NeuroFutures2019 Poster Abstracts

Friday July 12th: Session 1

Poster

1. **Cell-Specific Mechanisms of CNS Disease in Leigh Syndrome**

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Background: Mitochondrial diseases affect over 1:4000 individuals (1). Leigh Syndrome (LS) is the most common pediatric form of mitochondrial disease. LS is incurable and universally fatal. Most patients are born overtly healthy, but within two years of life present with ataxia, cachexia, and disease-defining progressive, symmetric necrotizing lesions in the brainstem and cerebellum (2). The cellular and molecular pathogenesis of LS remains unknown. Leigh Syndrome is often caused by mitochondrial electron transport chain complex I (ETC CI) deficiency due to loss of subunits such as NDUFS4. The *Ndufs4(KO)* mouse model closely resembles human LS. In mice, disease onset begins at approximately postnatal day 35 (P35). After P35, KO mice begin to show neurological symptoms such as ataxia, loss of balance, and progressively lose weight (3). In addition, loss of NDUFS4 specifically in the nervous system recapitulates all aspects of LS (4). We hypothesize individual LS features are the result of ETC CI deficiency in distinct neuronal sub-populations.

Results:We are currently defining which neural cells produce individual LS phenotypes. We and others have generated cell-specific *Ndufs4(KO*) mice with *Ndufs4* deleted in only in GABAergic, cholinergic, or glutamatergic neurons (5). Our data confirm reports that glutamatergic-neuron specific (VGlut2-cre driven) loss of *Ndufs4* results in CNS lesions, overt neurological symptoms, and progressive weight loss observed in the whole body and pan-neuronal (Nestin-cre) KO mice. GABAergic (Gad2-cre driven) loss of *Ndufs4* results in only lethal seizures.

Discussion: Impaired glutamatergic neuron function appears to play a paramount role in the majority of LS features.

2. ***Dynamo: A python software toolkit for comprehensive manual and automatic analysis of dynamic neuronal morphologies across time.***

Patrick Coleman, Haas Lab, UBC

Neurons often have a complicated tree structure, and much can be learned about their processing abilities and networking by analyzing quantitative aspects of their tree morphologies. Tools exist for analyzing images of neurons and calculating these metrics for a single arbor - however we extend these to also track the changes over time. This temporal tracking is important as this gives insight into how the dynamic morphological changes are controlled by the underlying cell biology, maturation, and firing activity. Insights into the rules guiding morphology development will assist in understanding high-level network properties of the brain, but also pinpoint causes of problems in developmental wiring. Dynamo is a python application for performing this dynamic morphometrics of cells: it incorporates a number of existing tools with a new drawing interface, helping to manage both manual and automatic tracing of arbor shape, plus tracking the changes through time and analysing the results in one application. In this poster we present an overview of Dynamo, showing its usage for the drawing of arbors and calculating metrics from these, as well as examples of how it is used within our lab's research.

3. **Brain Volumetrics in Ovariectomized Aged Rhesus Macaques with and without Hormone Replacement Therapy.**
Steven Dash[1], Zheng Liu[1], Chris Kroenke[1,2], Henryk Urbanski[1,2], Mary Lou Voytko[3], Steven Kohama[1]. .
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Studies of the effect of hormone therapy (HT) on cognitive function in post-menopausal women have been equivocal; however in some studies HT was initiated long after onset of menopause. There is some question as to whether or not there is a "window of opportunity" for HT effectiveness, especially with initiation closer to the onset of menopause. We tested a group of aged female rhesus macaques on a spatial working memory and a visuospatial attention task, after ovariectomy (ovx) and HT. On both tests, E-replaced animals performed better than the intact and ovx controls and the E-group supplemented with progesterone, supporting the window hypothesis. Moreover, while the animals continued on treatment (but no further cognitive testing), longitudinal anatomical MRI scans of the brain were collected on a 3T Siemens Magnatom system. T1-weighted MPRAGEs were collected in quadruplicate at each scan time-point to increase the signal to noise ratio, on treatment years 3, 4 and 5. Using a volumetric analysis pipeline, scans were averaged for each animal at each time-point, then masked and skull stripped. We found no change in total brain volume, as a factor of treatment, age or the interaction. Ventricular volume, while suggestive of an age-related increase, fell short of significance. The volumes of gray and white matter analysis across age is currently being performed. We also plan a sub-regional approach to examine the effects of age and treatment. In the absence of overt pathology, age-related volumetric changes in the aged macaque brain appears to be minor.
Support: This work was supported by National Institutes of Health Grants AG-019100, AG-024978, AG-026472, AG-036670, and OD-011092.

4. **Long lasting contextual effects in non primary auditory cortex.** Mateo Lopez Espejo. OHSU. Neuroscience Graduate Program. David Lab.
Natural sounds are characterized by rich temporal dynamics. In speech these dynamics span a range of timescales, from fast transitions between phonemes at tens of milliseconds, to slower cadence of words and sentences lasting seconds. While studies have demonstrated that the auditory cortex represents fast temporal features of sound with high fidelity, it remains unknown how slower features are represented. To encode slow temporal features, the auditory cortex must integrate sound information over the relevant time scales. To test this integration, we designed a stimulus paradigm in which a probe stimulus was presented following different stimuli that formed distinct contexts. The context could be the naturally contiguous sound, a different natural sound, or silence. Using extracellular recordings from the primary (A1) and non-primary auditory cortex (peri ectosylvian gyrus, PEG) of awake, passively listening ferrets, we characterized how the neural representation of the probe stimulus changed as a function of context. We quantified the amplitude and duration of the context effect over the probe by calculating the pairwise difference between the peristimulus time histogram (PSTH) response to a single probe after different pairs of contexts. In A1, the context-dependent differences were small and short lived, while in PEG the effect lasted several hundred milliseconds in some neurons. In particular, same-sound contexts typically produced relatively weak responses to the probe, while transitions from silence or a different natural sound produced a much larger response. Our results indicate that long-lasting contextual effects emerge at the single-unit level in non-primary auditory auditory cortex.

5. Reduced white matter microstructure is associated with escalating depressive symptoms in female adolescents

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Research has demonstrated associations between adolescent depression and alterations in white matter microstructure, particularly in tracts that mediate emotion regulation. The present study explored sex-specific premorbid white matter microstructure correlates of escalating depressive symptoms during adolescence. Adolescents from the National Consortium on Alcohol & Neurodevelopment in Adolescence (NCANDA) who were 14-16 years old at study entry and exhibited an increase in depressive symptoms, as measured by Center for Epidemiologic Studies Depression Scale (CES-D) scores, during three years of follow-up were selected for inclusion (N=177, n=81 females). Using diffusion tensor imaging, whole-brain regression analyses were employed to examine relationships between baseline fractional anisotropy (FA; voxel threshold $p<0.01$, cluster-forming threshold $p<0.05$) and peak increase in depressive symptoms during follow-up, as a function of sex. Other relevant covariates were statistically controlled for post-hoc. Among female adolescents, lower baseline FA in the right superior corona radiata and external capsule was associated with greater peak increases in CES-D scores during follow-up ($b = -0.0183$, $p = 0.0024$, $\beta = -0.2361$). Among males, higher baseline FA in the right middle cerebellar peduncle was associated with greater increases in CES-D scores during follow-up ($b = 0.0218$, $p = 0.0012$, $\beta = 0.2728$). These findings suggest that, for female adolescents, less coherence in major integrative white matter pathways may represent a significant risk factor for subsequent escalation in depressive symptoms during adolescence, while male adolescents show a different pattern. Such results may serve as a neurobiological marker of risk and target for prevention of depression during adolescence.

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6. Aging-associated changes in cerebral vasculature and blood flow as determined by quantitative optical coherence tomography angiography.

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Normal aging is associated with significant alterations in brain's vascular structure and function, which can lead to compromised cerebral circulation and increased risk of neurodegeneration. The in vivo examination of cerebral blood flow (CBF), including capillary beds, in aging brains with sufficient spatial detail remains challenging with current imaging modalities. In the present study, we use three-dimensional (3-D) quantitative optical coherence tomography angiography (OCTA) to examine characteristic differences of the cerebral vasculatures and hemodynamics at the somatosensory cortex (S1) between old (16-month-old) and young mice (2-month-old) in vivo. The quantitative metrics include cortical vascular morphology, CBF, and capillary flow velocity. We show that compared to young mice, the pial arterial tortuosity increases by 14%, the capillary vessel density decreases by 15%, and the CBF reduces by 33% in the old mice. Most importantly, changes in capillary velocity and heterogeneity with aging are quantified for the first time with sufficiently high statistical power between young and old populations, with a 21% ($p<0.05$) increase in

capillary mean velocity and 19% ($p \leq 0.05$) increase in velocity heterogeneity in the latter. Our findings through non-invasive imaging are in line with previous studies of vascular structure modification with aging, with additional quantitative assessment in capillary velocity enabled by advanced OCTA algorithms on a single imaging platform. The results offer OCTA as a promising neuroimaging tool to study vascular aging, which may shed new light on the investigations of vascular factors contributing to the pathophysiology of age-related neurodegenerative disorders.

7. Imaging mesoscale cortical activity across behavior training on a visual change detection task

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The cortex is extensively interconnected through both direct and indirect neuronal pathways. Over the course of learning sensorimotor skills and tasks, distributed cortical regions must coordinate their activity to link sensory inputs to reliable decision and motor signals. However, we currently lack a complete understanding of where and when changes to neural circuitry occur to support learning, as well as the extent to which neural activity remains stable once behavioral performance has reached consistent, expert levels. To address these questions, we used widefield fluorescence imaging of transgenic mice to make longitudinal measurements of mesoscale activity across the cortex during each day of training on a visual change detection task. We imaged activity in mice expressing GCaMP6s in most excitatory neurons of the forebrain. In the task, a head-fixed mouse is presented with a series of flashed full-field gratings and must indicate changes in the orientation of the grating by licking a reward spout. We used event-triggered analysis of sensory and motor responses to assess which cortical areas were engaged by distinct task components. In naïve mice, posterior visual cortical areas were consistently activated by flashed stimuli while frontal areas were not. Over learning, we observed the emergence of a stimulus-entrained response in the frontal areas. Visual cortex responses remained over the learning but became more consistent in their timing. These mesoscale activity changes could support enhanced coordination and efficiency of neural interactions to support task performance.

8. Cortical survey of contrast tuning reveals large cell-type-specific biases in contrast and direction selectivity

Daniel Millman, Gabe Ocker, Peter Ledochowitsch, Michael Oliver, Jerome Lecoq, Clay Reid, Michael Buice, Saskia de Vries
Allen Institute for Brain Science

In visual cortex, the contrast tuning of single cells to visual stimuli have been reported to be diverse. However, the relationship between genetically-identified cell types and contrast tuning profiles is not known. Here, we survey contrast tuning to grating stimuli in cells of awake mice in six transgenically-defined Cre-lines, four excitatory and two inhibitory, collectively covering all cortical layers in V1 as well as five higher visual areas. Among excitatory cells, contrast response profiles are comparable across visual areas but vary in a gradient across depth with a greater proportion of deep cells exhibiting high-pass tuning profiles. Notably, we find striking differences between the two types of inhibitory cells. Consistent with previous results from the Allen Brain Observatory in which only high-contrast full-field gratings were shown, vasoactive intestinal peptide-expressing (Vip) cells are suppressed-by-contrast at the highest contrast stimuli used. However, Vip cells have robust responses to low-contrast (<20%) stimuli with orientation selectivity on par with that of excitatory cells. Alternatively, somatostatin-expressing (Sst) cells, which are known to be inhibited by Vip cells, exclusively prefer high-contrast (>20%) stimuli with weak orientation tuning. Moreover, ~90% of Vip cells prefer vertical gratings over any other orientation. Excitatory cells across layers and areas also exhibit a slight bias in orientation preference toward vertical gratings, but much less pronounced than Vip cells. One possible explanation for these data in light of reports that Vip cells disinhibit excitatory cells is that Vip cells both inherit and amplify the orientation bias of excitatory cells.

9. Molecular specialization of the songbird motor cortex.

Alexander A. Nevue, Peter V. Lovell, Claudio V. Mello
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The human cerebral cortex has evolved specialized areas responsible for sensory perception and cognitive function. Despite marked differences between the mammalian layered cortex and the nucleated pallium of birds, recent evidence has revealed that the human laryngeal motor cortex (LMC) and the main vocal motor output nucleus of the zebra finch pallium (robust nucleus of the arcopallium, RA) share a remarkable set of molecular markers that together define a suite of molecular specializations that convergently evolved for vocal production. How these specialized vocal regions evolved, however, is unknown. Here we examined in detail the expression of these molecular markers using *in situ* hybridization and focused on RA and an adjacent area (dorsal intermediate arcopallium, AId) in adult male zebra finches. Although the organization and function of AId are not well understood, this area is thought to play a general role in motor control, and is hypothesized to be the pre-existing structure from which RA evolved in vocal learning birds. A subset of convergent LMC/RA markers represent molecular specializations unique to RA (e.g. *SLIT1*, *GABRB3*, *C1QL3, NEUROD6*), whereas another subset of markers is shared between RA and AId (e.g. *PVALB, GPM6A, PCDH17, SNCA*). The latter indicates a close relationship between RA and AId and suggests that RA may have evolved as a specialization of AId, consistent with the motor theory for vocal learning origin. We were also able to molecularly define AId in female zebra finches, who do not learn a song, and in two non-vocal learning suboscine species, consistent with a general motor role of AId rather than a specific involvement in vocal learning. These convergent markers provide a foundation for future studies on the molecular basis of vocal learning and cortical evolution, and represent a putative molecular underpinning for the evolution of learned vocal production.

10. Direct comparison of nonlinear sensory encoding models in ferret primary auditory cortex

Jacob Pennington, Alexander Dimitrov (Washington State University Vancouver), Stephen David (OHSU)

A common framework for describing the function of auditory cortical neurons is the linear-nonlinear spectro-temporal receptive field (LN STRF). This model casts the time-varying neural spike rate as a linear weighted sum of the immediately preceding sound spectrogram, followed by nonlinear rectification. Two models have expanded on the LN STRF to account for sensory contextual effects, using short-term plasticity (STP) or contrast-dependent gain control (GC). Both improve performance over the LN model, but they have never been compared directly. Thus, it is unclear whether they account for distinct processes or describe the same phenomenon in different ways. To address this question, we recorded activity of single primary auditory cortical neurons (n = 423) in awake ferrets (n = 7) during presentation of natural sound stimuli. We fit STRFs incorporating one nonlinear mechanism (GC or STP) or both mechanisms (STP+GC) on this single dataset. We compared model performance using the correlation coefficient (Pearson's R) between predicted and observed time-varying spike rate for each neuron. Our results indicate that the STP model performs significantly better than the GC model, and that the STP+GC model performs significantly better than either individual model. This finding indicates that the STP and GC models explain distinct aspects of neural activity. Further, the success of the combined model suggests that auditory cortical neurons utilize at least two independent mechanisms to adapt encoding properties to different sensory contexts. Future neuromorphic sound processing technologies may therefore improve their performance by incorporating both STP- and GC-based computations.

11. Human electrocortical fluctuations during naturalistic wrist movements

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Human neuroimaging experiments predominantly use controlled laboratory paradigms. However, it is unclear how well these results generalize to natural settings, where actions occur spontaneously throughout the day. In particular, neuroimaging in naturalistic settings can be used to investigate how context alters cortical activity, indicating a need to analyze long-term neural activity "in the wild." We

analyzed electrocortical activity from multiple patients with intractable epilepsy using electrocorticography (ECoG) as they performed spontaneous wrist movements across several days of clinical recording. Wrist movement events were identified by applying computer vision techniques to clinical video recordings. We quantified movement- related electrocortical activity using time-frequency power spectrograms at every contralateral surface electrode, averaged across events. Based on previous results from controlled experiments, we expected increased ECoG power at high-frequencies (76–100 Hz) and decreased power at low-frequencies (8–32 Hz) near sensorimotor cortex following wrist movement initiation. Our results using naturalistic events corroborated these expectations. Additionally, high-frequency power fluctuations were primarily limited to sensorimotor areas, while low- frequency power fluctuations occurred more widely across the cortex. The spectral power pattern was robust, overlapping across subjects and days. Using this framework, we are further exploring how electrocortical power varies in a greater number of subjects and amid various physical, sensory, and social contexts. Such an approach could enhance our understanding of how cortical activity relates to unconstrained, natural behavior outside of traditional experimental settings.

12. **Investigating the neural circuits of spinal cord stimulation**.
    Andrei Sdrulla
    Oregon Health & Science University
    Spinal cord stimulation (SCS) provides an important alternative strategy for treating chronic pain conditions when other therapies have failed. The “gate control theory” continues to be the leading explanatory model, however the mechanisms underlying the analgesic actions of SCS remain poorly understood. We take advantage of two-photon microscopy of genetically encoded calcium indicators expressed specifically in dorsal horn neurons to delineate the effect of Aβ electrical stimulation (Aβ-ES) on activity of these populations in real time in SDH. We found that a short train of Aβ-ES modulates excitatory and inhibitory populations in opposite directions, in an age and preparation dependent manner. We measured neuronal responses in the presence of continuous Aβ-ES conditioning and found that it depressed both excitatory and inhibitory populations. Our experiments provide direct insights into the cellular mechanisms of SCS, with direct translational implications.

13. **How the mind wanders in adults with ADHD**
    Brittany Alperin, Brian Shirley, Joel Nigg, Sarah Karalunas
    Oregon Health & Science University
    Mind-wandering, or a shift in attention away from a task, is a common phenomenon that is often extreme in psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD). However, mind-wandering is multi-faceted. A growing literature is beginning to better define mind-wandering, differentiating spontaneous/constrained and stimulus-dependent/independent dimensions of thought; however, few studies have applied this methodology to studies of ADHD or other disorders. The current study examined whether adults with ADHD have more spontaneous/variable thoughts during mind-wandering than their peers. EEG was recorded while adults completed a sustained attention task and periodically reported their thought content. Individuals with ADHD reported more variable thoughts during mind-wandering as compared to non-ADHD individuals. EEG complexity measures will be used to corroborate self-report measures and better understand the neural processes engaged during mind-wandering. These results begin to differentiate the relative contribution of different aspects of mind-wandering to clinical problems.

14. **The rhesus macaque as a model for healthy aging: what can the oldest-old population tell us?**
    Gail Stonebarger.
    Department of Behavioral Neuroscience, OHSU.
    In the USA, there are >50 million adults aged 65+, and by 2050 that number is projected to nearly double. Currently, the mechanisms underlying human brain aging are poorly understood, largely because of a lack of appropriate animal models for experimentation. However, the rhesus macaque shows ~93% base pair

homology with humans, has a staged lifespan that is more comparable to that of humans than rodents (measured in decades rather than months), and undergoes many of the same age-related physiological changes. Interestingly, macaques do not seem to develop neurodegenerative diseases of human aging such as Alzheimer's disease (AD), even at very old ages. Therefore, the goal of this study was to examine which aspects of normal and pathological human brain aging are recapitulated in the oldest known rhesus macaques in the world, and to determine if differences between them may contribute to the macaque's resistance to development of AD. Brain tissue was obtained from some of the oldest known rhesus macaques (22-44 years), and dorsolateral prefrontal cortical (PFC) sections were examined immunohistochemically for amyloid beta (Aβ) plaques and neuron number. Using bright-field microscopy and unbiased stereology, the results were compared to data obtained from humans. Like aging humans, the old macaques showed a marginal age-related increase in Aβ deposition. However, no age-related neuron loss was observed. Although rhesus macaques do not show significant age-related neurons loss in the PFC, they may represent valid models for studying the early developmental stages of AD as well as the progression of non- pathological aging.

15. MRI assessment of glymphatic function in the non-human primate brain

Ian J Tagge, Steven Kohama, Ted Hobbs, Jeffrey Pollock, Thierno Madjou Bah, Jeffrey Iliff, William D Rooney
Advanced Imaging Research Center, OHSU

Introduction**:** The astrocyte mediated exchange of cerebrospinal fluid and interstitial fluid comprise the glymphatic system, a physiology that facilitates waste removal in the brain parenchyma. Impaired solute and waste clearance may contribute to neurodegenerative conditions, and may also be associated with age. Here, we present preliminary measurements of glymphatic function in healthy adult and aged rhesus macaque brain via intrathecal injection of a gadolinium-based contrast agent (GBCA) and DCE-MRI.
Methods**:** MRI data were acquired from three male rhesus macaques (age 6, 9, and 27 y/o) on a whole-body Siemens Prisma 3T MRI instrument. Baseline anatomical and R_1 images were acquired, followed by intrathecal injection of 100μL GBCA. One animal (6 y/o) was returned to the MRI immediately after intrathecal injection to observe kinetics during the first 3 hrs after GBCA administration. The other two animals were imaged in 1 hr intervals for up to 6.5 hrs post-intrathecal injection; anesthesia was maintained with isoflurane between imaging sessions. k_{in} and k_{out} maps (time average dR1/dt during wash-in and wash-out, respectively) were calculated for each voxel.
Results**:** CSF-ISF interchange was reduced in the aged animal compared to the younger animals both in terms of rate of transport (k_{in}) and maximum R_1 enhancement. Efficiency of transport, estimated by k_{in}, appears greatest in close proximity to large vessels, particularly around the middle cerebral arteries.
Conclusion**:** We demonstrate that kinetics of GBCA distribution in the CNS occur on timescales amenable to study using DCE-MRI techniques. Our preliminary results indicate that impairment in glymphatic physiology occurs with age in the rhesus macaque.

16. Accelerating high dimensional visualizations of scRNA-seq data

John Tigue

The use of dimensionality reduction techniques (for examples, tSNE and UMAP) during visual exploratory data analysis has seen wide adoption in recent years. The original tSNE algorithm has been around since 2008. Over the years descendant algorithms have improved (quadratic time to log-linear in 2014 down to linear in 2018). In the same period GPUs have become widely available (e.g. Google will let you play with an NVIDIA Tesla T4 GPU for free on Colab for up to twelve hours). Currently there are GPU accelerated implementations of both tSNE and UMAP. The embeddings can be generated much more quickly and cheaper than eleven years ago.Over the same period, the user interfaces for exploring and interpreting embeddings have also evolved. User friendliness has also been improved by setting sane defaults for parameters. Hyper-parameter auto-setting via brute force search is another level of hands-off operations that became available as of 2017. More recently UI tools provide ways of interpreting embeddings (e.g.

Latent Space Cartography), thereby accelerating humans comprehension of the data.
This poster presents various open source Jupyter notebooks for running scRNA-seq analysis workflows for free on Google's Colab, no credit card required just a gmail address. The notebooks include highly interactive widgets for exploring the embeddings. Everything runs in the cloud.

17. *Neural Development of Macaque Monkey Foveal Vision*

Sofia Kahler-Quesada, Robert M. Friedman, Trevor J. McGill, Mykyta M. Chernov, Derek Zaraza, Lauren M. Renner, Anna W. Roe
Division of Neuroscience, Oregon National Primate Research Center OHSU, Beaverton, OR USA

The retinal fovea is unique to humans and nonhuman primates. As the center of gaze, the fovea permits high spatial acuity and color vision, and is important for the development of reading, visuomotor ability, visual attention, and social behavior. In adults, more visual cortex is dedicated to central vision. In macaques as in humans, the fovea forms after birth. However, little is known about how foveal cortical representation develops. In this study, we used optical imaging to map cortical retinal topography to determine cortical magnification of the fovea (mm cortex/degree of visual space) in infant and adult rhesus macaques. Preliminary findings suggest that cortical magnification increases as cone density in the fovea increases during the first postnatal month. Understanding visual cortical development will impact postnatal intervention and treatment of developmental visual disorders such as amblyopia and strabismus.

18. Perturbed fetal mid- and hindbrain maturation in a macaque FASD model featuring voluntary alcohol drinking

Xiaojie Wang, Verginia Cuzon Carlson, Colin Studholme, Natalie Newman, Kathleen A. Grant, and Christopher D. Kroenke
Oregon Health & Science University

Fetal alcohol spectrum disorder (FASD) is a widespread neurodevelopmental disorder in the United States and worldwide. One factor that contributes to its current prevalence is binge-like consumption of alcohol prior to pregnancy awareness. It is known that therapeutic interventions are more effective with early recognition of FASD. Here, a novel rhesus macaque model of FASD, involving voluntary drinking of 1.5 g/kg ethanol per day, beginning prior to pregnancy and extending through the first 60 days of a 168-day gestational term, was developed to determine whether fetal MRI could be used to detect alcohol-induced abnormalities in brain development. Fetal MRI revealed developmental differences between ethanol-exposed and control fetuses at gestation day 135 (G135), but not G110 or G85. At G135, ethanol-exposed fetuses had reduced cerebellar volume and water diffusion anisotropy in several white matter tracts, compared to controls. Ex vivo electrophysiological recordings performed on fetal brain tissue obtained immediately following the MRI procedures demonstrated that the anatomical abnormalities observed at G135 are of functional significance. Specifically, spontaneous excitatory postsynaptic current amplitudes measured from individual neurons located in the primary somatosensory cortex and putamen closely correlated with diffusion anisotropy in the white matter tracts that connect these structures. These findings demonstrate that fetal MRI can detect perturbations to specific fetal brain regions associated with early gestation alcohol exposure. They also indicate that fetal MRI has the highest sensitivity in detecting abnormal brain development associated with alcohol exposure at the third trimester.

19. Relationship between apoE levels and MRI measures in the Radiation Survivor Cohort

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While a lot has been learned from radiation studies in rodents, a gap in knowledge is how radiation might long-term affect the brain in primates. The unique Radiation Survivor nonhuman primate Cohort at Wake Forest allows addressing this gap in knowledge. This knowledge is pertinent to the CNS side effects of radiation treatment in cancer patients and to environment exposure to radiation, for example following a nuclear accident or terrorist attack. Apolipoprotein E (apoE) plays a role in cholesterol metabolism and response after injury. ApoE might serve an anti-inflammatory role in the central nervous system and serve a protective role against radiation-induced brain injury. We investigated the relationship between regional apoE immunoreactivity and relative regional brain volumes, assessed by anatomical MRI, in rhesus macaques irradiated several years prior to necropsy. There was a region- specific negative correlation between amygdalar apoE levels and relative limbic volume and regional specificity for apoE levels and relative brain volume for hippocampal and dorsolateral prefrontal areas. Thus, elevated apoE levels might be a biomarker of accompanying volumetric decline following radiation.

20. *Adult-born neurons inhibit developmentally-born neurons*

Alyssa Ash, Erin Chahley, Dr. Desiree Seib, Dr. Jason Snyder
University of British Columbia

Recent reports indicate that lateral inhibition plays a powerful role in selecting which dentate gyrus (DG) neurons are recruited during memory formation. This raises the question of whether developmentally-born and adult-born DG neurons have distinct roles for inhibition, particularly in vivo when neuronal ensembles are selected during memory encoding. To address this we combined chemogenetics and immunohistochemistry for BrdU+Fos to silence and measure activity in developmentally and adult-born neurons as rats learned a spatial water maze task. Specifically, retrovirus was injected into the DG of male rats at 6 weeks of age to express the inhibitory DREADD receptor, HM4Di, in neurons born in adulthood. The same rats were also injected with BrdU to label developmentally or adult-born neurons. At 10 weeks of age rats were injected with either the HM4Di agonist CNO or vehicle, then trained in the water maze (8 trials). We found that silencing a subset of adult-born neurons (aged 4 weeks) increased activity levels in the developmentally-born neuron population. However, silencing adult-born neurons did not affect activation in other adult-born neurons within the DG, suggesting limited interaction amongst the adult-born population. We are currently looking at activation of interneurons (PV+ and SST+) within each treatment group to determine if silencing adult-born cells impacts downstream activity in inhibitory interneurons. Preliminary findings implicate PV+ interneurons in the modulatory sub-circuit between neuron populations within the DG.

21. Development of multimodal wireless brain interfaces in nonhuman primates.

Derek Zaraza, Mykyta M. Chernov, Robert M. Friedman, Anna W. Roe
Oregon National Primate Research Center

The goal of this project is to make a wireless multimodal device capable of stimulating and recording from multiple cortical functional modules with a spatial resolution of several hundred microns. Decades of studies in animals have been conducted in conditions of strict experimental control of perception and behavior in order to understand the functions of the brain. These animal paradigms require long training periods (months to a year). While such studies have advanced our knowledge of brain function tremendously, a recurring question is how relevant the gathered data are to natural behavior. Today, the availability of cutting-edge technologies and computational power can free us from these limitations of the classical experimental paradigms and usher in a new generation of neuroscience questions focused on how the functioning of the brain in real world settings. We present preliminary results in our development of a small multimodal device for stimulating and recording domain-based cortical activity in freely moving primates. We collected intrinsic optical imaging data during optogenetic stimulation in macaque visual cortex using a multimodal device that consists of a small head mounted camera and a wireless multisite LED stimulator.

The end goal is the production of a multimodal device, constructed from off the shelf components, that provides unrestrained, multiareal and targeted (to specified cortical domains) stimulation and recording capabilities. The successful outcome of this project will contribute to our understanding of cortical encoding of perception and behavior and will have clinical relevance for the development of brain-machine interfaces.

Saturday July 13th: Session 2

1. Pathfinder: Open Source Software for Analyzing Spatial Navigation Search Strategies.

Matthew B. Cooke
University of British Columbia

The Morris Water Maze is a widely used task developed to test spatial navigation in rodents. Rodents are trained to learn the location of a platform that offers escape from the pool. Classically, measures such as latency to the escape platform and total distance traversed have been used in order to score spatial learning on this task. However, these measures offer little insight into the underlying navigational strategies that the animals employ. Recently, a number of studies have begun to classify water maze search strategies in order to clarify the precise spatial and mnemonic functions of different brain regions, and to identify which aspects of spatial memory are disrupted in disease models. While search strategies can be intuitively defined relative to escape locations and maze geometry, they have not been widely adopted, presumably due to the lack of available software. In order to address this issue, we developed Pathfinder, an open source application for analyzing spatial navigation behaviour. Here we show that Pathfinder effectively identifies a variety of search strategies, that vary in their spatial specificity, as rodents learn the location of the escape platform. Pathfinder has the ability to automatically determine the platform location as well as the size of the pool and related pool parameters. It can generate heatmaps of trials, analyze navigation with respect to multiple goal locations and, due to the open source nature of the project, can be easily updated to accommodate future developments in the study of spatial navigation.

2. A multi-species model for selective pruritus via the direct activation of TRPA1

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In mammals, itch is thought to ensue when transient receptor potential (TRP) ion channels on peripheral somatosensory neurons are activated downstream of G-protein coupled receptors (GPCRs) that bind to pruritic (itch-inducing) stimuli. By contrast, chemically- and thermally-induced pain is elicited when these TRP ion channels are directly activated by algogenic (pain-inducing) stimuli. Using various experimental paradigms, we determined that the TRPA1 ion channel on peripheral somatosensory neurons can be directly activated to elicit both pain and itch behaviors. These different behaviors appear to result from the differential activation of distinct subsets of TRPA1-expressing neurons. We found that low-intensity stimuli, such as low concentrations of the TRPA1 agonists, elicit pruritic behaviors and activate one subpopulation of TRPA1 neurons. Neurons within this subpopulation also respond more robustly to other noxious stimuli, indicating that they likely comprise an intrinsically more sensitive subset of neurons. Conversely, the remaining TRPA1-expressing neurons are less sensitive to noxious stimuli, and are only activated by high-intensity stimuli (i.e., high concentrations of TRPA1 agonists) that provoke nocifensive behaviors. Intriguingly, we replicated these findings in the zebrafish. TRPA1-dependent pruritogens evoked robust lip-rubbing behaviors (analogous to mammalian scratching) in the zebrafish, while algogens elicited nocifensive behaviors such as freezing and reduced swimming velocity. These behaviors also correlated with the activation of different subpopulations of TRPA1-expressing neurons. Together, these results

suggest a simple, evolutionarily- conserved model for selective itch via activation of a specialized subpopulation of somatosensory neurons with a heightened sensitivity to noxious stimuli.

3. Real-time neural feedback of mesoscale cortical GCAMP6 signals using Raspberry-Pi

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Mice can learn to control specific neuronal ensembles using sensory (eg. auditory) cues (Clancy et al. 2014) or even artificial optogenetic stimulation (Prsa et al. 2017). Real-time neurofeedback of brain activity can be used in goal-directed training and learning. In our work, we measure mesoscale cortical GCaMP6s signals and provide graded auditory feedback (within ~100 ms after GCaMP fluorescence) based on changes in neuronal activation within a specified region of interest (ROI). We define a compact, low-cost optical brain-machine interface capable of image acquisition, processing, and conducting closed-loop auditory feedback for water reward experiments, using a multithreaded program on a single Raspberry Pi. The ROI activation level, calculated as the fraction of pixels that exceed their running baselines, determines the pitch of the audio feedback (1-24 kHz in quarter-octave steps). Water rewards are delivered if the activation level surpasses a preset threshold. To investigate learning in this context, water-deprived tetO-GCaMP6s mice (N=4) were trained for about 45-minute sessions per day for six days. Results **across daily training sessions** indicate that mice **increase the number of brain-activity mediated water reward deliveries ($p<0.001$, over 6 days) even at increasing thresholds (25-80% activation of ROI). In this regard, training increased the number of rewards($p<0.001$) and allowed all the mice to perform at a higher threshold ($p=0.002$).** In conclusion, we developed an open-source system for closed-loop feedback that can be added to experimental scenarios for brain activity training and could be possibly effective in inducing neuroplasticity.

4. Effects of arousal on population coding of natural sounds in primary auditory cortex

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Behavioral state variables such as arousal and task-engagement have been shown to reduce shared variability, i.e., stimulus-independent, pairwise correlations between neurons, in primary sensory cortices. This may reflect state-dependent processing to remove noise and enhance accurate sensory encoding. However, many questions remain regarding the origin of shared variability and how it impacts sensory coding. Here, we investigated shared cortical variability and its dependence on arousal state in the primary auditory cortex of awake, passively listening ferrets. The simultaneous activity of multiple single units was recorded during the presentation of natural sounds and arousal levels were monitored via pupillometry. We found that arousal influences correlated variability on multiple, distinct timescales. Consistent with the time course of fluctuations in arousal itself, we observed strong covariation in spike rate from trial to trial, on the order of seconds. This was expected, given that arousal is known to modulate the excitability of cortical neurons. At these slow timescales, we saw no change in the magnitude of shared variability between high and low arousal states. On timescales faster than one second, however, arousal suppressed shared variability. Notably, the degree of suppression for a given pair was not predicted by tuning similarity, but seemed to be consistent across all pairs. Using a linear stimulus decoder trained on pairs of simultaneously recorded units, we show that this global suppression improved decoding accuracy only for very similarly tuned, or anti-tuned pairs. This suggests that in populations of diversely tuned neurons, global correlations need not impair encoding accuracy.

5. mPFC disruption alters hippocampal-dependent deliberative behavior

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When making decisions, individuals must often choose between two or more options under uncertainty. Occasionally, decisions are reversed during enactment of a choice, leading to a behavior known as vicarious trial and errors (VTEs). Neural decoding analyses from rodents suggest that during VTEs,

hippocampal (HPC) place field sequences sweep ahead of subjects in the same order they traverse their paths – first toward their initial choice, then toward their final choice. While it is clear the HPC plays an important role in VTEs, it is unknown how the HPC interacts with broader decision-making circuitry to guide this behavior, or when these interactions occur in relation to the behavior. Based on findings showing increases in VTEs when the HPC is disrupted, and evidence showing interactions between the HPC and medial prefrontal cortex (mPFC) during goal-directed navigation, we tested the hypothesis that intact communication between the mPFC and HPC is necessary for VTEs. To address this question, we optogenetically stimulated the mPFC during different behavioral epochs (delay, choice, return) in a delayed spatial alternation (DA) task, then assessed the impact of stimulation on VTEs. We show that VTEs normally occur on ~20% of trials, and these predict correct choices ~94% of the time. Preliminary data suggest that mPFC disruption decreases the prevalence of VTEs as compared to baseline sessions.

6. In vivo striatal neural activity during motor skill learning in Huntington's disease mice

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Huntington's disease (HD) is a genetic neurodegenerative disorder characterized by motor, cognitive and psychiatric deficits. The dorsal striatum is the major site of neurodegeneration in HD, along with atrophy of other areas including cortex. HD patients and animal models display deficits in striatum-dependent learning, such as motor skill learning, that worsen with disease progression. The YAC128 mouse model of HD shows progressive deficits in the accelerating rotarod motor learning task. These mice also display aberrant cortico-striatal signalling, including changes to glutamate release and deficits in cortico-striatal plasticity. The contribution of these changes in cortico-striatal signalling to motor skill learning deficits *in vivo* has never been tested. Here, we have combined the accelerating rotarod task with GCaMP7f imaging using fiber photometry to correlate activity in striatal neurons with task performance and motor learning. We have found that population activity in the dorsal striatum increases and remains elevated during rotarod performance. Over days of training, the amplitude of population activity during rotarod performance reduces as mice become more proficient at the task. We also measured GCaMP7f activity of mice freely moving in an open field to assess anxiety-like behaviour and locomotor activity and the corresponding neural activity in striatum. We plan to examine GCaMP7f dynamics during these behavioural tasks in YAC128 mice compared to their wild-type littermates at different disease stages. This research contributes to our understanding of the changes to striatal signalling that may contribute to motor, cognitive and psychiatric symptoms in HD.

7. Short-term effects of vagus nerve stimulation on auditory learning and stimulus-specific activity in auditory cortex.

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Previous studies of vagus nerve stimulation (VNS) have shown that chronic stimulation can facilitate central plasticity. VNS is believed to trigger release of neurotransmitters that mediate plasticity. To study short-term VNS effects, we measured learning and auditory cortical activity following brief and acute VNS. We implanted cuff electrodes onto ferrets' vagus nerve and trained them by classical conditioning to associate one specific tone (T1) with a reward and another tone (T2) with no reward. Frequencies of T1 and T2 were changed every 2 days. When T1/T2 were overlapped with VNS, rates of learning the reward association increased on day 1. In contrast, animals' learning rates were lower when VNS was not overlapped with T1/T2. Afferent VNS pathways involve nuclei that mediate arousal, which is reflected by changes in pupil size. A phasic pupil dilation was observed for several seconds following VNS, suggesting an increase in arousal promotes greater learning efficiency. To measure effects of VNS on cortical activity, we recorded neurophysiological activity in A1 of passively listening animals pre- and post-VNS. Neural responses in a subpopulation of neurons were decreased in the condition when VNS was overlapped with the neuron's best frequency tone. Neural activity was also positively correlated with pupil size. Regressing out effects of pupil-indexed arousal decreased the response difference of post- versus pre-VNS. Significant

reduction of neural responses remained in post-VNS. Taken together, the results of this study support a role for VNS in auditory learning and help establish VNS as a tool to facilitate neural plasticity.

8. Automatic segmentation of rhesus macaque brain striatum based on functional connectivity using K- nearest neighbor classifier

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A critical step in the analysis of neuroimaging data is the segmentation of gray matter into functionally-related structures. Conventionally, segmentation is performed by first co-registering the individual scan with a brain template, and then by mapping the template atlas to the original space using registration parameters. However, registration operations can be imprecise, due to poor contrast delineating the borders between adjacent structures, such as the caudate or putamen with the nucleus accumbens (NAc). Therefore, manual corrections are necessary, and this results in labeling inconsistencies and errors. Here, a method based on a machine learning model, i.e. K-nearest neighbor classifier (K-NN), is proposed to achieve automatic striatal segmentation based on functional connectivity in limbic, associative, and sensorimotor circuits. We acquired resting state functional connectivity MRI data with T2-weighted SPACE anatomic images from 18 rhesus macaques (12f, 6m; 5- 12 years). All processed results, including voxel-based functional correlation coefficients in circuits and anatomical image intensities, were aligned to a reference template space[1] to construct voxel-specific feature vectors. The conventional registration-based segmentation method was applied to generate the initial segmentation of the striatum. An erosion operation was performed to obtain the feature vectors of voxels in the center part of caudate, putamen, and NAc, and these were used to train the classifier. Subsequently, voxels in the ROI perimeter were classified by the trained classifier. The K-NN model was implemented by Matlab R2017a with 5 neighbors and Euclidean distance. This method was applied for the automatic segmentation of striatum in Huntington's disease (HD) study-specific template with a higher accuracy than the conventional segmentation. In the future, it will be applied for the individual subject. This work is supported by NIH/NINDS R01 NS099136.

9. Neuroeducation: Instructional techniques from neuroscience, cognitive psychology, and language.

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Neuroeducation is a field of study that triangulates scientific literature from the domains of neuroscience, cognitive psychology, and language (Arwood, 2011). This poster details a single-subject qualitative case study in which a special education teacher provided educational remediation to a 14 year old girl (participant) diagnosed with autism. Over the course of one year, the practitioner utilized instructional techniques informed by all three lenses of neuroeducation. Drawing, writing, and other visual language strategies were designed to harness maximum connectivity between visuo-motor cortical brain regions. Adult-child interactions during remediation efforts were structured to enhance information storage into long-term memory by use of increased semanticity and activation of higher order thinking capacities. The participant was encouraged to become an active participant in the case study by providing material culled from her own life, where adult practitioner would help student problem solve and learn coping strategies for her anxiety disorder.

Pre/post measurements were taken of participant's levels of language function by sampling her drawn, written, and oral language using the TEMPRO analysis device (Arwood, 1983). Results noted significant increases in participant's ability to use language for schoolwork and tasks of everyday living. In addition, the participant showed growth in social-emotional agency in the ability to self-direct and achieve goals – all measures of increased levels of executive functioning.

This poster introduces the topic of neuroeducation by explaining how the three lenses of study for the theoretical foundation for one-on-one and classroom pedagogical applications. In addition, drawing, writing, and measurements samples from the case study will be explored.

10. **Estrogen regulated G-protein Receptor Kinase 2 (GRK2) inhibits both KOR agonist and antagonist effects.**

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We previously found that female mice in high estrogen phases of the estrus cycle are less sensitive to both kappa agonism and antagonism than males. The mechanism of estrogen effect was determined to be a consequence of increased phosphorylation of G protein-coupled receptor kinase 2 (GRK2). Estrogen- stimulated phosphorylation of GRK2 increased its sequestration of Gβγ, thereby preventing the Gβγ signaling required for the analgesic response. When the GRK2/3 inhibitor CMPD101 was given prior to U50,488, intact female C57BL/6 mice showed equivalent analgesic responses to males. Similarly, when CMPD101 was given with norBNI to female mice, the analgesic response to U50,488 in the tail flick assay was blocked. To assess the utility of receptor-inactivating antagonists, we tested the effects of a range of doses in both male and female mice. Daily low dose administrations for 5 days completely blocked U50,488 antinociceptive effects. Daily low dose administration of norBNI produced slowly accumulating inhibition and completely blocked the antinociceptive effect of U50,488 after 20-30 days. Thirty days of low dose norBNI also completely blocked U50,488 analgesia in ovariectomized mice. Receptor inactivation in both male and female mice treated for 30 days with low dose norBNI persisted for greater than 1-week. Based on these preclinical findings, we predict that women will respond to low doses of receptor-inactivating KOR antagonists during low estrogen periods in their menstrual cycle and that accumulating receptor inactivation may still be therapeutically effective because of the low turnover rate of KOR.

11. **Testing the contribution of social context to preclinical efficacy of potential treatments for alcohol use disorder**

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To date, only three drugs are available for alcohol use disorder (AUD), and their use is restricted by inconsistent efficacy and/or high rates of patient noncompliance. The lack of progress in developing new AUD therapeutics may be surprising given the number of preclinical research studies identifying novel targets that modulate alcohol behaviors in rodents. For example, drugs identified preclinically as efficacious in decreasing alcohol intake in rodents, such as corticotropin-releasing factor (CRF) receptor antagonists, failed to show efficacy in humans. One source of this discrepancy may be differences in social environment during testing. Despite social pressure being one of leading causes of AUD relapse in humans, rodents are commonly tested in isolation. Here, the influence of social environment on treatment efficacy was assessed in C57Bl/6 mice housed either socially or in isolation using the HM-2 cage system - a novel system that monitors individual animals' fluid intake through radio frequency identification. In a continuous access, two-bottle choice model (water vs. 4-8% alcohol), administration of the selective CRF1 receptor antagonist, CP-376,395 at a dose previously identified to decrease alcohol intake in individually-housed mice in standard cages also decreased alcohol intake in mice housed individually in the HM-2 cages. However, no change in alcohol intake was observed in mice housed socially. Our results suggest that social environment may alter the efficacy of drugs known to decrease alcohol intake in rodents housed in isolation, and that considering social environment is vital in potentially increasing the translational value of rodent models of AUD.

12. **A 3-D digital human brain common coordinate framework (hCCF): manual annotation of cortical and subcortical regions of MNI_ICBM152 MRI template**

Josh Royall
Allen Institute for Brain Science
Multi-scale human brain mapping has become a routine approach for understanding brain structure, function, lesion and treatment in the neuroimaging community, requiring accurate and consistent anatomical annotation. Due to limited resolution of current neuroimaging techniques, it remains difficult to annotate detailed anatomical structures on neuroimaging slices. In contrast to cortical regions, few subcortical structures have been annotated on the MNI template, limiting brain-wide analysis of structures, functions and networks. To improve this situation, we present here a 3-D digital human brain CCF annotated on the MNI_ICBM152 template. Cortex was delineated on the basis of sulcal patterns while subcortical structures on the basis of intrinsic template signal and histology-based parcellations of the human brain (Allen Human Brain Reference Atlas; see Ding et al. J Comp Neurol, 524: 3127-3481, 2016) using ITK-SNAP. In this hCCF, we delineated and segmented approximately 53 cortical gyri/regions using the ontology created for Allen Human Brain Reference Atlas, including subdivisions of the previously defined large fusiform gyrus into perirhinal gyrus (anterior part) and real fusiform gyrus (posterior part). In subcortex, a total of 66 parent and/or large structures were segmented in basal forebrain, basal ganglia, amygdaloid complex, thalamus, hypothalamus, cerebellum, and brainstem. 21 representative white matter fiber bundles and ventricular structures were also annotated for landmark reference. This 3-D human brain CCF represents the first manual segmentation of whole human brain structures on the commonly used MNI_ICBM152 template and will serve as a useful tool for visualization and analysis of large-scale mapping data.

13. Regulation of subcellular dendritic synapse specificity by axon guidance cues
Emily C Sales, Emily L Heckman, Timothy L Warren, Chris Q Doe
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Neural circuit assembly occurs with subcellular precision, yet the mechanisms underlying this precision remain largely unknown. Subcellular synaptic specificity could be achieved by molecularly distinct subcellular domains that locally regulate synapse formation, or by axon guidance cues restricting access to one of several acceptable targets. We address these models using two Drosophila neurons: the dbd sensory neuron and the A08a interneuron. In wild-type larvae, dbd synapses with the A08a medial dendrite but not the A08a lateral dendrite. dbd-specific overexpression of the guidance receptors Unc-5 or Robo-2 results in lateralization of the dbd axon, which forms anatomical and functional monosynaptic connections with the A08a lateral dendrite. We conclude that axon guidance cues, not molecularly distinct dendritic arbors, are a major determinant of dbd-A08a subcellular synapse specificity.

14. Using Forced Choice Trials to Investigate the Cognitive Processes Associated with Delay Discounting
Deborah Sevigny-Resetco, Hannah Bues, and Suzanne H. Mitchell
Department of Behavioral Neuroscience, OHSU
Delay discounting (the relative preference for smaller, sooner rewards over larger, later rewards) has been identified as a contributing factor in the development of substance abuse disorders. Discounting is often conceptualized as a single cognitive process, however this study examines individual differences in preferences for the smaller, sooner rewards to better understand the cognitive components of delay discounting. In this study, 89 genetically heterogeneous rats (39 female, 50 male) completed a seven-phase lever press-based training and 36 delay discounting sessions with various delays (0, 2, 4, 8, 16, 24s) for a sucrose solution reward. During training, all subjects were introduced to a forced-choice trial requirement to ensure exposure to reward contingencies on the non-preferred lever. Completing the force-choice trials efficiently required subjects to inhibit their internally guided behavior (choice based on preference) to an externally guided response. This poster analyzes the subjects' behaviors when they were first introduced to the forced-choice trials and will compare these initial responses to their behaviors during the 36 delay discounting sessions. Preliminary analyses suggest individual differences in the rate of learning in forced-choice trial behavior, in which some animals demonstrate continued pressing of the

preferred lever rather than switching to the cued forced-choice lever. Future analyzes will examine the relationship between these differences and delay discounting to determine whether lack of inhibition in this context is associated with a higher preferences for smaller, sooner rewards. This type of analysis is a first step towards identifying processes that might contribute to performance on a delay discounting task.

15. Nonlinear coding of naturalistic sound streams in marmoset primary auditory cortex.

Luke Shaheen
OHSU

The human auditory system is adept at isolating and comprehending a single sound out of multiple sources (auditory streaming). The early auditory system encodes sound across a population of neurons, each sensitive to distinct low-level features, such as spectral frequency, spatial location, and modulation frequency. Because natural sound sources can contain overlapping features, the activity of individual neurons at early stages reflects a mixture of multiple sources. As signals pass through the auditory hierarchy, they undergo a series of nonlinear transformations which have been proposed to support emergent stream segregation. Evidence for streaming effects is well-documented for static, synthetic stimuli in auditory cortex (ACtx). How these mechanisms extend to natural, dynamic stimuli such as human speech is unknown.

To study streaming of naturalistic sounds in single-neurons, we recorded ACtx activity in passively-listening marmosets during presentation of a two-“voice” stimulus that retained the temporal dynamics of speech but had static spectra. Each voice consisted of a harmonic complex tone (HCT) with a unique fundamental frequency, modulated by a temporal envelope drawn from human speech.

Responses to two dynamic HCTs were poorly predicted by responses to static HCTs or by the sum of responses to each voice in isolation. Neurons predominantly encoded a mixed representation of both streams. Where selectivity exists, encoding of the weaker-represented voice was usually suppressed. Thus selectivity must either emerge in later cortical areas, or only when the animal is selectively streaming.

***16.* Working memory and inhibitory control in healthy adult rhesus macaques: performance norms and DTI correlates.**

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Our laboratory recently created a virally mediated nonhuman primate (NHP) model of Huntington’s disease (HD). Using this model we are tracking HD-related disruptions in brain circuitry with diffusion tensor imaging (DTI), and linking alterations in cortico-basal ganglia connectivity and white matter microstructure to functional changes in cognition. Similar to clinical neuropsychological batteries, different cognitive tasks rely on different neural substrates and so performance is thought to reflect the functionality of particular brain regions. Here, we describe performance norms and neuroimaging correlates for healthy adult rhesus macaques on our battery of cognitive tasks. Prior to receiving intracranial injections of our viral HD construct, 18 rhesus macaques were trained to perform cognitive tasks that assess spatial working memory (3-choice), non-spatial working memory (delayed nonmatch to sample, DNMS), and attention/inhibitory control (Go/NoGo). The same animals received MRI scans 7-10 days later to collect DTI data, and registration-based segmentation was performed on the white matter. We observed that cognitive performance correlated with fractional anisotropy (FA) in numerous tracts, but with a distinct pattern for different tasks. In general, FA within white matter was positively correlated with performance on the 3-choice task, and on trials of the Go/NoGo task requiring active (“Go”) responses; whereas FA was negatively correlated with performance on the DNMS task, and on trials of the Go/NoGo task requiring responses to be withheld (“NoGo”). In the future, we will use these tasks to track cognitive impairment in

our HD-NHPs and relate the progression of cognitive deficits to region-specific alterations in brain microstructure.

17. Sleep-Wake Lactate Dynamics in Human Brain

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Glymphatic system, a brain-wide glial vascular physiology, facilitates the clearance of solutes and metabolic wastes from the brain interstitium. Mainly active during sleep or anesthesia relative to wakefulness, glymphatic pathway is suggested to be an important clearance system for removal of soluble Aβ from the interstitium, and (a less well-functioning) glymphatic system is associated with slowed amyloid beta clearance and more rapid amyloid plaque deposition. More recently, glymphatic system is also associated with the clearance of lactate in mice brain during sleep or anesthesia. While rodent brain lactate concentrations have been investigated for more than 70 years with sharp reductions in lactate levels during sleep or anesthesia relative to wakefulness, sleep-dependent lactate dynamics in human brain have never been reported, particularly in the context of glymphatic function. We have recently developed simultaneous of magnetic resonance spectroscopy (MRS) and polysomnography (PSG) measurements to evaluate the human brain lactate concentrations across sleep-wake cycles. The effects sizes of our study, first in-vivo demonstrations of sleep-wake lactate dynamics in human brain, are consistent with the previous rodent studies reporting reduced brain lactate levels during sleep compared to wakefulness (12-35 %). We believe the significant reduction in brain lactate during sleep, particularly slow-wave sleep, compared to wakefulness is supported by glymphatic pathway function.

18. Differential effects of ECS and TMS on adult hippocampal neurogenesis

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Hippocampal neurogenesis has been shown to play a critical role for antidepressant effect, is negatively regulated by stress, and neurostimulation therapy very potently increases neurogenesis. To further elucidate specific changes in hippocampal neurogenesis following stimulation therapies, we examined the timeline of neurogenesis after electroconvulsive shock (ECS), in mice, and compared with repetitive transcranial magnetic stimulation (rTMS, 10 Hz) and intermittent theta burst stimulation (iTBS).
We first assessed new-born cell survival, proliferation, and maturation following a single session of neurostimulation. We found that just one session of ECS increased the number of surviving cells significantly immediately starting on day 1, declining to baseline on day 3. We saw similar changes with iTBS, but not rTMS. Cell proliferation levels following ECS was similar to shams on day 1, peaked on day 3, and declined to basal levels on day 7. One session of iTBS and rTMS did not change cell proliferation. The data indicates that there is a delayed and transient increase in neuronal proliferation following ECS,

and a loss of earlier-born cells. For neuronal maturation, we did not see differences across days for all forms of neurostimulation.
Since neurostimulation is applied chronically in the clinic, we also investigated whether 10 sessions of iTBS impacted neurogenesis. Using an Ascl1-CreER mouse, we found that the morphology of adult-born tdTomato+ neurons was also not affected by subsequent chronic iTBS treatment, in terms of dendritic length and spines. Ongoing work is examining the effects of chronic neurostimulation on neurogenesis marker levels.

19. CRISPR/SaCas9 combinatorial strategies for gene mutagenesis in mice.

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A major challenge to understanding how genes modulate complex behaviors is the ability to restrict genetic manipulations to defined cell populations or circuits. To circumvent this, we created a simple strategy for limiting gene knockout to specific cell populations using a viral-mediated, conditional CRISPR/SaCas9 system in combination with intersectional genetic strategies. A small single guide RNA (sgRNA) directs *Stepholococcus aurorus* CRISPR-associated protein (SaCas9) to unique sites on DNA in a Cre-dependent manner resulting in double strand breaks and gene mutagenesis *in vivo*. To validate this technique we targeted five different genes of diverse function in distinct cell types in mice and performed an array of analyses to confirm gene mutagenesis and subsequent protein loss, including IHC, FACS and sequencing, electrophysiology, Western blots, and behavior. We show that these vectors are as efficient as conventional conditional gene knockout and provide a viable alternative to complex genetic crosses. This strategy provides additional benefits of targeting gene mutagenesis to cell types previously difficult to isolate, and the ability to target genes in specific neural projections for gene inactivation. Our studies illuminate AAV-CMV-FLEX-SaCas9-U6-sgRNA as a valuable tool for rapid, efficient and robust analysis of gene function.

20. Characterization of CeA dynorphin and its role in discriminative fear learning .

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Within the amygdala, the central amygdala (CeA) has emerged a dynamic population critical for cued fear. This GABAergic region is highly heterogeneous and is known to express a variety of stress-associated neuropeptides including dynorphin (dyn) and its receptor the kappa opioid receptor (KOR). While, dynorphin is hypothesized to be released in the CeA in response to stress, little is known about the role of dynorphin in CeA circuitry and fear. First, we histologically confirmed the presence of CeA^{dyn} nueurons in the lateral and medial subdivisions of the CeA, which display dense local projections and weaker projections to the the bed nucleus of the stria terminalis (BNST) and parabrachial nucleus (PBN). Using the RiboTag technique of cell-type specific RNA isolation, we discovered that CeA^{dyn} neurons also co-express a variety of neuropeptides and their receptors, including KOR. Next we explored the necessity of CeA^{dyn} neurons in fear learning and anxiety. Silencing of CeA^{dyn} neurons blocks low intensity discriminative fear learning without inducing changes in anxiety, but conditional knockout of local CeA dynorphin results in little or no behavioral disruption. Alternatively, knockout of dynorphin from all CeA-projecting cells elicits fear generalization and enhanced anxiety. These results suggest that dynorphin relase into the CeA by non-local cells is critical for normal cue-specific discriminative fear learning, as its dysregulation leads to higher anxiety and cue generalization. We continue to investigate the dynorphin-expressing inputs to the CeA and the critical sites of KOR activation to further understand the circuitry by which dynorphin mediates discriminative fear.

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21. Vertebral Fracture Segmentation and Assessment with Hypergraph.

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Spine pathology needs an automatic quantification of vertebral segmentation. Medical Image Analysis was done to detect the vertebral fractures from CT scan images. Radiologists can make use of this application to diagnose Vertebral Fracture in patient care. Data of 100 MDCT scans of vertebrate from Department of Neuroradiology, School of Medicine, Technical University Munich, Germany was used. Hypergraph Based Segmentation, Random-Walk Based segmentation and watershed Segmentation was implemented in Python 3.4 and extracted the fracture area using 3D Slicer environment. Through this implementation, it was observed that random-walk was better than the other two algorithms and also it was seen that it can retrieve the contents that are not uncovered by watershed algorithm.