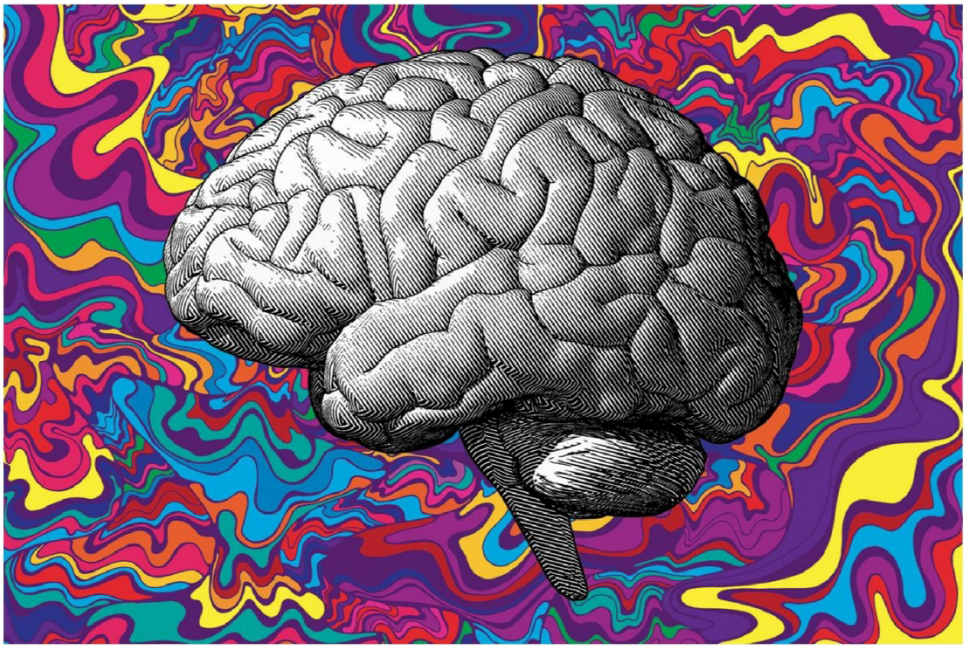
Society for Neuroscience

Oregon & Southwest Washington

MEETING



May 12-13, 2023 - Edgefield Winery

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Atheir Abbas, M.D., Ph.D.
Assistant Professor, Behavioral Neuroscience, OHSU

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Assistant Professor, Biology and Mathematics, University of Oregon

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Assistant Professor, Psychiatry, OHSU

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- Jessica Ewton and Varsha Karthikeyan: *Exosomes isolated from conditioned media of immortalized kisspeptin neurons exert diverse effects on immortalized GnRH neurons in vitro.*
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Brian T. Anderson, M.D.
Assistant Professor, Psychiatry, University of California, San Francisco

Saturday, May 13

7:00 Breakfast

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Larry S. Sherman, Ph.D.
President, Society for Neuroscience, Oregon and SW Washington Chapter
Professor, Division of Neuroscience, Oregon National Primate Research Center and Oregon Health & Science University

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Bret Pearson, Ph.D.
Associate Professor, Pediatrics, OHSU

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Lauren Miller
Department of Cell, Developmental and Cancer Biology, OHSU

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Kayleana Green
Department of Biochemistry & Biophysics, College of Science, Oregon State University

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Kathy Magnusson, Ph.D.
Professor, Biomedical Sciences, Oregon State University

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Kaitlyn Kim
Linus Pauling Institute and Department of Biomedical Sciences, Oregon State University

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Mathew R. Frischman
Linus Pauling Institute and Department of Biomedical Sciences, Oregon State University

11:45 *The Hyaluronidase Cell Migration Inducing and Hyaluronan Binding Protein is Elevated in Inflammatory Demyelination and Inhibits Myelin Formation*
Alec Peters
Division of Neuroscience, Oregon National Primate Research Center

12:00 Lunch

1:00 *Increasing Access to Electrophysiology Experiments*
Kenton C. Hokanson, Ph.D.
Assistant Professor, Department of Biochemistry & Biophysics, Oregon State University

1:15 *Neural Mapping of Sensorimotor Function in Humans*
Michelle Marneweck, Ph.D.
Assistant Professor, Human Physiology and Neuroscience, University of Oregon

1:45 Awards and Adjournment

Mini-symposium on the Neuroscience of Psychedelics

KEYNOTE SPEAKER

The Psychedelic Translatome of the Prefrontal Cortex

Andrea Gomez, Ph.D.
Assistant Professor, Molecular and Cell Biology, University of California, Berkeley

Andrea Gomez is an Assistant Professor in the Department of Molecular and Cell Biology and the Helen Wills Neuroscience Institute at the University of California, Berkeley. She is also a member of the Executive committee at the UC Berkeley Center for the Science of Psychedelics. Gomez received her Ph.D. in Developmental Genetics from New York University and conducted postdoctoral research at the University of Basel, Switzerland. Her work is devoted to understanding the instructive cues that sculpt patterns of brain activity. Her efforts led to the discovery of RNA-based programs that are critical for synaptic organization and plasticity. Gomez started her lab at UC Berkeley in January 2020 and has received several awards, including the European Molecular Biology Organization Advanced Fellowship, a Brain and Behavior Research Foundation Young Investigator, a Rose Hills Innovator Award, and is a Sloan Research Fellow.

ABSTRACT:
A single dose of psychedelics robustly yet transiently elevates neural activity, leads to a large-scale engagement of neural plasticity, and provides immediate and enduring relief from treatment-resistant depression, end-of-life anxiety, or withdrawal symptoms in addiction. We focus on the multiple neuron types that mediate excitatory or inhibitory activity in the prefrontal cortex and address the lack of a high-resolution, genome-wide understanding of how psychedelics induce plasticity in distinct cell types at the transcriptomic level. In parallel, we measure how psychedelics induce long-lasting plasticity in select cell types in the prefrontal cortex at the physiological level. Our results demonstrate distinct transcriptional engagement of excitatory synaptic components in select cell types and propose that psychedelics selectively recapitulate developmental-like states of synaptic function.

From Receptor to Synapse to Circuit: Mechanisms of Psychedelic Action

Atheir Abbas, M.D., Ph.D.
Assistant Professor, Behavioral Neuroscience, OHSU

Atheir Abbas is an Assistant Professor in the Department of Behavioral Neuroscience and in the Department of Psychiatry at Oregon Health & Science University and a Consultation-Liaison Psychiatrist at the Portland VA Medical Center. He completed his combined MD/PhD training at Case Western Reserve University under the mentorship of Dr. Bryan Roth, characterizing the role of the 5-HT2A receptor's C-terminal tail in linking to glutamatergic signaling pathways. He then completed his Psychiatry residency and postdoctoral research training at Columbia University, where he trained under Dr. Josh Gordon, studying the contributions of prefrontal interneuron subtypes to working memory processing. His research includes pharmacologic and electrophysiologic characterization of novel and other psychoactive compounds, including psychedelics. He also conducts research focused on understanding the circuit basis for psychiatric disorders with a focus on schizophrenia and substance use disorders.

ABSTRACT:
Psychedelic drugs have been in use in some cultures for millennia. Within the last few decades, pharmacology and neuroscience research has led to new discoveries related to psychedelic mechanisms of action and their potential as therapeutics for depression and other brain disorders. Dr. Abbas will discuss some of this research, exploring the pharmacologic, synaptic, and circuit basis for psychedelic actions in the brain.

A Mechanistic Theory of Serotonergic Neuromodulation

Luca Mazzucato, Ph.D.
Assistant Professor, Biology and Mathematics, University of Oregon

Luca Mazzucato is a theoretical physicist by training. After obtaining his PhD in Physics (SISSA, Trieste, 2005), he spent several years unsuccessfully trying to unravel the mysteries of string theory at Tel Aviv University (2005-2008) and at the Simons Center for Geometry and Physics (2008-2011). He began his neuroscience research in 2012 at Stony Brook University, where he was a Swartz Fellow in Theoretical Neurobiology investigating the neuroscience of taste, and then as a Research Scientist at the Center for Theoretical Neuroscience (Columbia University, 2017-2018). He started his computational neuroscience lab at University of Oregon in 2018, where he is an Assistant Professor of Biology, Mathematics, and Physics. He is the recipient of a NIH Career Development Award (2014), and NIH R01 Awards from the BRAIN Initiative (2020), the National Institute on Drug Abuse (2021), and the National Institute for Mental Health (2022).

ABSTRACT:
Sensory perception arises from the integration of externally and internally driven representations of the world. Disrupted balance of these representations can lead to perceptual deficits and hallucinations. The serotonin-2A receptor (5-HT2AR) is associated with such perceptual alterations, both in its role in schizophrenia and in the action of hallucinogenic drugs, although little is known about the circuit level effects of 5-HT2AR activation. In this talk, I will present ongoing efforts from a collaboration at the University of Oregon, aimed at uncovering the effects of 5-HT2AR activation on sensory cortex. We found that 5-HT2AR activation via DOI leads to a reduction in sensory responses, as well as disrupted temporal dynamics. Although single-cell tuning properties remained largely intact, the encoding of sensory stimuli was strongly degraded at the population level, consistent with a drug-induced modulation of neural variability. Our results provide support for models of hallucinations in which reduced bottom-up sensory drive is a key factor leading to altered perception.

Psilocybin-Assisted Psychotherapy for Substance Use Disorders

Christopher Stauffer, M.D.
Assistant Professor, Psychiatry, OHSU

Chris Stauffer, MD is Assistant Professor of Psychiatry at Oregon Health & Science University (OHSU) and dual board-certified in Psychiatry and Addiction Medicine. Dr. Stauffer is the Director of the Social Neuroscience & Psychotherapy (SNaP) Lab, which aims to maximize the benefits of psychotherapy through the adjunct use of social psychopharmacology, such as oxytocin, MDMA, and psilocybin. Current studies include psilocybin-assisted psychotherapy for methamphetamine use disorder and MDMA-assisted group therapy for PTSD. He serves as Supervisor and Educator of MDMA Therapy through the Multidisciplinary Association for Psychedelic Studies (MAPS) and is a member of the Oregon Governor's Psilocybin Advisory Board. www.chrisstauffermd.com

ABSTRACT:
Substance use disorders are chronic relapsing conditions associated with substantial mental, physical, and social harms and increasing rates of mortality. Psilocybin-assisted psychotherapy is emerging as a promising treatment for a range of difficult-to-treat conditions, including substance use disorders. Dr. Stauffer will provide a background of the evidence for psilocybin-assisted psychotherapy in the treatment of substance use disorders and discuss proposed neuroscientific and psychosocial mechanisms.

Poster Session I

Cell-type specific cellular actions of psilocin on mouse and human cortical pyramidal neurons

M. KIM[1], D.W. KIM[1], S. VARGAS[1], L. NG[1], B. KALMBACH[1,2], S. OWEN[1,3], C.D. KEENE[4], J. HAUPTMAN[5,6], C. COBBS[7], A. KO[5], J. OJEMANN[5,6], H. ZENG[1,8], E. LEIN[1,4,5], J. TING[1,2,9], C. KOCH[1]

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Psilocybin and other serotonergic hallucinogenic drugs profoundly acutely alter consciousness, including loss of self. They have recently come to the forefront in brain research regarding their longterm therapeutic potential for treating a range of debilitating psychiatric conditions. Although it is known that psilocybin and its psychoactive metabolite psilocin bind to and activate specific serotonin receptors, relatively little is known in the rodent and virtually nothing in human about acute cell-type specific actions of these drugs in the brain. In this study, we adopted two experimental approaches to investigate cell-type specific drug actions. First, we measured immediate early gene activation in response to psilocybin administration in mice in vivo followed by mPFC tissue dissection, dissociation, and single-cell RNA-seq. Second, we performed Patch-seq to measure the electrophysiology, morphology, and transcriptomic profiles of single mouse and human layer 5 (L5) cortical neurons following focal application of psilocin in ex vivo brain slice preparations. We recorded from the broad subclass of L5 excitatory neurons (i.e., intratelencephalic (IT), extratelencephalic (ET), and near-projecting (NP) neurons) in mPFC of the mouse genetically labeled with fluorescent reporter for targeted recordings in brain slices. In these slice physiology experiments, we measured drug effects on both subthreshold (at resting) and suprathreshold modulation of action potential firing. We also recorded from a variety of L5 pyramidal cells from resected neurosurgical tissue from diverse cortical regions, including V1, temporal and frontal cortex. Our main findings are as follows: 1) we identified specific neuron types that were significantly activated by psilocybin in mouse mPFC using Act-seq in vivo, including L5 IT and NP types but not ET neuron types, 2) we found that distinct cellular actions on psilocin in mouse mPFC slice preparations in vitro, i.e., L5 ET, hyperpolarizing vs L5 NP, depolarizing effect, and 3) similar cellular responses in L5 IT neurons compared to human L5 IT neurons. Interestingly, the cellular actions of psilocin in these three distinct populations of L5 excitatory neurons of mouse mPFC are likely achieved by combination of distinct serotonin receptor type expressions and distinct intrinsic membrane properties. These results indicate cell-type specific acute neuromodulatory effect of psilocin on mouse mPFC L5 neuron types, namely a projection target-specific mechanism of action. Establishing whether this cell type specific effect of psilocin is conserved in human cortical L5 neurons requires further investigation.

Self-Medication for Functional Neurological Disorders (FND) Using Psychoactive Substances: A Qualitative Investigation to Inform Future Research

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[1]The Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

Functional neurological disorder (FND) is a common and often disabling condition significantly associated with distress and diminished quality of life with limited evidence-based treatments. The qualitative investigation seeks to find out from patient perspectives if self-medication with psychoactive substances has an effect on FND symptoms. I helped design and then led on ethical approval and recruitment for this study which was carried out as part of a patient-involvement initiative for an upcoming open label trial of psilocybin in FND. The qualitative investigation included semi-structured interviews and thematic analysis which has not been carried out before with this disorder regarding psychoactive substance use in relation to FND symptoms. The qualitative investigation included three participants diagnosed with FND by health professionals who have used psychoactive substances (e.g., cannabis, psilocybin, and ketamine) since being diagnosed. The preliminary results suggest that psychoactive substances may be effective in managing FND symptoms as self-reported by patients. This may be a self-management strategy alongside conventional medical management. Adverse effects were rated as minimal to experiencing some complications (e.g., feeling stoned and intoxicated, not being able to communicate as well, intensity experienced by the user dependent on dose, and experiencing some paranoia). Effectiveness of self-management strategies were rated as very to extremely effective (e.g., reduction of symptoms including pain and fear, prevents tremors and spasms, increased mobility, improved speech production, and promotes feelings of relaxation). Overall themes generated in the thematic analysis include lack of support and knowledge by health professionals, self-medication as alternative management, harm reduction and drug policy reform. This is the first qualitative investigation to explore the experiences and perspectives of FND patients' self-medication with psychoactive substances in relation to symptom management. By elucidating patients' perspectives on self-medication and management of FND symptoms, this could better inform clinical practice and help design medical trials using psychoactive substances to explore novel therapeutic treatments for this poorly understood disorder.

Keywords: Psychoactive Substances, Functional Neurological Disorder (FND), Self-Medication, Patient and Public Involvement (PPI), Thematic Analysis.

Heavy drinking leads to increased hyaluronan synthesis and catabolism in the non-human primate dentate gyrus

Rainie Codding[1], Weiping Su[2], Kanon Yasuhara[2], Virginia Cuzon Carlson[2], Kathleen A. Grant[2], Larry S. Sherman[2]

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Alcohol Use Disorder (AUD) is a chronic relapsing condition associated with habitual alcohol use and detrimental neural adaptations. Recent findings have indicated that aberrant neurogenesis, particularly by neural stem cells (NSCs) in the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG), plays a role in determining vulnerability to relapse in animal models of addiction. The normalization of alcohol-impaired neurogenesis during abstinence may therefore contribute to the reduction in vulnerability to relapse and aid in recovery.

Our data show that disruption of the glycosaminoglycan hyaluronan (HA) by a hyaluronidase in the SGZ leads to increased NSC proliferation and neuronal progenitors whose maturation is delayed in the granule cell layer of the DG. Similarly, mice lacking the major transmembrane HA receptor CD44 demonstrate increased NSC proliferation in the SGZ and delayed granule cell layer neuronal progenitor maturation. These mice also demonstrate cognitive deficits related to altered hippocampal function. Here, we used a non-human primate model of alcohol self-administration in which animals become chronic drinkers that exhibit patterns and levels of intake similar to humans. We find that compared to light drinkers, heavy drinkers with an average daily intake >3.0 g/kg (abut 12 drinks/day) and weekly blood alcohol concentrations indicative of intoxication over the 12 months of daily alcohol access have significantly elevated expression of CD44 and elevated levels of HA in the SGZ and hilus of the dentate gyrus. In addition, we find that heavy drinkers have increased levels of the cell migration-inducing and hyaluronan binding protein (CEMIP) in the SGZ. CEMIP functions as a hyaluronidase, and CEMIP-generated HA digestion products can activate receptors that regulate NSC proliferation and differentiation. Collectively, these data support the hypothesis that heavy drinking alters HA synthesis and catabolism in the SGZ, and that these changes in HA can influence neurogenesis and neuronal maturation. Targeting this extracellular domain with therapeutic approaches holds promise in treating or reversing the neurologic deficits associated with AUD.

Safety and Effectiveness: Core Measures to Assess Psilocybin Services

Adrianne R. Wilson-Poe[1], P. Todd Korthuis[2], Kim Hoffman[2], Jason B. Luoma[3], Alissa Bazinet[4], David Morgan[5], Sarann Bielavitz[2], Dennis McCarty[2], Christopher S. Stauffer[2,6]

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Promising clinical trial data suggest that serotonergic psychedelics such as psilocybin may be safe and effective treatments for mood and behavioral disorders. However, most previous studies have been conducted in controlled research centers with carefully-screened, college-educated, affluent, white, male research participants. Little is known about the safety or effectiveness of psilocybin in diverse populations where results may fail to generalize and adverse events could be more common. Thus, it is critical to assess the safety and effectiveness Oregon's nascent program permitting psilocybin services in community-based settings. Unfortunately, there are currently no consensus-based measures with which to evaluate these services. To meet this time-sensitive need, we recruited a diverse group of psilocybin experts (n=36; 53% female; 71% white; 56% heterosexual), and used a three-phase modified Delphi approach to generate core measures of safety and effectiveness. In Phase I, experts provided open-ended text recommendations via online survey regarding service structure, service delivery process, and outcomes suggestive of high-quality psilocybin services. In Phase II, experts rated the importance and feasibility of measures identified in Phase I. In Phase III, in-depth interviews refined the top-rated measures. Thematic analysis of Phase I qualitative responses yielded 55 candidate measures. Measures were stratified as structural (facilitator training in trauma informed care, referral capacity for medical/psychiatric issues), process (number of preparatory hours with client, documentation of touch/sexual boundaries), and outcome (adverse events, well-being, anxiety/depression symptoms). In Phase III, experts are identifying the top 15 candidate measures which balance both importance and feasibility. Experts identified several candidate measures which could easily be collapsed or combined (for example, issues around informed consent). Despite moderate importance ratings in Phase II, expert interviews in Phase III highlighted the importance of capturing data about 1) the dose of psilocybin administered in every session and 2) the extent and nature of client preparation before psilocybin administration. Combined, these consensus-based measures coalesce into a novel and critical tool to assess the safety and quality of community-based psilocybin services. A diverse group of stakeholders including citizens, health agencies, researchers, and policy makers stand to benefit from deploying this tool.

Perineuronal Net Removal in the Rat Medial Prefrontal Cortex Attenuates Prefrontal-Hippocampal Coupling During Cocaine Cue Acquisition

Jonathan Ramos[1], Jereme C. Wingert[1], Sebastian Reynolds[1], Angela E. Gonzalez[1,2], and Barbara A. Sorg[1,2]

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2.Washington State University, Vancouver WA

Environmental stimuli become paired with exposure to drugs of abuse and play an important role in the maintenance of drug memories. In the medial prefrontal cortex (mPFC), parvalbumin (PV) interneurons regulate pyramidal cells critical for cocaine memory consolidation. Most PV neurons are coated with a perineuronal net (PNN), an extracellular matrix structure essential for supporting fast firing rates and precise spike timing of PV neurons. These qualities of PV cells help generate oscillations and mediate coupling within and between brain regions, which play an important role in memory consolidation. Removal of PNNs with chondroitinase ABC (Ch-ABC) disrupts acquisition of cocaine memories, but it is not known why this occurs. After microinjection of either saline (control) or Ch-ABC into the mPFC of male Sprague Dawley rats, tungsten electrodes were implanted into the mPFC and hippocampal dorsal CA1. Rats were given intravenous infusions of saline paired with one cue light or cocaine paired with a second cue light over eight alternating days. On the last day, rats were presented both cue lights in a pseudo-randomized order. Rats exhibited event-related phase resetting in response to cue presentation; however, both phase-amplitude coupling and phase-phase coupling between the mPFC and CA1 were vastly attenuated in Ch-ABC compared with control rats following cocaine cue presentation. Cocaine cue presentation also increased beta power in controls that was attenuated in Ch-ABC rats. Overall, PNN removal in the mPFC diminishes communication between the CA1 and mPFC, which may underlie the inability of these rats to consolidate drug-associated memories.

Funding support: NIH DA 040965; Good Samaritan Foundation of Legacy Health.

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

Gonzalez, AE[1,2] and Sorg, BA[1,2]

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2.Washington State University, Vancouver WA

Strong drug-associated memories are difficult to disrupt. The medial prefrontal cortex (mPFC) is involved in the reconsolidation of cocaine-associated memories. Recent work has shown that presentation of novel information during memory retrieval may render a drug-associated memory vulnerable to disruption in the presence of amnestic agents. Unpublished data from our lab showed that novel memory retrieval in combination with enzymatic disruption of perineuronal nets (PNNS) in the mPFC reduced cue-induced reinstatement in cocaine self-administering rats. Ketamine has been shown to disrupt drug-associated memories and PNNs. We hypothesized that ketamine would reduce cocaine reinstatement if given during a novel memory retrieval session. 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 or given no retrieval session. Saline (control) or ketamine (6 mg/kg, i.p.) was administered 10 min pre- retrieval. In a second experiment, saline or ketamine (20 or 50 mg/kg, i.p.) was administered immediately after a VR5 retrieval. In both experiments, the following day, rats were subjected to 30 min of extinction followed immediately by 30 min cue reinstatement. In the first experiment, there was a weak trend toward a reduction of cue-induced reinstatement compared to saline treatment. In the second experiment, there was a trend ($p < 0.07$) at reducing cue-induced reinstatement with a 20mg/kg dose, but no change with the higher, 50mg/kg dose. This suggests that administering a higher dose might promote the expression of the original memory, and that ketamine has potential to reduce drug-seeking behavior, but might require different temporal parameters to successfully reduce drug-seeking behavior.

Funding support: Washington State University Alcohol and Drug Abuse Research Program (ADARP); NIH DA 040965; and the Good Samaritan Foundation of Legacy Health.

Psychedelics impact active sampling and odor perception in freely-moving mice

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Olfactory hallucinations occur in many disorders, including Parkinson's disease, epilepsy, schizophrenia, and migraines, but the mechanisms underlying these hallucinations are unknown. Mechanistic studies of hallucination in animal models are fundamentally limited, since animals do not verbalize what they perceive. However, in lieu of a verbal report, internal states can be inferred from an animal's externally observable behavior. Using computational tools, our lab has shown that a mouse's perceptual states can be inferred from close analysis of strategic sniffing behavior. We have found that injection of the psychedelic DOI alters the rhythmic structure of sniffing behavior and the accuracy of odor report. In ongoing work, we are investigating how DOI impacts population dynamics in the olfactory bulb. This work will provide fresh insights into the link between active sampling, olfaction, and psychedelics.

Promoting Neuroscience Among Youth: The Oregon Youth Neuroscience Conferences

TARA SUBRAMANIAM

Lincoln High School, Portland, Oregon

Neuroscience is a field applicable to the lives of all students, regardless of their intended field. However, there is little awareness of the vast possibilities in the neuroscience field among youth. In Oregon middle and high schools, the incorporation of neuroscience into school curricula is a rarity. Additionally, it is difficult for young students to hear from neuroscientists to gain deeper insights of the field (Myslinski, 2022).

This paper details the process of creating the Oregon Youth Neuroscience Conferences—a program for students, led by students—to broaden access to neuroscience education among local middle and high schools. For each conference, a theme was set that would be compelling to youth, such as “Neurotechnology” and “The Brain and Aging”. Then, conferences were held at local high schools, where the venues were free. Professors in fields related to each theme from the University of Oregon and Oregon Health and Science University were invited to present about the background of their specialized field, career path, and research. After their presentations, a Q&A session was held for students to engage with speakers. Presentation topics ranged from alcohol’s effects on the teenage brain, research on Alzheimer’s disease, and nanotechnology in neuroscience research. When it was difficult to find speakers, organizations such as the Oregon Geriatric Association and Oregon Alzheimer’s Association directed us to interested neuroscientists. After the first conference, feedback from students suggested that more interactive activities would improve the experience. When the nonprofit, NW Noggin, brought a team of volunteers with cadaver brains and neuroscience-themed art projects that students could learn brain anatomy from, student engagement drastically improved. Social media campaigns, science teachers, school newsletters, and flyers across the state publicized the event, resulting in attendees from fifteen schools. Through the program’s website, organizers could predict attendance and effective publication methods. At the end of the conference, a social session was designated for students to socialize over their shared interests. Ultimately, the conferences provided students with an insight into the excitement in the field of neuroscience, as well as their own minds.

Generating communication-deficient and -hyperactive neurons to determine effects on multicellular information networks

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Multicellular coordination in response to environmental stimuli is essential in biology, and this coordination is often achieved by a division of labor to establish leaders and followers in a cell population. This is called emergent leadership, but how a cell adopts its role and effectively exchanges information with peers is poorly understood. This project investigates these intercellular communication strategies by measuring calcium dynamics within neuronal cell monolayers responding to external ATP stimuli. Using the KTaR-1 neuronal cell line, immortalized from arcuate Kisspeptin neurons of an adult female mouse, we employed CRISPR plasmid systems to generate communication-deficient and -hyperactive cells in which specific gap junction proteins are knocked down or overexpressed, respectively. In a previous publication, we revealed that cells orient themselves into decentralized and stationary networks where gap junctional communication dominates. Network connectivity is externally regulated by the temporal profile and internally regulated by intracellular communication. In the current study, we utilized a novel micropatterning technique to modify intercellular communication by altering cell monolayer shape, limiting gap junction-mediated communication via a spatially confined topology. This micropatterning allows us to control intercellular communication more precisely to investigate the contribution of electrical coupling in synchronization. We calculated cross-correlation and deviation scores between cellular node pairs. In unaltered KTaR-1 cells, ATP stimulation consisting of shorter 40s periods led to increased synchronization with increases in edge probability. In contrast, long 200s periods of ATP stimulation accompanying increases in edge probability resulted in decreases in synchronization. We were able to recapitulate low edge probability environments by co-culturing Cx43-knockdown KTaR-1 subcloned cells with unaltered KTaR-1, mimicking the results of our micropatterning experiments. Lastly, Cx43-overexpressing cells were compared with Cx43-KD cells in further ATP stimulation experiments, revealing synchronization increases in Ca2+ signal in comparison to knockdown KTaR-1 neurons. Together, these results provide insight into the contribution of electrical coupling in neuronal synchronization among homogenous neurons, and provide a framework on which to explore how other contemporaneous intercellular signaling pathways may impact cell synchronization.

Characterization of novel immortalized KNDy neurons derived from ovine hypothalamus

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Reproduction requires the proper function of the hypothalamic-pituitary-gonadal axis (HPG), which has been well-modeled in mice, but often underexplored in other mammalian species, particularly seasonal breeders. To investigate molecular regulation of neuroendocrine components of the HPG axis, our laboratory previously generated immortalized neuronal models of murine kisspeptin (Kiss-1) neurons *in vitro*, possessing many characteristics of Kiss-1 neurons in female mice *in vivo*. We have continued this work by generating immortalized ovine kisspeptin/neurokinin/dynorphin (KNDy) neurons from a fetal sheep brain using similar T antigen lentiviral infection strategies. Using standard RT-PCR and real-time qPCR to probe cDNAs derived from isolated RNA, we found these cell lines (oMBH) express *kiss1*, *tac3*, and *pdyn*, as well as the receptors *tacr3* and *opkr1*, and steroid hormone receptors *esr1* (estrogen receptor α), *esr2* (estrogen receptor β), and *pgr* (progesterone receptor), similar to that observed in mouse lines. Additionally, inhibition of *tac3* and *kiss1* expression was observed in these cells following exposure to estradiol (E2), retaining functionality observed in the *in vivo* KNDy population. Increasing E2 concentrations repressed *kiss1*/*tac3* up to 75 pM, after which no further inhibition was observed. In contrast, progesterone (P4) treatment stimulated *kiss1* expression at 40nM doses. Recapitulation of estrous cycle E2 and P4 levels at a dose range of 5pM to 100pM E2 in combination with 4 to 40 uM P4 reveals maximal *kiss1* expression in the proestrus and estrus phases, with minimal expression in diestrus and metestrus.

Unlike murine lines, these cells can provide insight into regulation of seasonal breeding, in which day-length cues modulate KNDy peptide expression and hormone release. Recent studies from others implicate thyroid hormone (T3), locally synthesized by tanycytes proximal to the pars tuberalis, in communicating the melatonin day length signal to the reproductive axis via KNDy neurons. oMBH neurons express high levels of thyroid hormone receptor alpha (*thra*), and triiodothyronine (T3) repressed *kiss1* expression at a dose range of 20 to 100 nM, supporting the hypothesis that T3 acts as a long-day signal to repress the reproductive axis in short-day breeders (sheep) at the level of hypothalamic KNDy neurons. These results suggest that our model ovine neurons can be used in future research into how seasonal circannual timing mechanisms interact with the neuroendocrine control of reproduction.

Exosomes isolated from conditioned media of immortalized kisspeptin neurons exert diverse effects on immortalized GnRH neurons *in vitro*.

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Pubertal progression and fertility require full functionality of multiple reproductive axis components, including the neuroendocrine hormones kisspeptin (KP) and gonadotropin-releasing hormone (GnRH). Sex steroid-sensitive Kiss-1 neurons, which release KP to stimulate GnRH secretion, are found in two populations in the female brain. The arcuate nuclei house multiphenotypic KP/neurokinin/dynorphin (KNDy) neurons, which regulate baseline GnRH pulse secretion and are responsive to estrogen (E2) negative feedback, while Kiss-1 neurons in the AVPV region mediate E2 positive feedback required for GnRH preovulatory surges. While direct KP-GnRH connections have been established, non-canonical communication among these neuronal populations is underexplored. Previous work in our lab characterized exosome-like extracellular vesicles (EVs) released *in vitro* from immortalized (KP) cell lines KTaR-1 (derived from ARC KNDy neurons) and KTaV-3 (derived from AVPV). Isolation of EVs from conditioned media was done via ultracentrifugation or ExoEasy filtration kit and validated using a NanoCyte. LCMS-MS analysis revealed abundant exosomal cargo proteins which vary depending on E2 exposure. Since many KP exosomal proteins regulated by E2 included candidates implicated in regulation of synaptic plasticity (i.e. connexins, SNARE complex proteins, etc.), we investigated changes in gene expression and protein abundance of several plasticity-associated factors in immortalized GnRH neurons (GT1-7 cells) exposed to purified KP-derived EVs. Notably, while GT1-7 cells do not express detectable amounts of the ATP-sensitive Cx43 hemichannels, EVs from E2-treated KTaR-1 neurons induced Cx43 (*gja1*) expression in GT1-7 cells, confirmed via western blot analysis. No changes in levels of the gap junction protein Cx26 (*gjb2*) were observed following EV exposure. Additionally, we are currently probing GnRH neurons for EV-induced changes in other proteins involved in synaptic plasticity and neuronal activation (*dlg4*, *syn1*), as well as *kiss1r.* Preliminary results using RT-PCR and real-time qPCR demonstrate the capacity of KP neurons to signal to GnRH neurons via exosomes in an E2-dependent manner, to perhaps alter downstream responsiveness to Kiss-1 release as part of a priming mechanism within positive and negative feedback loops.

An *ex vivo* mouse brain slice model to study acute cerebral vasoactivity of *Centella asiatica* water extract

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Scientific evidence has supported 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. Understanding 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 of benefit of *C. asiatica* is through an acute effect on the tone of cerebral small vessels, which could support cognition by increasing blood flow. A mixture of triterpenes from *Centella asiatica* has been shown to improve peripheral microcirculation, but its effects on central vessels have not been reported. A protocol was designed to assess whether a *C. asiatica* water extract (CAW) exhibits acute vasodilatory effects when applied to *ex vivo* mouse brain slices. 300 µm thick coronal brain slices were prepared from young adult C57BL/6J mice and stored in oxygenated artificial cerebrospinal fluid (aCSF). Then the brain slices were imaged using differential interference contrast optics while continuously superfusing with oxygenated aCSF. Capillaries were identified and imaged for a 2.5 min baseline period. Then the capillary was pre-constricted by applying 200 nM U46619, a vasoconstrictive thromboxane A2 analog, in the aCSF, which is necessary to match physiological vessel tone. After preconstriction, CAW was added to the bath for 20 minutes. Vessel response was quantified as the maximum change in diameter after CAW application, normalized to the pre-U46619 baseline. The investigation began with a concentration of 100 µg/ml CAW. As expected, capillaries pre-constricted to the application of 200 nM U46619, demonstrating the capacity for vasoactivity in the vessels in slices. However, evidence was not found in support of significant dilation from CAW at 100 µg/ml. Research into the acute effects of varying doses of CAW is ongoing. CAW at 100 µg/ml failed to elicit a direct, acute vasodilatory effect on cerebral small vessels in mouse brain slices. Further studies are underway to assess the effects of alternative dosages of CAW and combinations of its isolated triterpenes and other molecular constituents. CAW compounds may require activation by biotransformation *in vivo*, which would not be detected in these experiments. CAW has been shown to combat oxidative stress *in vivo*. Future research will investigate whether pretreatment of mice with CAW increases resilience to vasoconstriction by decreasing oxidative stress.

Meeting Keynote Lecture

Psychedelic Neuroscience in Context: Learning to Listen to the Concerns of Communities

Brian T. Anderson, M.D.
Assistant Professor, Psychiatry, University of California, San Francisco

Brian Anderson, MD MSc, is a psychiatrist in the Psychiatric Emergency Services at Zuckerberg San Francisco General Hospital, and an Assistant Clinical Professor in the UCSF Department of Psychiatry and Behavioral Sciences. He is affiliated with the UC Berkeley Center for the Science of Psychedelics and UCSF Neuroscape. His research includes clinical trials as well as quantitative and qualitative observational methods to assess the safety, clinical implementation, and regulation of the uses of controlled substances (such as psychedelics) and their related health outcomes.

ABTRACT:
In this talk, I will review examples of how biomedical research has over the years been conducted in collaboration with communities of people who use psychedelics. Advantages and limitations of such community-engaged research are discussed. We then consider current opportunities to partner with such communities for research, examining scientific methods and practices that can advance science while securing the support of the community.

Speaker Session I

A scientist walks into a bar… tactics for communicating the value of neuroscience to a public audience

Larry S. Sherman, Ph.D.

Oregon National Primate Research Center and Oregon Health & Science University

In our modern world, it is common to hear from people that do not believe in science, or who deny science for many different reasons. From climate science denial to vaccine misinformation, science denial can have severe impacts on our society and planet. In this update from his 2018 TEDx talk, Dr Sherman explores the history and patterns of this disbelief, giving credit to the scientists, where it is due, and discussing ways that science communication could help overcome these challenges.

No Brain? No Problem! Understanding Neural Regeneration Using Freshwater Planarians

Bret Pearson, Ph.D.
Associate Professor, Pediatrics, OHSU

Bret Pearson has been studying how stem cells make their cellular lineages for over 20 years. He trained for his PhD with Dr. Chris Doe at the University of Oregon where he worked on how neural stem cells in the developing fly embryonic nerve cord can give rise to different progeny on consecutive divisions (multipotency). As a postdoctoral fellow with Dr. Alejandro Sánchez-Alvarado at the University of Utah, he switched from *Drosophila* to a non-traditional model system: the freshwater planarian. Dr. Pearson was interested in following up his neurobiology and stem cell work from flies in a system that can be used to study gene function and stem cells in adult animals i*n vivo*. He was interested in defining the pathways that planarians use to generate new neurons in the uninjured brain as well as during whole-brain regeneration.

In 2010, Dr. Pearson started his own lab at the Hospital for Sick Children/University of Toronto using planarians to understand conservation of mechanisms of stemness and pathways of adult neurogenesis and regeneration. However, he was recently recruited back to the US in the fall of 2021 to Oregon Health & Science University (OHSU) in the Department of Pediatric Neuro-oncology. He is continuing his work to identify the neural stem cells and pathways of neurogenesis in planarians during both homeostasis and regeneration, and continues to take unique approaches to long-standing unknowns in neural cancer stem cells and neural regeneration.

ABTRACT:
Loss of central nervous system tissue due to acute injury or disease in humans is usually irreparable, resulting in life-long disability for individuals and associated annual health care costs in the billions of dollars. Interestingly, the freshwater planarian (a flatworm), can regenerate from virtually any injury, including decapitation, and has the ability to remake an entire new brain and functionally reintegrate the new and old tissues – all in the span of a week. All planarian regeneration is reliant on a large population of adult stem cells (ASCs) within the body of the animal and our long-term goal is to understand how the ASCs can be coordinated to regenerate a functional nervous system. Here I will describe how we take single-cell genomic approach combined with gene-function analyses to understand the changes in cell state that allow stem cells to enter a neurogenic program. We find that the *aristaless-like homeobox 3* (*alx-3*) transcription factor is required for neuronal turnover in the uninjured brain and is induced in stem cells upon injury where it is required for head regeneration. In total, *alx-3* is a rare factor that has roles in neurogenesis as well as integrating injury responses and patterning pathways to achieve successful head regeneration.

Role of retrograde neurotrophic factor signaling during mechanosensory circuit formation

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During development, neurons wire into functional circuits by extending projections from their cell body toward their targets. In many cases, this process is mediated by neurotrophic signaling. Target-derived neurotrophic factors bind receptors on terminals of extending axonal projections. Activated receptors are internalized and retrogradely transported to the soma where they initiate a transcriptional program required for neuronal survival, axon extension and circuit formation. Despite being essential for nervous system development, the nature of the transcriptional response induced by retrograde neurotrophic signaling and how it influences neuronal development and circuit formation remain largely unknown. I use posterior lateral line (pLL) mechanosensory neurons in zebrafish to investigate this transcriptional response. pLL neurons express the neurotrophic factor receptor Ret and their target cells express Ret ligand Gdnf. To identify genes that are regulated by retrograde Ret signaling, I compared transcriptomes of pLL neurons with disrupted retrograde Ret signaling to wildtype. One differentially expressed gene, *adarb1a*, is downregulated in *ret*mutant pLL neurons. It is an adenosine to inosine (A-to-I) RNA editor and edits at least 20 genes critical for nervous system development. I have preliminary evidence that A-to-I editing is reduced in zebrafish with disrupted retrograde Ret signaling. I am therefore in the process of validating a sequencing method that couples long read sequencing with traditional scRNA-seq to determine differential editing of Adarb1a target genes in *ret*mutant pLL neurons. As many targets of A-to-I editing in pLL neurons regulate Ca^{2+} signaling, I investigated Ca^{2+} dynamics in post-synaptic pLL neurons. Disruption of Ret signaling increases calcium responses in pLL neurons normally expressing *ret*, indicating that retrograde Ret signaling modulates sensory nervous system development and circuit formation. A potential mechanism for this Ret-controlled modulation of circuit formation is through modulation of A-to-I editing by Adarb1a. This work is supported by NIH 5R01NS111419.

Using Whole-Cell Patch Clamp to Characterize Immortalized Hypothalamic Kisspeptin Neurons In Vitro

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Reproduction in female mammals requires temporal coordination of signals within the hypothalamic-pituitary-gonadal axis, in which both negative and positive feedback loops are integrated into select neuronal centers. Neurons expressing Kisspeptin (Kiss-1) are critical mediators of reproductive patency and pubertal progression. Females possess two distinct Kiss-1 neuronal populations, which respond differently to feedback from circulating sex steroids. Kiss-1 neurons from the ARC down-regulate menstruation when estrogen (E2) levels are high. Alternatively, Kiss-1 neurons residing in the AVPV participate in a positive feedback loop when stimulated by E2. Mechanisms underlying how steroid hormones influence gene expression and neuronal activity throughout reproductive cycles are incompletely characterized, due in part to the difficulty of studying these dynamic phenomena in vivo. Dr. Chappell's laboratory previously immortalized Kiss-1 expressing cells from the arcuate (ARC) and AVPV hypothalamic regions of a female mouse and has explored steroid-influenced expression patterns of multiple genes. Since E2 has previously been shown to modulate neuronal activity in vivo, we can use these cell lines to more precisely describe the impact of E2 on cellular function; however, baseline activity properties of these cells must be established first. Here, we conducted an electrophysiological characterization of one of these cell lines. Using whole-cell patch clamp electrophysiology, we have assessed intrinsic electrical properties and excitability. We report measures including whole-cell capacitance and resistance, and current-voltage relationships while holding the cells at a range of voltages. We determine that the cell line displays little intrinsic excitability, suggesting it may correspond to the "silent" arcuate Kiss-1 neuron type, or that immortalization may have suppressed its electrical function. We have begun pharmacological manipulation based on known in-vitro gene expression profiles and qPCR investigations of the cell line to further assess the identity and function of these cells. Future experiments will combine electrophysiology, pharmacology, and gene expression studies to explore pathways through which sex steroids may drive changes in gene expression, neuron activity, and circuit activity.

Poster Session II

Sharing interdisciplinary neuroscience paywall-free at SfN

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Nonprofit NW Noggin (nwnoggin.org) organizes collaboration and community around interdisciplinary neuroscience. Undergraduates, graduate students and artists inspired by brain research join us in public schools, correctional facilities, houseless youth centers and more to hear what people already know and want to know, and to see where lab and classroom discoveries can contribute. We've met over 60,000 people since 2012!

The last time we traveled to San Diego for the Society for Neuroscience conference, we gave the 2018 keynote address on brain awareness, and joined a panel on outreach. Representatives of resource-rich institutions described well-staffed offices, paywalled conferences, expert-judged Brain Bees and annual Brain Fairs. In contrast, we introduced over 70 all-volunteer, paywall-free visits we'd made to community spaces that don't often get exposure to neuroscience, bringing specimens and art projects, and centering the questions, stories, knowledge and interests of those we met. We invited everyone to join us in K-12 classrooms, where we'd arranged with San Diego Unified staff and teachers for two days of direct public engagement over neuroscience and art!

We are fascinated by the money spent by government and private foundations aimed at increasing diversity, equity, inclusion and interdisciplinary approaches to "brain awareness" in education and research, much of which flows to the same universities, private schools and institutions receiving funding in the past. That is not our approach, so while we miss big structurally segregated dollars, we enjoy the privilege of going places and hearing directly from those not currently overrepresented in neuroscience, both inspiring and being inspired by questions, insights and art.

During the 2022 Society for Neuroscience conference in San Diego, we not only presented original posters, caught up with colleagues and walked the cavernous convention halls, but also joyously re-connected with district staff and teachers, organizing two additional days of engagement in public schools! We met with over 500 students at Webster and Freese elementary, examined brains we'd driven 1000 miles from Portland, Oregon, discussed new research and made art. We also met with people passing by The Brain Observatory, a striking local laboratory and exhibition space founded by Dr. Jacobo Annese, who dissected the brain of amnesia Patient H.M.

Building awareness of discoveries, educational options and careers through outreach engaging those not served by institutional "brain awareness" funding trains scientists to collaborate, reaches more people, and increases public support for investment in research and art.

The rhesus macaque as an experimental model for human aging and Alzheimer's disease pathology

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Amyloid beta (Aβ) plaques and phosphorylated Tau protein (pTau) are well-established hallmarks of Alzheimer's disease (AD) pathology in the brain. However, progress in identifying the underlying cause of these pathological changes has been hampered by the lack of appropriate animal models for experimentation. Therefore, in the present study we used old rhesus macaque monkeys to test whether estradiol hormone replacement therapy (HRT) could delay development of Aβ and pTau in the amygdala. Like women, adult female rhesus macaques show ~28-day menstrual cycles and eventually undergo menopause with similar neuroendocrine changes; and so represent an ideal translational animal model. In our study immunohistochemistry was performed on amygdala sections from animals aged 20-29 years of age, using specific antibodies against Aβ (4G8) and pTau (AT8). Approximately half of the animals were subjected to 2-4 years of HRT, while the remained served as untreated controls. Aβ plaque density was especially pronounced in ovariectomized controls but not in the age-matched HRT animals. In contrast to Aβ, only one animal showed pTau expression in the amygdala, which agrees with previous reports of pTau expression being observed much later in life than Aβ. Interestingly, this animal was the same one that showed the highest density of Aβ plaques, suggesting a possible causal relationship between these two pathological markers. Taken together, the results establish the rhesus macaque as an incomplete model for AD but with significant translation potential. Specifically, the results suggest that estradiol supplementation may significantly delay or block AB plaque deposition in postmenopausal women, which in turn could delay the progression of AD.

Mutations in the SWI/SNF chromatin remodeling factor *SMARCB1* gene induce pain

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Schwannomatosis patients typically present with intractable pain. A significant proportion of patients with schwannomatosis have mutations in the *SMARCB1* gene (also called INI1, BAF47 and SNF5). We found that inducible conditional disruption of the *Smarcb1* gene in mouse Schwann cells causes increased sensitivity to capsaicin. Dorsal root ganglion (DRG) neurons from mice with Schwann cell-targeted disruption of *Smarcb1* express elevated levels of TRPV1, a non-selective cation channel that can be activated by a number of noxious stimuli including capsaicin. We also find that TRPA1, an ion channel that acts as a sensor for environmental irritants, is elevated in the DRG and trigeminal neurons of these mice. Wild type DRG cells grown in *Smarcb1*-null Schwann cell conditioned media or conditioned media from schwannoma cells derived from schwannomatosis patients with *SMARCB1* mutations expressed elevated levels of TRPV1, TRPA1 and CGRP as indicated by immunocytochemistry. Proteomic analysis demonstrated that the secretome of *Smarcb1*-mutant Schwann cells is distinct from wild type Schwann cells and includes elevated levels of cytokines and chemokines that have been implicated in pain. *Smarcb1* interacts with the promoters of these genes and directly represses their transcription. Furthermore, agents that block at least some of these proteins can reverse the induction of TRPV1 in DRG cells treated with *SmarcB1*-mutant Schwann cell conditioned media and reduce pain responses to conditioned media in mice. Collectively, these data indicate that loss of *Smarcb1* in Schwann cells leads to the increased transcription of factors that induce the expression of pain mediators in sensory neurons, and suggest a mechanism for schwannomatosis pain in patients with *SMARCB1* mutations.

Single-cell sequencing of *Drosophila melanogaster* human tauopathy model

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Frontotemporal dementia (FTD) is a neurodegenerative disease associated with mutations in the microtubule binding protein Tau. The clinical presentation of FTD is heterogeneous with patients exhibiting parkinsonism, dementia, atrophy in the temporal lobes, and personality changes. Current treatments can mitigate aspects of the behavioral changes associated with FTD, however, no therapies are available to slow the progression. Since patient sample procurement is restricted to post-mortem tissue, our understanding of the progression and underlying pathogenic mechanisms of this disease is limited. Recent work in model systems and post-mortem tissue has shown that expression of FTD-associated mutant Tau may lead to epigenetic modifications that alter gene expression. In our lab, we model FTD using *Drosophila*, which allows us to conduct longitudinal studies to observe FTD progression throughout the adult lifespan. The adult *Drosophila* expressing FTD-associated mutant human Tau (hTau) have age-dependent neurodegenerative vacuoles, axonal changes, locomotion defects, impaired memory and disrupted sleep while flies expressing normal hTau did not. This confirms that our models show pathogenic phenotypes associated with Tauopathies and it provides the basis to now use these models to identify molecular mechanisms of pathogenicity. We also found changes in a chromatin associated protein, Heterochromatin Protein 1 and hypothesized that FTD mutant Tau could alter chromatin accessibility. We used single-cell sequencing techniques to probe chromatin accessibility and gene expression to assess human Tau FTD mutations in the young and aged adult *Drosophila* brain. Comparing our wildtype hTau insertion line to the FTD mutants revealed differentially accessible regions in both neuronal and glial cell populations. To validate our findings, we are creating double transgenic flies with the $hTau^{KI}$ mutation and our candidate genes, which show altered chromatin accessibility and gene expression compared to wildtype hTau. We are screening these flies for disease-related behavioral phenotypes of decreased locomotion and sleep fragmentation with aging.

Age-related Regulation of Aquaporin-1 in Prefrontal Cortex and Hippocampus of Old and Oldest-old Rhesus Macaques

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Aquaporins enable the flow of water across cell membranes, and are required for brain cerebrospinal fluid production and water homeostasis. Aquaporin-1 (AQP1) is found in astrocytes of the primate brain, but levels increase in human neuropathology, such as Alzheimer's disease (AD). Limited research has been conducted on AQP1 regulation during normative human aging, and no studies have characterized AQP1 in old non-human primate brains. Rhesus macaques are an ideal translational model of normative brain aging, with long lifespans and a complex gyrencephalic brain. Rhesus brains don't develop advanced AD pathology, with no significant neuronal loss over time, but do show increased astrogliosis with age. The goal of this work is to assess changes in AQP1 expression in old and oldest-old rhesus brains. For this study, postmortem fixed brain tissue was obtained from 36 animals (female and male, aged 22 to 44 years) that had been involved in a longitudinal caloric restriction (CR) study conducted by the National Institute of Aging. Frozen brain sections of 30-µm thickness were treated for antigen retrieval, then immunologically stained for AQP1 (Proteintech, Rosemont, IL) using the ABC-DAB method. Percent area coverage and stain intensity of AQP1 in temporal and prefrontal cortex sub-regions were evaluated for effects of age, sex, and diet (+/- CR) using ImageJ free-ware. As expected, AQP1 staining labeled the choroid plexus, glial limitans, and fibrous astrocytes throughout all white matter. In addition, AQP1 immuno-labeling revealed a variety of astrocyte phenotypes in the cortical grey matter. Quantitation of the percent area coverage AQP1 in temporal sub-regions was unaffected by age, whereas the stain intensity increased in the hippocampus proper ($p=0.016$). In the prefrontal cortex, four sub-regions showed an increase in both AQP1 area and intensity with age ($p<0.05$). In the frontal lobe, the anterior cingulate and straight gyrus of the medial frontal cortex had the most AQP1 compared with other cortical areas. No effects of sex or diet on AQP1 expression were detected in this analysis. Further efforts can confirm astrocytic expression of AQP1 through double-label immuno-fluorescence staining, and look for association with late-appearing amyloid. Future work is needed to determine the causes of regional differences in AQP1 expression with age and whether regulation is a compensatory mechanism or an aberrant response to brain aging.

Loss of NRF2 Worsens Pathological Outcomes in Alzheimer's Disease Mouse Models

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Keywords: Alzheimer's disease, antioxidant, beta-amyloid, tau

Background
Decreased antioxidant capacity and increased markers of oxidative stress are evident in the blood and brains of Alzheimer's disease (AD) patients. Rodent models of AD have likewise demonstrated a correlation between antioxidant capacity and memory. The transcription factor NRF2 (nuclear factor erythroid-derived 2) regulates the endogenous antioxidant response pathway. Activation of NRF2 has been shown to attenuate mitochondrial dysfunction, prevent cytotoxicity, and improve cognitive functions in mouse models of AD. Here we evaluate the effect of loss of NRF2 on AD pathology in the 5XFAD mouse model of β-amyloid (Aβ) accumulation and the PS19 mouse model of tauopathy.

Methods
NRF2 knockout (NRF2KO) mice were crossbred with 5xFAD and PS19 mice to generate the 5xFAD-NRF2KO and PS19-NRF2KO offspring. At six-months of age, brains were harvested and stained immunohistochemically for Aβ or phosphorylated tau (pTau).

Results
Loss of NRF2 resulted in increased Aβ plaque burden in both the hippocampus and cortex, relative to the 5xFAD mice that did express NRF2. Similarly, pTau was also increased in PS19-NRF2KO mice in both brain regions relative to the NRF2 expressing PS19 mice, although in female mice this increase did not reach significance in the cortex.

Conclusions
This data indicates that the loss of NRF2 exacerbates AD pathology. While further studies are needed to confirm these findings in a larger cohort, these results suggest that NRF2 may be involved in limiting AD pathology and thus may be an effective therapeutic target.

Investigation of Infectious Theory of Alzheimer's Disease using HSV-1 in a 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 (Aβ) plaques, and hyperphosphorylated tau proteins. It has been traditionally believed that the Aβ plaques form first, then phosphorylation of tau which leads to neurodegeneration. 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 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 Aβ 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 Aβ plaques in these regions, it did not reach significance. Cytokines (TNFα and IL-1β) 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. However, an expanded study is necessary to determine whether these are related to changes in Aβ plaques.

Gardenin A decreases neuroinflammation, activates antioxidant response and improves cognitive and motor function in A53T alpha synuclein overexpressing mice

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Background:
Oxidative stress and neuroinflammation are widespread in the Parkinson's disease (PD) brain and contribute to the synaptic degradation and dopaminergic cell loss that result in cognitive impairment and motor dysfunction. The metabolite Gardenin A (GA) has been shown to activate the NRF2-regulated antioxidant pathway and inhibit the NFkB-regulated pro-inflammatory pathway in a *Drosophila* model of PD. Here, we evaluate the effects of GA on A53T alpha-synuclein overexpressing (A53TSyn) mice.

Methods:
A53TSyn mice were treated orally for 4 weeks with 0, 25, or 100 mg/kg GA. In the fourth week, mice underwent behavioral testing and tissue was harvested for immunohistochemical analysis of tyrosine hydroxylase (TH) and phosphorylated alpha synuclein (pSyn) expression, and quantification of synaptic, antioxidant and inflammatory gene expression. Results were compared to vehicle-treated C57BL6 mice.

Results:
Treatment with 100mg/kg GA improved associative memory and decreased abnormalities in mobility and gait in A53TSyn mice. GA treatment also reduced cortical and hippocampal levels of pSyn and attenuated the reduction in TH expression in the striatum. Additionally, GA increased cortical expression of NRF2 regulated antioxidant genes and decreased expression of NFkB regulated pro-inflammatory genes. GA was also readily detectable in the brains of treated mice.

Conclusions:
GA significantly improved cognitive deficits and motor dysfunction, and attenuated several pathological features in the brains of alpha-synuclein overexpressing mice. While these results are promising, future studies are needed to confirm these effects in other PD models, optimizing dosing and to more fully elucidate the mechanism of action of GA.

The CD74 inhibitor DRhQ improves cognition and mitochondrial function and reduces neuroinflammation in 5xFAD mouse model of Aβ accumulation

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Neuroinflammation and mitochondrial dysfunction are early events in Alzheimer's disease (AD) and contribute to neurodegeneration and cognitive impairment. The CD74-MIF (macrophage migration inhibitory factor) axis is a mediator of the neuroinflammatory response. DRhQ competitively inhibits MIF-CD74 binding and elicits beneficial effects in other neurodegenerative disease models. Here we evaluate its effects in β-amyloid (Aβ) overexpressing mice. 5xFAD mice and their wild type littermates were treated with DRhQ (100 µg) or vehicle for 4 weeks. In the fourth week, mice underwent cognitive testing and Aβ pathology, microglial activation, mitochondrial function and expression of mitochondrial and inflammatory markers was analyzed. DRhQ improved recognition memory, reduced Aβ plaque burden and microglial activation and attenuated mitochondrial dysfunction in the brains of female 5xFAD mice. Similar, but non-significant, effects were observed in male 5xFAD mice treated with DRhQ. No differences in the cortical expression of mitochondrial or inflammatory genes were seen with DRhQ treatment.These data suggest that DRhQ is beneficial in female 5xFAD mice. Future studies are needed to elucidate the reason for this possible sex-dependent response as well as to optimize the dose, and timing of DRhQ treatment and gain a better understanding of its mechanism of action.

Effects of the Intra-Uterine Environment on the number of Tyrosine Hydroxylase-Positive Neurons in the Ventral Tegmental Area and Substantia Nigra of Fetal Sheep

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Evidence suggests that differences in the number of dopaminergic neurons may be established prior to birth and could contribute to sex biases in adult behaviors. Studies in sheep indicate that injections of testosterone (T) into pregnant ewes significantly alters the number of tyrosine hydroxylase positive (TH+) neurons in the brains of developing fetuses (Brown et al., 2015).

Here, using a sheep model, we assess whether the brains of female fetuses may be altered by sharing the intra-uterine environment with a male fetus. Twelve fetal sheep were delivered by cesarean section on day 133-136 of gestation. Brains were sectioned and immunohistochemistry was used to visualize TH, the rate limiting enzyme for dopamine synthesis, in the ventral tegmental area (VTA) and substantia nigra (SN). TH+ cells were counted by researchers blinded to the four groups: 1) Male Singletons n = 4, 2) Female Singletons, n = 2, 3) Males in the womb with 2 Females, n = 2 and 4) Females in the womb with one Male, n = 4.

Results from two-Way ANOVAs indicate that the Female fetuses that developed in utero with a Male, exhibited 46% more TH+ cells in the VTA than the Female Singletons. Moreover, these Females that shared the womb with a Male fetus also exhibited more TH+ VTA cells than the Male Singletons and those Males that shared the intra-uterine environment with two Females. A similar pattern was found in the Substantia Nigra. The Female fetuses that were in utero with a Male exhibited 26% more TH+ cells in the SN than Female Singletons.

These findings are consistent with the notion that dopaminergic circuitry, such as the mesolimbic neurons originating in the VTA and the nigrostriatal neurons of the SN, are sensitive to intrauterine factors and that these early baseline differences between sexes might underlie some of the sex biases observed in dopamine-mediated behaviors in adulthood.

P2X7 Activation by Nitrated Hsp90 in U87 Glioblastoma Cells

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Tumors like glioblastomas are associated with oxidative stress and high levels of protein tyrosine nitration. Under these conditions, peroxynitrite causes tyrosine nitration of the molecular chaperone heat-shock protein 90-kDa (Hsp90). P2X7 is a nonselective cation channel, whose excessive activation induces macropore formation and apoptosis. Although canonically activated by high concentrations of ATP, P2X7 is also activated by nitrated Hsp90 (NO_2-Hsp90). In motor neurons, NO_2-Hsp90 mediates cell death and is elevated in conditions like amyotrophic lateral sclerosis and spinal cord injury. Contrastingly, NO_2-Hsp90 is pro-survival in cancerous cells. Nitration of Hsp90 on tyrosine 56 increases glycolysis through P2X7 activation while nitration on tyrosine 33 downregulates mitochondrial activity. This is consistent with the Warburg effect, a common tumor metabolic phenotype. Prevention of tyrosine nitration accordingly decreased survival and migration in U87 human glioblastoma cells. It is not known how activation by NO_2-Hsp90 changes P2X7 channel or pore activity. Through patch clamp electrophysiology, I will directly observe how activation by NO_2-Hsp90 affects P2X7 function in a human glioblastoma cell line (U87). Analysis of over 100 U87 cells were used to optimize cell culture conditions, health, and break-in probability by examining the impact of the density of cells, days *in vitro*, electrode size, and cell size, as well as strategies for approaching and breaking into the cells. P2X7 agonists and antagonists will confirm the presence of P2X7 in our U87s. Then, Hsp90 or NO_2-Hsp90 will be added to the intracellular solution, along with extracellular P2X7 agonist. Incremental voltage-clamp steps from -160 to +80 mV will measure the movement of ions across the cell membrane. I will use those recordings to determine how NO_2-Hsp90 impacts P2X7 function to better understand its role in glioma pathophysiology.

Speaker Session II

Impacts on Cognitive Aging

Kathy Magnusson, Ph.D.
Professor, Biomedical Sciences, Oregon State University

Kathy Magnusson received a D.V.M. degree from the University of Minnesota College of Veterinary Medicine in 1982 and pursued a Ph.D. in Veterinary Anatomy/Neuroscience, which she earned in 1989. Following her Ph.D., she has taught and done research at Colorado State University and the WWAMI Medical Program at University of Idaho. She is currently a Professor in the Department of Biomedical Sciences, Carlson College of Veterinary Medicine and a Principal Investigator in the Linus Pauling Institute at Oregon State University. She has 55 peer reviewed publications and 3 reviews and chapters, which are specifically on the aging brain. She has been funded by NIH for a majority of her research career, including several Career Development awards. The primary research focus in the Magnusson lab is designed to understand the effects of aging on cognition in humans and rodents, including learning, memory and cognitive flexibility.

ABSTRACT:
Much of our current knowledge of aging involves veterans of major wars and most of what we know about cognitive aging in veterans involves either generalized or single function tests or veterans with health or neurological disorders. The current study aimed to examine prior military service within the context of an aging study involving generally healthy individuals to address impacts on normal cognitive aging. Another goal was to expand the functional assays for our virtual Morris water maze (vMWM) to include cognitive flexibility (reversal) and working memory (delayed match-to-place (DMP) tasks and to compare the functionality our VMWM tasks to already established cognitive tests. Forty-six young and old male and female humans were tested with NIH Toolbox (NIH-TB) Cognitive Battery, Wechsler Memory Scale (WMS) Logical Memory I and II, and vMWM tasks. Significant age-related deficits were seen on a wide array of NIH-TB fluid cognition tasks and vMWM tasks. Age x gender interactions were also seen in crystallized cognition and logical memory tasks. The vMWM learning trials in which participants had knowledge of stability of platform location correlated with NIH-TB tasks of memory, cognitive flexibility and pattern comparison when all participants were considered. The DMP and reversal trials both showed relationships to flexibility and pattern comparison tasks, but DMP trials also showed a relationship to NIH-TB list sorting working memory task. This suggests that the vMWM tasks were recruiting cognitive abilities for which they were designed. Despite these relationships, the vMWM tasks were more sensitive to prior military service than the NIH Toolbox tasks, specifically with respect to the assessment of cognitive flexibility and working memory. Compared with male non-veterans of comparable age and/or younger; older male veterans exhibited significant deficits in spatial learning, cognitive flexibility, and/or working memory on vMWM tasks we designed to measure these cognitive functions. Overall, this study is novel for highlighting prior military service as a “hidden” variable that requires attending to when investigating normal biological declines of cognitive functions. As such, we recommend the inclusion of prior military service in future studies of cognitive aging.

Early Changes in N-Methyl-D-Aspartate Receptor Subunits in the Development of the 5xFAD Alzheimer's Mouse Model

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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 0.5-4 months of age, which could lead to alterations in memory. The 5xFAD mouse model has five mutations that are linked to familial (inherited) AD. We hypothesized that early changes in NMDAR synaptic responses in 5xFAD mutants are related to alterations in NMDAR protein expression. Based on our electrophysiological data that suggested changes in NMDAR function occur during development, we used brains obtained from a variety of ages (1-2 days and 0.5. 1, 2, 3, and 4 months) of wildtype and 5xFAD heterozygous male and female mice to examine the synaptic and extrasynaptic protein expression of NMDAR subunits in the hippocampus with the use of semi-quantitative Western blots. After analyzing males and females separately, we found that 5xFAD males showed higher overall expression of GluN2B in the hippocampal synaptic region than their wildtype counterparts, while 5xFAD females showed lower overall expression of GluN2B. 1-2 day old males showed lower overall expression of GluN2B in the hippocampal crude synaptosomes. This suggests that amyloid overexpression affected NMDA receptor expression and had different effects on males and females. In addition, the effects appeared to change across early development in males.

Identifying Mechanisms of Selective Vulnerability in Alzheimer's Disease Using Spatial Transcriptomics

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Alzheimer's Disease (AD), the leading cause of dementia, has no viable treatment and little research done at the preclinical stage, which stands to be a promising window for treatment. In this study, we examined preclinical differences in hippocampus subregions using spatially-resolved transcriptomic profiling with Nanostring's GeoMx DSP. Eight one-month-old 5xFAD (C57BL/6 background) heterozygote mice and wild-type littermates had brains harvested and fresh-frozen. Cryostat sections through the dorsal hippocampus were mounted onto slides and shipped to Nanostring, Inc., where they were treated with indexing oligo-labeled cDNA probes. The expression of mRNA was measured separately within the cell body layers of the CA1, CA3, and DG hippocampal subregions of each mouse. Each subregion was analyzed for differential transcript expression and pathway differences between wild-type and 5xFAD. The extensive heterogeneity observed revealed numerous spatially-distinct transcripts and pathways dysregulated in the preclinical state and most strongly implicates mitochondrial changes in the early progression of AD.

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THE HYALURONIDASE CELL MIGRATION INDUCING AND HYALURONAN BINDING PROTEIN IS ELEVATED IN INFLAMMATORY DEMYELINATION AND INHIBITS MYELIN FORMATION

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Multiple Sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) that causes motor, sensory, and cognitive dysfunction in patients[1]. Chronic MS lesions exhibit impaired remyelination and an accumulation of oligodendrocyte progenitor cells (OPCs) that fail to differentiate into myelinating oligodendrocytes (OLs)[2]. Hyaluronic acid (HA) is a major component of the CNS extracellular matrix, and HA metabolism is often altered during disease, including in MS[3]. We found that high molecular weight (HMW) HA accumulates in demyelinating lesions in MS patients and in animal models of MS[4]. We further found that OPCs have hyaluronidase activity and that HA fragments of specific sizes (~175-300kDa) impair OPC differentiation[5]. Blocking hyaluronidase activity accelerates functional remyelination in an animal model of demyelination[6].

Here, we provide evidence that CEll Migration Inducing and hyaluronan binding Protein (CEMIP) is responsible for the production of inhibitory HA fragments during inflammatory demyelination. CEMIP is expressed by OPCs, and CEMIP expression (and not that of other hyaluronidases) is elevated in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. Elevated CEMIP expression in EAE is primarily localized to lesion sites that exhibit both demyelination and reduced HA levels. Furthermore, CEMIP hyaluronidase activity produces HA fragments in the size range previously shown to impair OPC differentiation, and these fragments inhibit *in vitro* OPC differentiation. We are currently investigating if HA fragments produced by CEMIP hyaluronidase activity delays *in vivo* functional remyelination.

We have also characterized multiple small molecule hyaluronidase inhibitors that are similar in structure to S3. We have found that each inhibitor blocks CEMIP hyaluronidase activity to a greater extent than S3 at the same concentration. Furthermore, each inhibitor rescues OPC differentiation in the presence of HMW HA. We are currently testing if one of these inhibitors, sulfuretin, can accelerate functional remyelination in an *in vivo* model of focal demyelination. Overall, our studies reveal that CEMIP expression is elevated during inflammatory demyelination at demyelinated lesions, and CEMIP hyaluronidase activity produces HA fragments in a bioactive size range that directly inhibit OPC differentiation and remyelination. These results highlight CEMIP as a therapeutic target to accelerate functional remyelination in patients with MS, and we are investigating if sulfuretin is a tractable candidate to serve this purpose.

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Speaker Session III

Increasing Access to Electrophysiology Experiments

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Whole-cell electrophysiology is a powerful technique that provides exquisitely detailed information about the function of excitable cells like neurons and muscles. These experiments involve preparing healthy, living tissue, identifying and contacting individual cells with microelectrodes sensitive enough to detect the opening and closing of individual ion channels, and combining pharmacology with manipulation of the cell's electrical state in order to probe its function. The depth and versatility of the data generated through this technique make it the gold standard for characterizing cellular electrical activity. Unfortunately, the complex logistics and expertise required to design, implement, and analyze such experiments are prohibitive for many laboratories. Oregon State University's Electrophysiology Facility has endeavored to make these techniques accessible to a broader range of research groups within and beyond our institution. We support a broad range of experimental approaches including multielectrode array and patch-clamp recordings on tissue ranging from mouse brain slices to human glioblastoma cells. Whole-cell patch-clamp electrophysiology of clonal cell lines has gained popularity, as cell lines can offer simplified preparation, lower cost, and reduced heterogeneity compared with primary tissue. However, this approach requires consideration of several crucial factors, including 1) the choice of cell line to best support scientific goals; 2) logistical concerns such as morphology and adhesion, 3) the line's proliferation and maturation profiles, and 4) design of growth and recording media. We will discuss how these factors influence the design of electrophysiological experiments, and how OSU's Electrophysiology Facility has leveraged this approach to lower barriers and increase access to this powerful technique, culminating in undergraduate researchers independently conducting electrophysiological experiments.

Neural Mapping of Sensorimotor Function in Humans

Michelle Marneweck, Ph.D.
Assistant Professor, Human Physiology and Neuroscience, University of Oregon

Originally from South Africa, **Michelle Marneweck** earned a Ph.D. at the University of Western Australia. Subsequently, she completed her postdoctoral training at Columbia University in New York, the University of California, Santa Barbara, and Monash University in Melbourne. Michelle joined the Department of Human Physiology at the University of Oregon in 2020.

ABTRACT:
How the human central nervous system combines different sources of information into a coherent understanding of the body situated in the world so a person can act is an ongoing and important topic of interest spanning developmental, clinical, translational, and basic neurosciences. Enamored by a toy, a toddler wants to grab it. A stroke survivor is asked to reach and grasp for a clinician's moving pen. A basketball player aims a free throw. A critical challenge for the motor system in executing each of these actions is extracting and integrating information from the sensorium and from previous sensorimotor experiences and transforming that information into an actionable motor plan with the effector of choice. I will focus on complementary projects in which we use multimodal methods combining fMRI, Bayesian analytic tools, and sensitive behavioral measurement to uncover how the human brain orchestrates and integrates sensory information for the execution of a skilled motor action. Our recent findings show superior parietal lobule to represent an object goal in multiple reference frames before action execution, suggesting it as a node for efficiently transforming an object goal extracted from the sensory system into an appropriate form for motor commands. In separate work, results point to the capability of the motor system to swiftly access and leverage sensory information at a functionally relevant time-point in dexterous manipulation of objects (at grasp *vs.* reach onset). Finally, I will cover some work in progress that seek to determine how the sensorimotor system changes with age, independent of degradation of basic sensory processing. How the central nervous system orchestrates sensorimotor processing for skilled action is highly relevant to work on brain-computer interfaces and other technologies that aim to restore this function in those who have lost it or to boost this function for performance optimization.

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