levels of amyloid. In sum, GFAP upregulates earlier during aging, followed by a late increase of vimentin and AQP1 in the PFC, coincident with an upregulation of amyloid. Future studies will utilize triple labeling to try to quantitate the timeline of this process.

Higher Brain-Wide Patterns of Resting State Functional Connectivity Following Chronic Ethanol Drinking in Macaque Monkeys

A. Grigorian[1], A.R. Weiss[1,4], K. Ruano Espinoza[1], C.D. Kroenke[1,2,3], K.A. Grant[1,3]

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Alcohol use disorder (AUD) is a long-term, relapsing disorder characterized by compulsive alcohol consumption. In 2021, an estimated 29.5 million Americans met the criteria for AUD. Chronic alcohol consumption in AUD leads to whole brain adaptations such as disrupted reward pathways extending from the cortex to the basal ganglia. Resting state functional MRI (rs-fMRI) is a non-invasive technique to evaluate localized brain activation and synchronous neural activity. Therefore, we investigated the effects of chronic alcohol consumption in rhesus monkeys using rs-fMRI connectivity to study changes in the organization of neural pathways and their function. Forty-four rhesus macaques (F= 22) were trained to self-administer 4% w/v ethanol (EtOH, n=36) or maltose dextrin (MD, n=8). Next, they entered a 6-month “open-access” period during which EtOH (or MD) and water were available 22 hrs/day. rs-fMRI were collected on a 3T MRI prior to training and following open-access. Dual regression was performed on four brain networks (visual, motor, sensorimotor and executive) identified using independent component analysis to assess changes in resting-state functional connectivity (rs-FC). The EtOH group, but not the MD group, exhibited significant increases in rs-FC after 6-months of chronic drinking in the 4 identified brain networks ($p < 0.05$). Changes in the dorsal striatum were among the observed brain-wide effects, with the putamen demonstrating the largest increase within the sensorimotor network. The global increases in rs-FC reported here may indicate compensatory mechanisms by which brain networks recruit additional resources to maintain function. Increased putamen-sensorimotor connectivity suggests an increase in sensory-driven mediation of drinking. The shared patterns of FC in reward systems reported in this non-human primate model, and in humans, may further our understanding of neural maladaptation to substance use and, in turn, improve treatment of AUD. Future studies are warranted to further characterize potential effects of sex, drinking amounts, and other behavioral characteristics such as cognition, on brain FC following alcohol exposure.

Speaker Session II

11:15 am *Electrophysiological characterization of immortalized ovine hypothalamic kisspeptin neurons*
Anna Nielson
Oregon State University

11:30 am *Assessing the role of inattention, response latency, and perseveration in predicting behavioral flexibility in rhesus macaques*
Daniel Smith
Oregon National Primate Research Center

11:45 am *Impact of ketamine and novelty on cue-induced reinstatement of cocaine self-administration in rats*
Angela Gonzalez
Washington State University

12:00 pm *Changes in cerebral morphology and microstructure associated with advancing age in rhesus macaques*
Alison Weiss
Oregon National Primate Research Center

12:15 pm *Molecular mechanisms of maternal care in a mouthbrooding cichlid fish*
Suzy Renn
Biology Department, Reed College

Electrophysiological Characterization of Immortalized Ovine Hypothalamic Kisspeptin Neurons

A.L. Nielsen[1], A. Starman[2], R. Bahn-Bales[2], R. Toyoizumi[4], P.E. Chappell[3], K.C. Hokanson[4]

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In females, reproduction is regulated via the hypothalamic-pituitary-gonadal axis. The timing of hormonal release is regulated by two populations of kisspeptin neurons in the hypothalamus. In the arcuate nucleus population, kisspeptin neurons modulate downstream hormone release in a negative feedback loop with estrogen. In an effort to further explore the mechanisms underlying this process Dr. Chappell's laboratory immortalized arcuate kiss1 expressing neurons from sheep. The ovine model is advantageous for studying neuroendocrine and reproductive systems given similarities in length and phase between the ovine estrous cycle and human menstrual cycle. Yet, we are not aware of any functional electrophysiological data from ovine hypothalamic neurons. Our study aims to characterize the intrinsic excitability and passive properties of this immortalized ovine mediobasal hypothalamic (oMBH) neuronal cell line, to validate its feasibility as a model for in vivo kisspeptin neurons. Whole-cell patch-clamp recordings from 42 oMBH cells reveal the presence of voltage-gated slow-inactivating putative potassium currents in 30-60% of cells. Similar voltage-gated potassium currents in primary mouse arcuate kisspeptin neurons are diminished by estradiol, raising resting membrane potential and increasing likelihood of firing in response to synaptic input (Moenter et al., 2019). Preliminarily, 10-20% of oMBH cells display a voltage-sensitive positive going current whose kinetics are consistent with voltage-gated sodium channels, suggesting that these immortalized neurons recapitulate crucial aspects of their predicted in vivo intrinsic excitability. oMBH neurons did not demonstrate senktide-gated ion currents (n=8), despite the presence of mRNA transcript of neurokinin B and its receptor. Overall, retention of functional voltage-gated channels in our immortalized oMBH neurons supports their feasibility as a model. We are working to confirm and identify ion channels using pharmacological manipulation, and to better understand the source of the variability in excitability seen in different cells within this clonal line.

Assessing the role of inattention, response latency, and perseveration in predicting behavioral flexibility in rhesus macaques

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Behavioral flexibility plays a vital role throughout our lives, and deficits in behavioral flexibility have been associated with multiple neurocognitive disorders and addiction. The performance index (PI) within the attentional set-shifting task (ASST) has emerged as a valid measure of behavioral flexibility in rhesus macaques, however there may be unknown indices that are associated with ASST performance, and thus behavioral flexibility. The purpose of this study was to determine if inattention (not completing trials) and side-bias are related to PI in the ASST, and to discern if other recently identified predictors of PI can be replicated within an independent cohort (n = 12; 6 females) of rhesus macaques. Our results indicate that low performers (LPs; n = 6) exhibited higher levels of inattention than high performers (HPs; n = 6); however, there was insufficient evidence to suggest that either LPs or HPs possessed a side-bias. Additionally, LPs tended to take less time to select an answer (response latency), engaged in a greater number of total perseverative errors, and committed more consecutive perseverative errors than HPs on average. These results serve as initial evidence for the role of inattention and repeated perseverations in predicting PI, and also replicate recent findings that link perseverative errors and response latency to PI within the ASST. To address neuroanatomical indices of ASST performance, studies are underway using functional magnetic imaging (rs-fMRI) and Positron Emission Tomography (PET) imaging, in the same population of animals characterized with ASST.

Impact of ketamine and novelty on cue-induced reinstatement of cocaine self-administration in rats

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Strong drug-associated memories are notoriously resistant to disruption. Novel information introduced during memory retrieval could potentially weaken drug-associated memories, making them susceptible to interference by amnestic agents. Our previous work in the mPFC demonstrated that combining novel memory retrieval with the enzymatic disruption of perineuronal nets (PNNs), which surround the majority of parvalbumin (PV) cells, decreased cue-induced reinstatement in cocaine self-administering rats. Ketamine is a dissociative anesthetic that primarily acts via NMDA receptor antagonism preferentially in PV cells and disrupts cortical PNNs. Ketamine has been shown to disrupt fear- and certain drug-associated memories. We tested whether ketamine administered with novel memory retrieval would decrease cocaine reinstatement. Rats were trained to self-administer cocaine on a fixed-ratio 1 (FR1) schedule and given a cocaine-reinforced 30 min memory retrieval session on either an FR1 or novel variable-ratio 5 (VR5) schedule. Saline (control) or ketamine (6 mg/kg, i.p.) was administered 10 min pre- retrieval. We also tested post-retrieval administration of control or ketamine (6, 20 or 50 mg/kg, i.p.). The following day, rats were given a 30 min extinction followed immediately by 30 min cue reinstatement. We found that ketamine/VR5 reduced cue reinstatement compared to ketamine/FR1 and saline/VR5 groups, while post-retrieval ketamine did not impact reinstatement. This suggests that pre-retrieval ketamine with novelty may weaken a cocaine self-administration memory, reducing drug-seeking behavior. We subsequently (90 min post cue reinstatement) conducted intensity analysis of PNNs, PV, Npas4 and c-Fos from the prelimbic mPFC of pre-retrieval groups. We found reduced intensity levels of PNNs, Npas4, and c-Fos, and increased intensity levels of PV in rats given ketamine/VR5 compared with those given saline/VR5. Interestingly, we also found a decrease in Npas4 and c-Fos in ketamine/FR1 compared with saline/FR1. Moreover, PNNs and Npas4 were decreased in saline/VR5 compared with saline/FR1. These findings suggest that novelty and ketamine both independently and together play a role in weakening cocaine-seeking behavior.

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Changes in cerebral morphology and microstructure associated with advancing age in rhesus macaques

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We report a cross-sectional study identifying microstructural biomarkers of aging in the naturally occurring rhesus macaque model of normative aging. In a cohort of 38 healthy animals (18F/20M) with ages ranging 5.3-28.2 years, we collected high-resolution diffusion weighted (DW) scans and T2w SPACE images. We characterized microstructural alterations in cerebral white matter with voxel-based analyses of diffusion tensor imaging (DTI) data. Significant age-associated changes in diffusion were observed in a number of white matter regions throughout the brain. Voxel-wise analysis highlighted frontal and temporal white matter areas, as well as regions of the internal capsule and corpus callosum, with significant age-associated Fractional Anisotropy (FA) reductions ($p<0.05$). No voxels with significant FA increases were found. We followed this analysis with the evaluation of age-associated changes in brain morphology in the same animals using Tensor Based Morphometry (TBM). Voxel-wise analysis highlighted areas of frontal and parietal cortex, and the striatum, with significant age-associated TBM changes (voxels with reduced values of the logarithm of the determinant of the Jacobian) indicative of contraction ($p<0.05$). Taken together, this work broadly suggests that aged macaques undergo morphological and microstructural changes in cortical, striatal, and thalamic regions, as well as in the white matter fiber pathways connecting these areas, that are detectable using high-resolution DTI and MRI. Future studies by our group will seek to link the trajectory of these changes with measures of brain inflammation and metabolism assessed via PET, as well as the association of these neuropathological features with cognitive performance.

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Suzy Renn (Biology Department, Reed College) is the Roger M. Perlmutter Professor of Biology and has been on faculty at Reed College since 2006. She holds a doctorate in neuroscience from the Washington University School of Medicine in St. Louis. For the past two years Suzy has been on leave to serve as Program Director for the National Science Foundation (NSF), where she has worked to manage grant funding and empower STEM talent through strategic initiatives within the agency.

Suzy's scholarly work includes studying the neural mechanisms that regulate maternal care and feeding behavior in a species of fish that brood their young in their mouths and thus do not eat for several weeks at a time. This NIH- and NSF-funded research has implications both for the evolution of parental care strategies and for the regulation of feeding behavior and related diseases such as anorexia or cachexia that occur when this regulation goes awry. In addition to student research on these projects, she has mentored thesis projects on topics ranging from communication in orcas to escape behavior of salamanders in Oaks Bottom Wildlife Refuge.

Molecular mechanisms of maternal care in a mouthbrooding cichlid fish

For over 30 years, the African cichlid fish, *Astatotilapia burtoni*, has been an important model system for studying the mechanisms underlying socially mediated behavioral change, with the focus being the dominance behavior of males. A more recently collected wild-stock of this species invigorates interest in parallel studies of females' behavior by describing a robust 'good-mother' phenotype. In this species, the females brood their young in the buccal cavity, an expensive form of maternal care referred to as "mouth-brooding". While the females of both the laboratory-stock and the wildstock brood the developing fry, only the WS continues to provide maternal care after initial release of the fry while the labstock engage in filial cannibalism. We describe behavioral, physiological, and neural changes that accompany the transition to mouthbrooding and the transition to active maternal care, emphasizing differences between the labstock and the wildstock. These two transition points provide robust examples of behavioral switching as mothers balance their own energy needs with the needs of offspring. By understanding the difference between these two fish stocks we aim to identify key mechanisms that allow for the evolution of mouthbrooding and possibly provide insight into human disorders that inappropriately decouple feeding behavior and metabolic rate.

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