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Wednesday May 10th, 2017

8:00 AM - 9:30 AM		**Check-In/Registration**
9:30 AM - 9:50 AM		**Opening Remarks:** Kamran Khodakhah, Ph.D., Chair, Dominick P. Purpura Department of Neuroscience
9:50 AM - 10:50 PM		**Scientific Session I**
		Neural Systems - Chairs: Amir Aschner, Kelin Brace
9:50 AM:	Sophie Molholm	Multisensory processing in typically developing children and children with autism
10:10 AM:	Christopher Henry	Behavioral and neurophysiological characterization of visual crowding in macaques
10:30 AM:	Ruben Coen-Cagli	Probing internal models for image segmentation in the primary visual cortex
10:50 AM - 11:10 AM		**Break**
11:10 AM - 12:10 PM		**Scientific Session II**
11:10 AM:	Saleem Nicola	Integrated control of cued approach by the nucleus accumbens
11:30 AM:	Gervasio Batista	Translational control of imprinting and structural plasticity in chickens
		From Gene to Circuits – Chairs: Kyle Jensen, Abigail Carbonell
11:50 AM:	Ariel Vitenzon	Activation of α1 adrenergic receptors is required and sufficient for stress-induced attacks of motor dysfunction in a mouse model of Episodic Ataxia Type 2
12:15 PM - 2:00 PM		**Lunch** (Main Building)
2:00 PM - 3:00 PM		**Scientific Session III**
2:00 PM:	Kaoutsar Nasrallah	Firing a single dentate granule cell induces a presynaptic form of LTP at Mossy cell-dentate granule cell synapse.
2:20 PM:	Bryen Jordan	Synaptic proteomics to probe normal and pathological brain function
2:40 PM:	Julie Secombe	A histone demethylase with important neuronal functions
3:00 PM - 3:15 PM		**Break**
3:15 PM - 4:15 PM		**Keynote Speaker:** Jonathan Alpert, M.D./Ph.D, Chair, Psychiatry and Behavioral Sciences
4:30 PM - 6:30 PM		**Poster Session** (Main Building)
6:30 PM - 8:00 PM		**Wine Tasting** (Main Building)
8:00 PM - 10:00 PM		**Dinner** (Main Building), cash bar available
		Followed by DJ with Karaoke

Thursday May 11th, 2017

8:00 AM - 10:00 AM		**Breakfast** (Main Building)
9:00 AM - 10:00 AM		**Ethics Session (Mandatory Participation)**
10:30 AM - 11:50 AM		**Scientific Session IV**
10:30 AM:	Sulagna Das	Visualization of single endogenous Arc mRNA dynamics in hippocampal neurons
		Development, Regeneration and Disease – Chairs: Mallory Kerner, Marta Gronska
10:50 AM:	Hannes Buelow	Stepwise assembly of dendritic arbors through non-autonomously acting factors
11:10 AM:	Tiago Gonçalves	Imaging the Growth and Pruning of Dendritic Trees Using *in vivo* 2-photon Microscopy
11:30 AM:	Lauren Boudewyn	N-butyl-deoxynojirimycin delays disease phenotypes in a mouse model of Mucolipidosis type IV
12:00 PM - 4:00 PM		**Lunch** (Main Building)
		Activities by the Lake
4:00 PM - 5:20 PM		**Scientific Session V**
4:00 PM:	Vytas Verselis	Cx26 and Sensorineural Syndromic Deafness
4:20 PM:	Jee-Yeon Hwang	The role of miR-34 in ischemia-induced neuronal death
4:40 PM:	Praveen Ballabh	Premature birth and heterogeneity of cortical interneurons
5:00 PM:	Joseph Arezzo	Translation of Basic Science Finding to Clinical Research
5:20 PM		**Concluding Remarks:** Kamran Khodakhah, Ph.D., Chair, Dominick P. Purpura Department of Neuroscience

Abstracts

Presenter: Ana Alves Francisco
Title: *Cross-sensory prediction in ASD*
Contributing Author(s): John J. Foxe, Hans-Peter Frey, Sophie Molholm

Multisensory integration allows us to take advantage of redundant and complementary multisensory cues, and form percepts that are more reliable. Modulations of the auditory event-related potential components N1 and P2 have been consistently implicated as indices of multisensory integration. In the general population, the auditory-evoked N1 and P2 components are attenuated and speeded up when the auditory signal is accompanied by predictive congruent visual information. The general assumption is that precedence of visual information reduces signal uncertainty and lowers the computational demands on auditory brain areas. In this study, we aimed to determine whether the multisensory facilitatory effects described above were present in a sample of children and adolescents diagnosed with an Autism Spectrum Disorder (ASD). Participants were presented with speech and non-speech multisensory stimuli, while high-density scalp electrophysiological measurements were taken. Preliminary analyses suggest that while multisensory predictive effects are present, they may be delayed in ASD.

Presenter: Joseph Arezzo
Title: *Translation of Basic Science Finding to Clinical Research*

The strength of our department has always been the exploration of basic science principles. However, the impact of these finding is often related to their ability to modify clinical deficit. We will explore four translational clinical studies conducted in the Einstein Neuroscience Department that have emerged from our basic science research.

• Exploration of the role of blocking NGF in modulating clinical pain. Initial finding suggest pain reduction matching that of opioids without the side effects – however, neuropathy in some patients is a concern.
• The use of VEGF, which induced both angiogenesis and vasculogenesis, as a means of altering ALS.
• The use of thalidomide (yes, thalidomide) to modulate cytokines as a means of reducing Complex Regional Pain Syndrome Type 1.
• The emergence of novel means of reducing the long-term neuronal damage associated with chemotherapies - including nanotechnology.

Presenter: Amir Aschner
Title: *Adaptation dynamically alters normalization signals in primary visual cortex*
Contributing Author(s): Samuel Solomon, David Heeger, Michael Landy, Adam Kohn

Adaptation is a ubiquitous aspect of sensory encoding. Adaptation's effects on neuronal responses have been extensively characterized; however, we lack a framework that integrates this phenomenology. We and others have proposed that adaptation effects may be explained through altered normalization signals. Normalization is a 'canonical' computation whereby a neuron's responses are suppressed by the summed activity of other neurons (normalization pool). Here we ask how adaptation alters normalization strength. Recent theoretical work proposes that normalization is strengthened when a neuron and its normalization pool are driven synchronously ('contingent adaptation') and weakened when they are driven asynchronously. To test this hypothesis, we performed extracellular recordings in primary visual cortex (V1) of anesthetized macaques. We measured responses to plaid

stimuli composed of gratings, before and after contingent or asynchronous adaptation. Our results indicate that normalization is shaped by adaptation. Specifically, co-activating a neuron and normalization pool strengthens normalization whereas asynchronous activation weakens normalization.

Presenter: Praveen Ballabh
Title: *Premature birth and heterogeneity of cortical interneurons*

Premature-born children and adolescents exhibit neurobehavioral disorders that may result from disturbance in the population of cortical interneurons. Here we show that parvalbumin+ and somatostatin were the principle type of fetal interneurons during late human pregnancy. In humans, premature birth resulted in a reduced population of parvalbumin+ or GAD67+ cells and an increase in somatostatin+ interneurons in the upper cortical layers. Importantly, estrogen treatment in premature rabbits (E28.5, Term 32D) increased the density of parvalbumin+ neurons in the upper cortical layers at both postnatal days 14 and 21, but not of somatostatin+ neurons. Moreover, GAD65, GAD67, and Ascl1 levels, which are key regulators of interneuron maturation, were expressed higher in estrogen-treated rabbits relative to controls. Hence, a reduced ratio of parvalbumin+/somatostatin+ cortical neurons in premature newborns is reversed with estrogen replacement therapy, which can be attributed to elevated Ascl1. As estrogen level drops with premature birth, estrogen replacement might enhance neurodevelopmental outcomes in extremely preterm infants.

Presenter: Gervasio Batista
Title: *Translational control of imprinting and structural plasticity in chickens*
Contributing Author(s): Jennifer Leigh Johnson, Elena Dominguez, Mauro Costa-Mattioli, Jose L Pena

While the molecular machinery regulating experience-dependent protein synthesis in adulthood has been extensively studied, the mechanisms underlying memory consolidation during early critical periods remain unknown. We addressed this question studying imprinting, a specific form of learning occurring within the first days after hatching, in newborn chickens. Since translation initiation is a rate-limiting step in protein synthesis, we focused on the role of the translation initiation factor eIF2α and the kinase complex mTORC1 during the critical period for imprinting. Using SUnSET, a method to visualize newly synthesized proteins in vivo, we found that imprinting to arbitrary sounds and virtual objects leads to increase in protein synthesis in specific forebrain regions, involved in imprinting, the mediorostral nidopallium/mesopallium (MNM) and the intermediate medial mesopallium (IMM). We assessed experience-dependent activation of eIF2α and mTORC1 in imprinting relevant areas using western blots. eIF2α was activated exclusively in MNM (auditory area) while mTORC1 was activated both in IMM (visual area) and MNM. Following this finding, a series of gain- and loss-of-function experiments demonstrated that the signaling pathways underlying imprinting in the auditory and sensory modalities were not identical. While visual imprinting only required mTORC1, auditory imprinting required dephosphorylation of the translation initiation factor eIF2α in addition to activation of the kinase complex mTORC1. To further understand how eIF2α and mTORC1 regulate imprinting we investigated experience-dependent structural plasticity. We found that training during the critical period triggers an increase in mushroom-type spines. Using pharmacology we showed that eIF2α dephosphorylation was required specifically for structural plasticity in the auditory pathway, while mTORC1 mediated spine remodeling in both auditory and visual nuclei. Subsequently, we asked whether targeting upstream molecules to enhance eIF2α and mTORC1 signaling, outside of the critical period, could

restore behavioral plasticity selectively in each modality. Indeed, facilitating eIF2α-mediated translation restored auditory imprinting and mTORC1 activation restored imprinting across sensory modalities. Thus we found two molecular mechanisms important for the formation of early imprinted memories and related structural plasticity. Moreover, we demonstrated that targeting eIF2α and mTORC1 pathways can rejuvenate plasticity once the critical period is closed.

Presenter: Michael Beckert
Title: ***Effect of direction-dependent feature selectivity on the representation of sound location in the owl's midbrain***
Contributing Author(s): Brian J. Fischer, Jose L. Pena

We investigated the relationship between the selectivity of neurons to identity and spatial features of sound. The selectivity of auditory neurons to identity features manifests as a reproducible timing of spikes across repeated trials of a sound. We found that this reproducibility was direction-dependent in space-specific neurons of the midbrain, reaching a maximum at their preferred direction. This suggests that spiking of neurons with similar feature selectivity may be more or less synchronized depending on sound identification. We confirmed this prediction in downstream neurons recorded with tetrodes. Using a decoding model we demonstrate that this synchrony can affect decoding of ambiguous stimuli by selectively weighting neurons that respond to the dominant stimulus. In conclusion, we found a co-dependency between the encoding of sound identity and location through spike timing in the midbrain of the barn owl.

Presenter: Shlomit Beker
Title: ***Components of cross-sensory oscillations in the human brain***
Contributing Author(s): Luke Shaw, Tufikameni Brima, John J. Foxe and Sophie Molholm

Information in the sensory environment tends to be highly predictive of upcoming events, allowing for online planning and decision-making. The neural processing of predictable stimuli is significantly facilitated compared to that of non-predictable stimuli. Thus, for example, temporally predictive visual information modulates the processing of incoming auditory information. The rhythmic patterns of stimulation coordinated across sensory modalities, such as audiovisual speech or the playing of a violin, are common in the environment and present a highly predictive state. To test the role of entrainment in cross sensory facilitation, we presented visual and auditory stimuli in which rhythmicity of temporally predictive events was manipulated, and measured cortical activity with high-density EEG from 16 human adults. We show that cortical entrainment, inferred by a cortical response to stimulus in different rhythms, is dependent on the degree of expectancy of the cross-sensory stimuli. This approach to understanding mechanisms underlying cross-sensory prediction provides a powerful tool to interrogate efficiency of brain anticipation for incoming stimuli.

Presenter: Helen Belalcazar
Title: *Defining the role of the transcriptional regulator KDM5 in neuronal development*
Contributing Author(s): Julie Secombe

The histone demethylase KDM5 family of proteins plays important roles during neuronal development. First, *in vitro* studies using mammalian neurons demonstrated that knockdown of KDM5C causes alterations in dendrite branching. Second, *in vivo* studies in *C. elegans* and mice showed that KDM5 proteins are required for correct axonal position, dendrite branching and spine density of specific neurons. Finally, mutations in KDM5A, KDM5B and KDM5C are observed in patients with intellectual disabilities. Yet, the molecular mechanisms linking KDM5 proteins to neuron development and function remain unknown. Because KDM5 proteins are transcriptional regulators, our overarching hypothesis is that this family of proteins mediate transcription programs essential to neuronal function. Using a combination of transcriptome, chromatin binding and genetic analysis, the main goal of this project is to elucidate the developmental pathways in the nervous system of *Drosophila* larvae that are regulated by KDM5.

Presenter: Lauren Boudewyn
Title: *N-butyl-deoxynojirimycin delays disease phenotypes in a mouse model of Mucolipidosis type IV*
Contributing Author(s): Jakub Sikora, Ladislav Kuchar, Jana Ledvinova, Yulia Grishchuk, Shirley Wang, Kostantin Dobrenis, and Steven U. Walkley

Mucolipidosis type IV (MLIV) is a lysosomal storage disease exhibiting progressive intellectual disability, motor impairment, and premature death. There is currently no cure or corrective treatment. The disease results from mutations in the gene encoding mucolipin-1, a transient receptor potential channel believed to play a key role in lysosomal calcium egress. Loss of mucolipin-1 and subsequent defects lead to a host of cellular aberrations, including accumulation of glycosphingolipids (GSLs) in neurons and other cell types, Purkinje cell abnormality, and microgliosis. Several studies have demonstrated that N-butyl-deoxynojirimycin (NB-DNJ, also known as miglustat), a partial inhibitor of the enzyme glucosylceramide synthase (GCS), successfully delays the onset of motor deficits, improves longevity, and rescues some of the cerebellar abnormalities (e.g., Purkinje cell death) seen in another lysosomal disease known as Niemann-Pick type C (NPC). Given the similarities in pathology between MLIV and NPC, we examined whether miglustat would be efficacious in ameliorating disease progression in MLIV. Using a full mucolipin-1 knockout mouse, we found that early miglustat treatment delays the onset and progression of motor deficits, delays cerebellar Purkinje cell loss, and reduces cerebellar microgliosis characteristic of MLIV disease. Quantitative mass spectrometry analysis provided new data on the GSL profiles of murine MLIV brain tissue and shows that miglustat partially restores a wild type profile in white matter but not in gray matter. Collectively, our findings indicate that early miglustat treatment delays the progression of clinically relevant pathology in a MLIV mouse model, and therefore supports consideration of miglustat as a therapeutic agent for MLIV disease in humans.

Presenter: Kelin Brace
Title: *Effect of Multitasking on Neural Representations of Sounds in Working Memory*
Contributing Author(s): Elyse Sussman

Although auditory multitasking is common in social settings, relatively little is understood about how the human brain processes stimuli in a complex auditory environment. Most studies that examine multitasking rely on behavioral measures of performance, providing no direct information about the processing of unattended stimuli. Electroencephalography (EEG) directly measures cortical activity, enabling a more complete study of how the brain processes discrete events and divides attention during multitasking. We hypothesize that auditory working memory stores neural representations of distinct auditory stimuli to facilitate simultaneous performance of multiple tasks. We will investigate this hypothesis by performing electrophysiological and behavioral analysis on human subjects performing auditory tasks with stimuli that approximate complex auditory scenes.

Presenter: Hannes Buelow
Title: *Stepwise assembly of dendritic arbors through non-autonomously acting factors*

The dendritic arbor of the somatosensory neuron PVD is established in a step-wise fashion. Primary dendrites grow out along the lateral mid-body toward, followed by successive orthogonal branching of 2º, 3º and 4º branches. We have recently identified factors that non-autonomously pattern 2º, 3º and 4º branches of the PVD dendritic arbor. Here we focus on the mechanisms required for formation and maintenance of the primary PVD dendrite. We demonstrate that growth and localization of the PVD primary dendrite depends on the axonal process of the ALA neuron, which is patterned by the extracellular matrix protein MIG-6/Papilin together with UNC-6/Netrin, and anchors the primary dendrite in the lateral nerve cord. Additionally, the conserved SAX-7/L1CAM cell adhesion molecule keeps primary PVD dendrites in place throughout life. Thus, step-wise dendritic patterning is non-autonomously controlled from both skin and muscle, but also through guidance and maintenance by neuronal processes of other neurons.

Presenter: Kelly Burke
Title: *Three distinct neural networks are responsible for cognitive flexibility in healthy adults*
Contributing Author(s): Sophie Molholm, John Foxe

Behavioral studies of cognitive flexibility have demonstrated three aspects within cognitive flexibility that can be independently studied and manipulated: *task-switching*, *incongruency*, and *response-switching*. Most studies investigate the brain regions involved in task-switching alone, therefore we sought to investigate, utilizing both fMRI and EEG, which regions were involved in all three, and how much of those networks overlapped. Our fMRI findings suggest that left inferior parietal cortex, left middle frontal, and right cerebellum are regions involved in all three aspects. However, anterior cingulate cortex and left fusiform gyrus were uniquely recruited for incongruent stimuli, while the thalamus and caudate were active during response-switching alone. The EEG data revealed consistent findings with the fMRI but allowed for better temporal resolution of the regions involved. Understanding distinct activity that allows for different types of cognitive flexibility may be relevant to better understanding deficits seen in populations such as autism, schizophrenia, and ADHD.

Presenter: Abigail Carbonell
Title: *AIDA-1 in Adult Neurogenesis and Rodent Behavior*
Contributing Author(s): Jaafar Tindi, Bryen Jordan

Adult-born dentate granule cells (abDGCs) have a prominent role in learning and an emerging involvement in anxiety- and depression-like behaviors. Increased adult neurogenesis is associated with improved mood, and the unique synaptic plasticity in new neurons is involved in memory and discrimination. While adult neurogenesis is important for diverse hippocampal functions, the mechanisms underlying the genesis and function of adult-born neurons remain unclear. In the hippocampus, the protein AIDA-1 regulates synaptic transmission and plasticity mediated by NMDA receptors. AIDA-1 is highly expressed in dentate granule cells and their mossy fibers, where its function is not known. We hypothesize that AIDA-1 modulates mood and memory by acting as a novel regulator of adult-born hippocampal neurons. In behavioral paradigms of cognitive and affective function, we find that deletion of AIDA-1 from the forebrain (AIDA-1 cKO mice) reduces anxiety and impairs object discrimination. We also find that AIDA-1 cKO mice display increased cell proliferation and decreased EphA receptor levels in the hippocampus, consistent with increased neurogenesis. Using molecular biology, electrophysiology, and behavioral techniques, we will continue to investigate the role of AIDA-1 in the generation and function of adult-born neurons. Elucidating the mechanisms by which AIDA-1 regulates brain function could improve insight into the physiological basis of neuropsychiatric disorders and provide novel targets for pharmacotherapy.

Presenter: Kevin Caref
Title: *Activation of nucleus accumbens mu-opioid receptors is required for conditioned approach to palatable food in sated but not hungry rats*
Contributing Author(s): Saleem M. Nicola

The contribution of the nucleus accumbens (NAc) to the regulation of food intake remains elusive. Activation of mu-opioid receptors (MORs) in the NAc selectively augments consumption of freely available palatable food; however, blockade of these receptors with antagonists does not consistently reduce consumption. Therefore, we tested the hypothesis that endogenous opioids in the NAc instead promote food seeking. We trained ad libitum-fed or food-restricted rats on a conditioned stimulus (CS) task in which an auditory cue predicted availability of a cream reward. Rats were fitted with bilateral cannulated microelectrode arrays that allowed for simultaneous unit recordings and drug infusions within the NAc. After obtaining a ~30 min baseline, the MOR antagonist CTAP was infused bilaterally into the NAc, allowing pre- vs post-injection comparison of behavior and neural activity. Many NAc neurons exhibited cue-evoked excitations that preceded the initiation of approach to the receptacle. In sated rats, both CS-evoked receptacle approach and the magnitude of CS-evoked excitations were significantly attenuated following CTAP injection in the NAc. Strikingly, in food-restricted rats, neither cued approach behavior nor the magnitude of cue-evoked excitations were affected by CTAP. These results suggest that endogenous opioids in the NAc promote seeking of palatable calorie-dense food in the absence of a homeostatic drive for caloric intake, potentially contributing to obesity.

Presenter: Ilaria Carta
Title: *Cerebellar inputs to the VTA: reward and social roles*
Contributing Author(s): Christopher Chen, Amanda Schott, Schnaude Dorizan, Kamran Khodakhah

The cerebellum is an important structure for movement. However, some of its projections terminate in brain areas that serve higher functions. Cerebellar fibers are found in the VTA, an area known to participate in reward, motivation and social behaviors. Increasing evidence links cerebellar dysfunction to neuropsychiatric disorders such as autism and schizophrenia, where such behaviors are impaired. To test whether the cerebellar input to VTA is important to influence these complex behaviors we selectively modulated the cerebello-VTA pathway with optogenetics while performing behavioral testing to assess sociability and reward seeking. We found that the social preference of mice is altered by optical stimulation and inhibition of the cerebello-VTA connection. Activity in the pathway correlates with episodes of interaction. Moreover, mice self-stimulate the cerebello-VTA pathway. Our data suggest that cerebellum might be an important upstream structure that shapes VTA response to salient stimuli thereby influencing reward and social behavior.

Presenter: Maryann Castillo
Title: *Dissecting the Mechanism of NMDAR-mediated Plasticity in the Dentate Gyrus*
Contributing Author(s): Alma Rodenas-Ruano, Pablo E. Castillo

The dentate gyrus is responsible for processing and encoding distinct contextual associations in response to highly similar inputs, allowing behavioral discrimination. The dentate gyrus principal cells, dentate granule cells (GCs), receive excitatory inputs from the entorhinal cortex via the lateral perforant path (LPP) and the medial perforant path (MPP), and proximal associational inputs from hilar mossy cells (MC). While fast excitatory synaptic transmission is largely mediated by AMPA receptors, there is growing evidence that NMDA receptor-mediated synaptic transmission contributes significantly to information transfer, particularly during periods of repetitive activity. Using acute rat hippocampal slices, we found that repetitive activation of MPP inputs, but not LPP or MC inputs, elicits LTP of NMDA receptor-mediated transmission at MPP-GC synapses. Unexpectedly, this LTP is associated with heterosynaptic plasticity at LPP and MC synapses. Using electrophysiology, selective pharmacology and optogenetics, we are currently characterizing the mechanism underlying this heterosynaptic form of plasticity. Supported by NIH-GM104547 and NIH-MH081935

Presenter: Ruben Coen-Cagli
Title: *Probing internal models for image segmentation in the primary visual cortex*
Contributing Author(s): Adam Kohn

Sensory signals from the natural environment are represented by the coordinated activity of neuronal populations in cortex. Understanding this coordination will be central to understanding perception, and much of cortical computation. Recent technological advances offer a promising avenue to monitor large neuronal populations, but absent a theory of how input should be encoded, it is easy to miss aspects of neuronal activity that are crucial to understand perceptual function. I will present a normative theory of how visual cortical neurons interact to represent the natural visual environment, based on a well-specified computational goal: the segmentation of images into groups of features that belong to different physical objects. I will then present data recorded using multielectrode arrays in macaque primary visual cortex (V1). Preliminary analysis supports several predictions of the theory, providing novel insights into the structure of population responses to natural images.

Presenter: Steven Cook
Title: *Comparative connectomics of the adult male and hermaphrodite C. elegans*
Contributing Author(s): Travis Jarrell, Yi Wang, Ken Nguyen, Christopher Brittin, Max Yakovlev, Leo T-H Tang, Emily Bayer, Esther Serrano-Saiz, Oliver Hobert, Hannes Buelow, David Hall, Scott Emmons

Here we present the updated adult male and hermaphrodite connectomes of *C. elegans* based upon reconstruction and analysis of serial section electron micrographs. These results are based upon previously analyzed hermaphrodite data (White et al. 1986) and new electron micrograph series of the male that cover the complete nervous system of *C. elegans* and its endorgans. In a graph representation of synaptic connectivity, we visualize information flow through a multi-layered structure from sensory neurons to motor output. We have described different classes of inter- and motorneurons. Sensory information enters the worm through several modalities, and is separated into a four-layered, feedforward structure. Graphical layout algorithms based on connectivity reveal that neural network structure is conserved across the sexes. Correspondence of the layout to the worm's neuroanatomy is consistent with economical wiring. While most synaptic connections are conserved across sex, we find that sex-specific neurons target similar downstream partners to yield distinct behaviors. While the connectomes we have generated are static, we are using them to generate experimentally testable hypotheses. To incorporate the dynamics of development and inter-individual variability, we have developed a method called iBLINC (in vivo Biotin Labeling of INtercellular Contacts). This fluorescent system directionally labels individual synapses in the worm using neuron-specific promoters. By employing iBLINC we have verified sexually dimorphic synapses, as well as synaptic connections that break the left-right symmetry of the nervous system. By comparing complete connectomes mathematically and experimentally it is possible to consider how diverse sensory cues are combined and processed by the nervous system to produce a coherent and adaptive behavioral output.

Presenter: Michael J. Crosse
Title: *The Developmental Course of Multisensory Speech Integration: A Hierarchical Perspective of the Neurophysiology*
Contributing Author(s): Aida M. Davila, John J. Foxe and Sophie Molholm

Electrophysiological investigations of audiovisual (AV) speech processing in children have typically used syllabic stimuli, which may only partially engage the underlying hierarchical network. Recent EEG studies using system identification have obtained neural correlates of multisensory integration in response to natural AV speech and isolated neural indices of speech processing along the auditory cortical hierarchy. Here, we consolidate these frameworks to track the developmental course of AV speech processing in a hierarchical manner. Movies of a speaker reciting children’s stories were presented to children and adolescents while recording high-density EEG. Stimuli alternated between A, V and AV speech and were accompanied by acoustic noise at 2 dB, −9 dB and −14 dB SNR. Speech stimuli were transformed into spectrotemporal and phonetic representations and mapped to the EEG responses. Neural indices of multisensory integration were derived using the respective low- and high-level forward models at each of the 3 different SNRs.

Presenter: Michael J. Crosse
Title: *Impaired Development of Audiovisual Integration in Autism and the Effects of Modality Switching*
Contributing Author(s): John J. Foxe and Sophie Molholm

Response times for multisensory stimuli are often shown to violate the “race model”, indicating integrated processing. This ability to integrate multisensory inputs is gradually fine-tuned across childhood and adolescence but is not observed in autism (ASD). Here, we demonstrated that this development is delayed until adolescence in ASD. However, ongoing work by Shaw et al. (2017) has revealed that switching modality from trial to trial gives rise to this apparent AV interaction. To remove this “switch cost”, we separated trials into those preceded by a different stimulus (switch) and those preceded by the same stimulus (repeat). AV integration was no longer observed in ASD participants. Furthermore, the race model violation in TD participants is likely due to a residual “mixing cost”. This mixing cost differentially effects behavior in TD and ASD participants, suggesting an underlying deficit in multisensory processing. To further understand these behavioral differences, we examined EEG responses separately to the switch and repeat trials.

Presenter: Charles Crouse
Title: *Studying Temporal Decision Making in a Free-Operant Foraging Paradigm*
Contributing Author(s): Saleem Nicola

The delay-discounting paradigm is used to study how animals make decisions about how long to wait to receive reward and analyze the brain areas involved. However, results from this paradigm conflict with ecological observations about animal foraging where food is distributed in discrete patches, bringing these conclusions into doubt. We are developing an operant-conditioning paradigm modeled on animal choice in the wild to study foraging behavior. Food-restricted rats are trained to press a lever to receive sugar, but each press increases the wait time before the next lever presentation. Pressing a second lever returns the wait time to its original value after a reset period, modeling the time to travel between patches of food. We have found that increases in the reset time causes animals to wait longer for rewards, suggesting that rats are responsive to the task parameters and validating predictions from foraging theory. Future experiments will create a model of optimal choice and test the role of nucleus accumbens dopamine in this task.

Presenter: Sulagna Das
Title: *Visualization of single endogenous Arc mRNA dynamics in hippocampal neurons*
Contributing Author(s): HyeYoon Park, Robert Singer

Neuronal activity triggers transcription of many Immediate Early genes. Among them, Arc (activity-regulated cytoskeletal-associated) plays a crucial role in synaptic plasticity and memory consolidation. Arc expression is regulated via transcription and mRNA targeting to potentiated synapses. While most in vivo studies provide insights about the spatial regulation of Arc mRNA, however, the temporal dynamics of endogenous Arc mRNA in response to neuronal activity or LTP is not well defined. We generated a transgenic mouse where Arc gene was modified in the 3’UTR to contain the PP7 stem loops (PBS) that bind the PP7 capsid protein. The capsid protein contains fluorescence-tag, allowing dynamic visualization of active Arc loci and individual transcripts. Using single molecule fluorescent *in situ* hybridization (smFISH) we detect and quantify individual Arc mRNAs after triggering neuronal activity. Also, by real-time imaging of transcription and dendritic mRNAs, we measure the kinetic profile of Arc transcription and mRNA localization at active versus inactive spines. This approach provides insights about

Arc mRNA regulation from ensemble to single cell and to single genetic locus level.

Presenter: Aida M. Davila
Title: *Investigating the Utility of Phoneme-Related Potentials (PRPs) to Study the Development of Audiovisual Speech Processing*
Contributing Author(s): Michael J. Crosse and Sophie Molholm

Electrophysiological studies offer insight into the neural underpinning and temporal dynamics of multisensory integration. However, the stimuli in such experiments typically consist of isolated events presented repeatedly. Such stimuli offer only limited insight into multisensory enhancement of speech processing. We extracted phoneme-related potentials (PRPs) to speech presented in a multisensory context. Children (*n* = 8) and adults (*n* = 8) were presented with natural continuous speech, at different signal-to-noise ratios (2dB, -6dB, -14dB) and in unisensory (A, V) and multisensory conditions (AV), while high-density EEG was recorded. Stimuli were phonetically transcribed, and the timing of each phoneme was used to extract the corresponding PRP in the neural response. Using this approach, we compared multisensory speech integration for different classes of phonemes, and how this differs in children and adults. This novel approach provides an ecologically relevant way to study the developmental trajectory of multisensory speech processing in young children and clinical populations.

Presenter: Roberto De Gregorio
Title: *Role for transient SERT expression in hippocampal pyramidal neurons during perinatal development in shaping stress response circuits*
Contributing Author(s): Zhigui Li, Emilie Petit, Maria Gulinello, Kostantin Dobrenis, Ji Ying Sze

Our laboratory is interested into delineating the genetic basis of early life programming of neural circuits, with a focus on the role of the neurotransmitter serotonin (5-HT). Serotonin uptake transporter (SERT) controls 5-HT signaling, by limiting 5-HT availability at 5-HT receptors. Importantly, the biological roles of SERT in the developing and adult CNS differ. SERT antagonists are the first-line treatments of psychiatric traits in adults. In contrast, disruption of SERT function genetically or pharmacologically in the developing brain leads to heightened anxiety behavior in human and rodents. We have recently identified a SERT mechanism operating only in the developing brain to prevent excessive trophic 5-HT in specific brain regions. Specifically, SERT is transiently expressed in a unique set of glutamatergic thalamic neurons projecting to sensory cortices and in pyramidal cells both in the prefrontal cortex and hippocampus (Hip), during a phase of exuberant neurite outgrowth and synaptogenesis that lays down the basic neural circuits. These neurons, termed "5-HT-absorbing neurons", do not synthesize 5-HT, but uptake extracellular 5-HT (Gaspar et al, 2003; Jafari et al, 2011). In previous work we have shown by conditionally knocking out (CKO) SERT in mice, that temporal-specific SERT expression in 5-HT-absorbing axons determines neuronal patterning and synaptic architecture of target brain regions, whereas SERT expressed in 5-HT-producing neurons is not required (Chen et al., 2015, 2016). The goal for this project is to determine the impact of disruption of SERT expression in Hip 5-HT-absorbing neurons on limbic circuit development, stress responses and behavior. We show that SERT expression in 5-HT-absorbing neurons coincides with pyramidal and granule cell lamination of the Hip. We found that disruption of the transient SERT expression in the Hip neurons is sufficient to impair adult neurogenesis in the dorsal Hip dentate gyrus. Given that exposure to stress is one of the best-known negative regulators of adult Hip neurogenesis (Lucassen et al.,

2015), ongoing experiments are consequently directed at assessing stress gene expression and stress behavior in our SERT CKO mice. We hypothesize SERT expressed in 5-HT-absorbing neurons underscores a developmental phase particularly susceptible to environmental and genetic perturbations leading to increased risks for anxiety-related disorders, whereas SERT expressed in 5-HT-producing axons primarily modulates adult processes promoting stress resilience. Using high-resolution imaging and gene expression profiling, we will determine the role of SERT in Hip synaptic architecture and stress gene expression changes during the circuit development and in the adult CNS.

Presenter: Christopher DeJesus
Title: *A Functional Role for REST Co-repressor 2 (Rcor2) in Corpus Callosum Development*
Contributing Author(s): Mark F. Mehler

The epigenetic regulator REST co-repressor 2 (Rcor2) is highly expressed in the developing telencephalon, yet its roles in cortical neurogenesis remain unclear. To address this we conditionally deleted Rcor2 in $EMX1^{+}$ dorsal neural progenitors. Loss of Rcor2 results in a dysgenesis of the corpus callosum. We found that the dysgenesis was due to a selective defect in early-born “pioneer” callosal projections approaching the midline. In Rcor2 knockout ($Rcor2^{cKO}$) mice, there is a reduction in the transcription of pioneer axon guidance cues Slit2 and Sema3c, and this reduction was caused by disorganization of midline guidepost structures that they emanate from. We next investigated upstream regulators of Sema3c expression; neurogenin1 and 2(ngn1/2) and found transcription of both were significantly reduced in $Rcor2^{cko}$mice. Finally, using chromatin Immunoprecipitation we found that Rcor2 occupies regulatory regions on both ngn1 and 2 genes suggesting a potential mechanism by which Rcor2 may facilitate callosal axon pathfinding.

Presenter: Sara Duran
Title: *Communication between the Zona Incerta and the Cerebellum*
Contributing Author(s): Ramakrishnan K.B, Kamran Khodakhah

The Zona Incerta (ZI) is a subcortical brain region and its caudal sector (cZI) has been identified as a promising therapeutic target for deep brain stimulation (DBS) for Parkinson’s disease (PD). The underlying therapeutic mechanism is unknown, but cZI-DBS results in dramatic improvement in motor function, particularly alleviating all of the tremor components. Increasing evidence suggest that the cerebellum (CB) contributes to the pathophysiology of PD and that over-activity influences tremor. We propose that the alleviation of tremor in DBS may be influenced by a connection between the cZI and CB. We hypothesize that ZI can communicate with the CB via the pontine nuclei (Pn). We injected an anterograde, transneuronal viral tracer in the ZI of mice and preliminary histological data indicates that the connection is made via the most medial and lateral areas of the Pn. In the CB, the viral tracer is consistently found in cells and fibers in the lateral hemisphere of the posterior CB, in particular Crus2 and the deep cerebellar nuclei. Furthermore, we examined whether the activity in the Pn is reliably being modulated by the input received from ZI by injecting Channelrhodopsin in the ZI and optically stimulating its axonal projections in the Pn with a single pulse of light while recording single neuronal extracellular activity. A fraction of cells increased their firing rate, while the other fraction of cells was inhibited. Future studies will investigate the functional significance of the entire pathway using optogenetics while recording in the CB. Further characterization of this pathway will be delineated by targeting the specific sub-divisions of the ZI.

Presenter: Scott Emmons
Title: *A molecular code for synaptic specificity in C. elegans*
Contributing Author(s): Byunghyuk Kim, Olha Ivashkiv

Most synaptic connections in animal nervous systems are genetically specified. How connectivity is encoded in the genome is largely unknown. The molecules thought to act as cell-recognition tags comprise a largely evolutionarily conserved set of transmembrane or secreted proteins with extracellular protein-protein interaction domains, such as IG, LRR, EGF, cadherin, fibronectin, and so forth. There are 106 such proteins encoded in the *C. elegans* genome. We have determined the expression pattern of almost the entire set of genes in the defined neural network of 238 neurons and muscles that subserve male copulatory behavior. Seventy-seven of the 98 genes tested so far (79%) are expressed in complex patterns. We now seek correlations with connectivity that we hypothesize will reveal the nature of an abstract, combinatorial code for synaptic specificity. We have experimentally verified the roles of 7 of the genes in formation of a specific set of connections.

Presenter: Dylan Festa
Title: *Variability of V1 population responses to natural images reflects probabilistic inference*
Contributing Author(s): Ruben Coen-Cagli, Adam Kohn

Natural visual stimuli are characterized by high statistical complexity, ambiguity and noise. Our nervous system is capable of processing them in a fast and efficient way, however the coding strategies and mechanisms underlying this process are mostly unknown. In previous work, Coen-Cagli et al (Nat. Neuro. 2015) could predict with high accuracy the neural responses to natural images in the primary visual cortex (V1) of macaques. Their model accurately explained surround-suppression effects, whereby the output of a neuron, which depends primarily on the signal falling on its receptive field, may or may not be modulated by visual stimuli surrounding the input. The model prediction, validated by data, is that modulation is strong for homogeneous images, and weak for heterogeneous ones. However, this past work only considered trial-averaged firing rates. Here we substantially extend the model to generate predictions about the across-trial variability of the population activity. Such variability in the current model arises from two main sources: first, observation noise, e.g. due to stochasticity of retinal responses; second, uncertainty about the value of the image features represented by the neurons, i.e. the intensity of the orientation channels. The main prediction is that V1 population variability is influenced by the statistical homogeneity of the visual inputs, independently from the modulation of firing rate. Preliminary data recorded in macaque V1 support these prediction.

Presenter: Carmen Freire
Title: *Sam68 role in the stress response: consequences in RNA metabolism and motor behavior in mice.*

How chronic stress responses unbalance protein homeostasis at the synapse exacerbating synaptopathies is still unknown. Regulation of translational and transcriptional pathways, constitutes part of the cell response to cope with environmental stress. Sam68 (Src associated protein in mitosis, 68kD) an RBP RNA-binding protein (RBP), mediates downstream signaling in response to neuronal activity, and other internal/external stimuli. Sam68 regulates the splicing, translation and transport of important synaptic mRNA cargoes and immune system components. We hypothesize that maladaptive responses to repetitive stress stimuli alter proteostasis through control of Sam68 function altering synaptic function. We address the effects on Sam68-dependent RNA

metabolism following pharmacologically induced stress in hippocampal cell cultures, and in vivo using Sam68 KO mice. Given the role of Sam68 in ataxia we also show how stress impacts certain aspects of the motor phenotype in Sam68 mutant mice.

Presenter: Basia Galinski
Title: *XPO1 Overexpression in Neuroblastoma at Ultra-High Risk for Treatment Failure*
Contributing Author(s): Marcus Luxemburg, Michelle Ewart, Jean Hebert, Daniel Weiser

Half of patient with high-risk neuroblastoma, a neural crest cell-derived childhood cancer, succumb to disease despite intensive therapy. We have identified that overabundance of Exportin-1 (XPO1), a nuclear export protein responsible for shuttling tumor suppressors and anti-apoptotic proteins, is associated with inferior outcome. Treatment with selinexor, a novel XPO1 inhibitor, inhibits translocation of these proteins implicated in oncogenesis. We hypothesized that XPO1 expression directly correlates with sensitivity to selinexor, a pharmacologic XPO1 inhibitor. Neuroblastoma cell lines were treated for 24 hours with selinexor or DMSO, RNA and protein was extracted, and subsequently used for rt-qPCR and western blot analysis. Treatment with selinexor increased XPO1 mRNA expression and slightly decreased protein levels of all neuroblastoma cell lines. Selinexor reduced proliferation of cell lines. To gain mechanistic understanding of XPO1 in cancer we are increasing XPO1 by plasmid transfection. Comparison of XPO1 in increased and native cell lines will provide rationale for XPO1 protein abundance and therapeutic response of selinexor.

Presenter: Tiago Goncalves
Title: *Imaging the Growth and Pruning of Dendritic Trees Using in vivo 2-photon Microscopy*

The dentate gyrus (DG) is one of two regions of the mammalian brain where neurogenesis takes place during adulthood. The integration of newborn neurons into DG circuitry has been extensively studied using histology and in vitro slice preparations but thus far it has been impossible to follow the same adult-born cell at several time-points during its maturation process. By placing an imaging ‘window’ implant into the hippocampus we are able to image retrovirally labeled adult-born granule neurons and follow them for 6+ weeks in vivo at different development stages, using 2-photon laser scanning microscopy. This approach allowed us to characterize the dendritic development time-course of individual adult-born dentate granule cells (DGCs). We found that DGC dendrites grow in size and increase their branching up to ~21 days post-mitosis, followed by a period of pruning that is characterized by a net removal of branches. By the end of the fourth week post-mitosis dendritic trees are generally mature and stable. Dendritic growth is influenced by both molecular cues and neuronal activity. Knocking-down CELSR3, a core component of the Wnt/Planar Cell Polarity (PCP) pathway resulted in stunted dendritic growth, confirming our previous findings (Schaffer et al. 2015). Interestingly, increased neuronal activity resulted in faster dendritic growth, more extensive arborization and earlier pruning. In summary we established a novel method for longitudinally following the morphological development of adult-born DGCs and we were able to characterize the effect of specific molecular cues and neuronal activity on dendrite growth and pruning.

Presenter: Marta Gronska
Title: *Adult hippocampal neurogenesis and its regulation by components of FGF signaling*
Contributing Author(s): Jean Hebert

Adult neurogenesis is a process of high interest due to the ability of newborn cells to integrate into the existing adult hippocampal circuits. Identification of the molecular pathways that determine different steps in the generation and maturation of newborn neurons would facilitate using adult neural stem cells (ANSC) to treat multiple brain disorders. We previously showed that loss of Fibroblast Growth Factor Receptors (FGFRs) 1-3 in ANSCs decreases cell proliferation and dendritic elaboration. However, the identities of downstream components of the FGFRs in adult neurogenesis are unknown. In addition, FGFRs' interaction with non-canonical upstream ligands such as L1CAM, a cell adhesion molecule, previously shown in cell culture to interact with FGFRs to promote neurite extension is unknown. We are determining how cell proliferation and dendritic elaboration in the adult dentate gyrus (DG) are affected in FGFR conditional mutant mice that lack binding sites for the downstream mediators phospholipase-C gamma (PLCγ) or Fgf receptor substrate (FRS), and in L1CAM conditional mutant mice. Our data suggest that PLCγ and FRS are nonredundantly required for cell expansion. Using Sholl analysis to quantify dendritic elaborations, our data is unclear whether PLCγ or RFS are required for dendritic elaborations as it seems that FGFR mutant cells may be outcompeted by the unrecombined "wild type" siblings. Thus, we are developing alternative genetic and AAV-Cre mediated infection methods to determine the role of PLCγ and FRS on dendritogenesis where we can bypass the loss of FGFRs in stem cells and progenitors. In addition, we tested the consequences of the mutations on learning and memory in hippocampus-related tasks, yet, no significant differences were noted. We are also testing whether L1CAM acts in a cell-type autonomous or non-autonomous manner to promote dendritogenesis in the DG. Determining which intra- and extracellular pathways deferentially affect hippocampal learning and memory will not only provide a better understanding of adult neurogenesis but will also provide targets for reversing deficiencies in this process, which leads to age-related memory decline.

Presenter: Christopher Henry
Title: *Behavioral and neurophysiological characterization of visual crowding in macaques*
Contributing Author(s): Adam Kohn

Visual crowding is a phenomenon whereby the features of objects viewed peripherally are rendered less discriminable by adjacent objects in the visual field. Crowding has been well studied in humans; yet little is known about crowding in animal models where neurophysiological recordings are experimentally tractable. We trained awake monkeys on an orientation discrimination task and used a psychophysical reverse-correlation paradigm to characterize visual crowding from adjacent locations in the visual field. Distractors at some locations led to errors that were consistent with the distractor orientations (indicative of substitution or averaging). At other locations, incorrect judgements were inconsistent with the distractor orientation (indicative of repulsion or induced tilt). Thus, even within a single stimulus array, stimuli at distinct locations in the visual field had opposing influences on the judgement of target features. Similar behavioral results were found in one human subject. In a parallel study, we asked how crowding affected the encoding of orientation information at the neuronal population level. We recorded the responses of neuronal populations in anesthetized macaque V1 to target gratings, presented in isolation or surrounded by distractor gratings. To assess the effect of crowding, we applied linear discriminant analysis to V1 population responses to pairs of targets with offset orientations. Decoders trained on responses to isolated stimuli had significantly worse performance on responses to crowded stimuli, across a wide range of task

difficulties. Performance deficits were also apparent when decoders were trained on crowded responses. Shuffling the neuronal responses to remove correlations reduced decoding performance, but the detrimental effects of crowding were still evident, suggesting that crowding arises in part from effects on the responses of individual neurons. This demonstrates that crowding involves a loss of sensory information at the first stages of cortical processing; however, as crowding effects in our population were weaker than those seen behaviorally, maladaptive pooling by downstream cortical neurons is also likely to be a contributing factor.

Presenter: Jee-Yeon Hwang
Title: *The role of miR-34 in ischemia-induced neuronal death*
Contributing Author(s): Pontarelli F, Court-Vazquez BL, Zukin RS.

Transient global ischemia arising as a consequence of cardiac arrest in humans causes selective, delayed death of hippocampal CA1 pyramidal neurons and cognitive impairment. Effective treatments to ameliorate the neurodegeneration and cognitive dysfunction associated with global ischemia are an unmet need. Emerging evidence points to a widespread role for microRNAs (miRNAs) as key modulators of target gene expression in neurons. Accordingly, dysregulation of miRNAs are implicated in the pathophysiology of neurodegenerative disease and neurological disorders. Our findings, derived via miRNA-seq, indicate that a subset of microRNAs is altered in postischemic CA1 including miR-34b/c. Dysregulation of miR-34 has been implicated in pathophysiology of neurological disorder such as Parkinson's disease and epilepsy. However, a role for miR-34 in the pathogenesis of global ischemia is, as yet, unclear. Here we show ischemia induces p53-dependent activation of miR-34b/c and downregulation of its target genes, which together promote neuronal death in selectively vulnerable hippocampal neurons. These findings have great potential for our understanding of how global ischemia induces neuronal death and identify a novel therapeutic target for amelioration of the neurodegeneration and cognitive deficits associated with ischemic stroke.

Presenter: Kyle Jensen
Title: *Excitatory and Inhibitory Plasticity at an Intrinsic Hippocampal Circuit*
Contributing Author(s): Yuki Hashimotodani, Kaoutsar Nasrallah, Pablo E. Castillo

Within the dentate gyrus of the hippocampus, both excitatory hilar mossy cells (MCs) and inhibitory interneurons (INs), form synapses onto proximal regions of dentate granule cells (GCs) (the principal cell-type and main output of the dentate gyrus). Although long-term synaptic plasticity of proximal inputs onto GCs could play multiple roles in learning and memory, there is almost no evidence of long-term plasticity of either excitatory or inhibitory proximal inputs onto GCs. We sought to characterize synaptic plasticity at excitatory MC or inhibitory IN inputs onto GCs. We discovered a novel type of presynaptically-expressed, NMDA receptor- independent form of long-term potentiation (LTP) at the MC-GC synapse and an endocannabinoid-mediated form of long-term depression at the IN-DGC synapse (iLTD). By shifting the excitatory/inhibitory balance at proximal synapses onto GCs, both forms of long-term plasticity could alter dentate gyrus output and therefore play an important role in learning and memory. Supported by R01 grants DA017392, MH081935

Presenter: Bryen Jordan
Title: *Synaptic proteomics to probe normal and pathological brain function*

Neuronal synapses are specialized cell junctions that are essential for higher order brain processes. Changes in synaptic composition mediate the long-lasting functional modifications that underlie synaptic plasticity, and learning and memory. Synaptic dysfunctions have been identified in numerous brain pathologies, including syndromic Autism spectrum disorders (ASDs), which are among the most heritable neuropsychiatric conditions. Large scale sequencing and genome wide association studies (GWAS) have identified several hundred ASD susceptible chromosomal loci and genes suggesting a highly heterogeneous genetic architecture. However, bioinformatic analyses and functional studies of syndromic ASD mouse models indicate that deficits in synaptic function may underlie these disorders. We've recently embarked on a project to test the hypothesis that ASD-linked susceptibility genes and influences ultimately converge on a common signaling pathway regulating synaptic function, and that this point of convergence is key to understanding the human disease. To test this, we will use an advanced proteomic methodology to compare synapses isolated from ten different syndromic and non-syndromic ASD mouse models. Results will be mined to identify shared changes in protein levels, complexes and molecular pathways. This proteomic approach overcomes critical confounds associated with genetic studies of ASD etiology that inappropriately assume transcript levels, single nucleotide polymorphisms (SNPs) or even copy number variations (CNVs) correlate positively with protein abundance. By leveraging optimized quantitative proteomic methods, we hope to identify high-value targets for pursuing therapies.

Presenter: Ramakrishnan K.B.
Title: *The subthalamic nucleus modulation of the pontine nuclei*
Contributing Author(s): Kamran Khodakhah

The subthalamic nucleus (STN) is part of the basal ganglia (BG) that plays a crucial role in motor, reward processing, addiction and cognitive functions. Previous anatomical study uncovered a disynaptic projection between the STN and the cerebellar cortex in primates. In Parkinson's disease (PD), the STN displays a continuous abnormal bursting activity whereas in physiological conditions it exhibits a regular pattern of discharge. Several studies have shown PD-associated pathological changes in the cerebellum as well. Deep brain stimulation (DBS) in STN is a well-established treatment for the PD patients whose condition is no longer responsive to medication. Bilateral STN-DBS produces long-term improvement in motor function in PD patients. Additionally, STN-DBS reduces motor symptoms in PD while normalizing cerebellar activity and function. Lately, STN has gained attention as target for DBS in neuropsychiatric disorders, including obsessive-compulsive disorder, eating disorders and addiction. Considering the importance of STN in normal physiology and significance of STN-DBS in improving the condition in several neurological disorders, we wanted to test if STN neurons convey their signals to the cerebellum and modulate activity. Based on previous anatomical study, we hypothesize that STN can communicate with the cerebellum via pontine nuclei (PN) in the brainstem. In order to test this, we examined whether STN input modulates the activity of the neurons in the PN. We investigated PN activity using optogenetics with single unit recordings in awake mice. Channelrhodopsin (ChR2) was injected in the STN and their axonal projections were optically activated in PN while recording the single neuronal activity using an optrode. We find that about 50% of recorded cells responded to the stimuli. Optical stimulation increased the firing rate in PN neurons with a short latency of approximately 2-4 milliseconds. The stimuli inhibited the spontaneous firing in about 15% of recorded neurons. To determine how robustly STN conveys information when

repeatedly activated, we examined the response of PN neurons to 20 Hz trains of stimulation. The train data demonstrated that the STN-PN pathway remained effective in producing responses. Overall, our results provide the first evidence that the STN drive activity in PN *in vivo*.

Presenter: Nachiket Kamatkar
Title: *Developing RNA based ligands (aptamers) for the FGFRs to manipulate astrocyte activation*
Contributing Author(s): Matthew Levy, Jean Hébert

The FGFs are a family of secreted proteins used for angiogenesis, wound healing, and multiple other roles in the developing organism and also play an important role in numerous pathological processes. To date, there are limited options for people who suffer from FGF signaling related diseases since there are no specific agonists or antagonists for the receptors of FGF signaling. I will develop novel molecular tools specific for all three fibroblast growth factor receptors (FGFRs) expressed in the brain and test them in a model of astrocyte activation. To achieve this goal, I will develop aptamers, nucleic acid ligands that have the potential to be specific antagonists and agonists that then modulate signaling through the FGFRs. To date, I have identified a number of nuclease-stabilized ligands that bind to FGFR3. I am currently testing these aptamers for specificity to FGFR3 using a neurosphere model.

Presenter: Marcin Kazmierczak
Title: *Impact of arousal on reward seeking in rats with dysregulated dopaminergic signaling.*
Contributing Author(s): Saleem Nicola

Dysregulated dopaminergic signaling is implicated in the pathophysiology of an astounding variety of disorders, encompassing motor diseases such as Parkinson's, as well as psychiatric illnesses including addiction, schizophrenia and depression. Besides motor control, dopamine is believed to be required for motivation and reinforcement and these functions are thought to underlie impaired reward seeking after disruption of dopaminergic transmission. However, dopamine is also essential for arousal. Notably, elevated arousal alleviates some motor Parkinsonian symptoms, such as freezing of gait, but the impact of arousal on reward-seeking behavior is largely unexplored. Using a rat model of cued reward seeking, we found that rats with blocked D1 receptors fail to respond to sucrose-predictive cues due to transient episodes of immobility. Arousing rats by touch restores cued approach behavior, but the same strategy is ineffective when D2 receptors are blocked. These results cannot be explained solely by the motivation and reinforcement theories and suggest that arousal may facilitate motor performance and reward seeking via a similar mechanism.

Presenter: Samantha Kee
Title: *Acute cerebellar knockdown of sgce reproduces salient features of Myoclonus-Dystonia*
Contributing Author(s): Rachel Fremont, Maria Camila Moreno, Kamran Khodakhah

Myoclonus dystonia (DYT11) is an inherited movement disorder caused by loss-of-function mutations in *SGCE* and characterized by involuntary jerking of the upper body (myoclonus) and sustained contraction of agonist and antagonist muscles that result in painful, twisted postures (dystonia). A striking feature of this disorder is that patients frequently report improvement of motor symptoms after consumption of alcohol. Unfortunately, the neural basis of DYT11 is unclear, although motor structures including the basal ganglia and cerebellum have been implicated. To better understand the neural causes of the symptoms in DYT11, we generated a mouse

model of DYT11 using short hairpin RNA (shRNA) to knock down *sgce*, the mouse homolog of SGCE, in the adult mouse. We found, using two different shRNA sequences, that knockdown of *sgce* in the cerebellum, but not the basal ganglia, produced dystonia and repetitive jerk-like movements in mice. Furthermore, we showed that the motor symptoms of these mice improved after administration of ethanol. In contrast, the motor symptoms of a mouse model of a different hereditary dystonia which in patients is not responsive to ethanol, DYT1, did not lessen following ethanol administration. To test whether aberrant cerebellar activity underlies the motor symptoms in our mouse model of DYT11, we performed extracellular recordings from dystonic mice. We found that, compared to mice injected with a control shRNA that does not target any gene in the genome, both Purkinje cells and deep cerebellar nuclei (DCN) neurons fire aberrantly in dystonic mice. Future studies will seek to determine whether alcohol relieves symptoms in these mice by restoring the regular activity of the neurons. In addition, we will examine whether the irregular activity of Purkinje cells and DCN neurons is due to a change in the intrinsic activity of the neurons or whether it is caused by a change in their synaptic inputs.

Presenter: Mallory Kerner-Rossi
Title: *Nociceptive Impairment and Related Neuropathology in a Mouse Model of Christianson Syndrome*
Contributing Author(s): Kostantin Dobrenis, Steven Walkley

Christianson syndrome (CS) is a newly described X-linked neurological disorder with clinical features that include severe intellectual disability, epilepsy, postnatal microcephaly, and a progressive ataxia frequently leading to loss of the ability to walk by adolescence [1]. CS is due to mutations in *SLC9A6*, which encodes the endosomal sodium-hydrogen exchanger, NHE6. NHE6 is located on early and recycling endosomes, where it helps regulate luminal pH. Previously, our lab has shown that *Slc9a6* knockout mice replicate several phenotypic features of CS at the behavioral level. Importantly, we have also found evidence of lysosomal dysfunction: most notably late endosomal/lysosomal accumulation of GM2 ganglioside in specific brain regions relevant to the clinical phenotype. In addition, we reported a progressive, patterned degeneration of cerebellar Purkinje neurons with axonal spheroids essentially identical to that occurring in mouse models of lysosomal storage diseases [2]. These findings suggest that the clinical features of CS may be due in part to pathogenic mechanisms common to a variety of primary lysosomal disorders. Parental reports of sensory disturbances in affected children, such as an apparent insensitivity to pain, led us to begin exploring sensory function in *Slc9a6* knockout mice, and to examine pathology of the spinal cord and peripheral nervous system. We found that *Slc9a6* knockout mice have an elevated threshold to thermal pain, as compared with wild type littermate controls. Post-mortem analyses of spinal cord revealed GM2 ganglioside accumulation throughout the gray matter in *Slc9a6* knockout mice but not wild type controls, beginning as early as 3 weeks of age. Intriguingly, staining was strongest within the substantia gelatinosa of the dorsal horn, and found at all spinal levels. Spinal cords of 28-week old knockout mice also exhibited marked astrogliosis and elevated CD68-positive microglia compared to those of wild type littermates. Therapies for CS may thus need to target the spinal cord as well as the brain. Further studies investigating the impact of substrate reduction therapy with the iminosugar miglustat, which has been shown to reduce neurodegeneration in animal models of lysosomal diseases through effects on ganglioside metabolism and/or neuroinflammation, on the neuropathology and sensorimotor abnormalities in *Slc9a6*-KO mice are underway. We are also exploring mechanisms by which a defect early on in the endosomal pathway can affect lysosomal function.

Presenter: Joanna Krzyspiak
Title: *Neural Stem Cell Transplantation: Damage Control and Preemptive Strikes in Neurodegeneration*
Contributing Author(s): Kamran Khodakhah, Jean Hebert

Several models of neurodegenerative disease and neuronal injury have shown improvement after neural stem cell (NSC) therapy using cells obtained from diverse sources. The benefits from these grafts have been observed in the form of slowing disease progression and presumptive cell replacement, respectively. However, little is known about either of these mechanisms. The extent, if any, to which new cortical projection neurons can functionally integrate into the adult neocortex remains a largely unexplored question. Additionally, neural stem cells appear to slow progression of neurodegeneration through a poorly understood phenomenon termed the "bystander effect," which involves transfer of compounds between adjacent cells through gap junctions or through extracellular routes. To test the effects of neural stem cell transplantation, we are using two experimental systems. One is a stab wound injury in an adult mouse motor cortex, which is immediately followed by transplantation of mouse embryonic cortical progenitor cells. Our goals are to understand how the differentiated progeny of the graft integrate with the host and what, if any, functional relevance it has to the host. We will do this through a series of experiments using genetically modified mice to analyze the neuronal activity of transplanted cells and their effects on host neurons. The second system is a mouse model of spinocerebellar ataxia type 1, which is caused by a trinucleotide repeat mutation in the ataxin-1 gene. The consequence of this mutation is a progressive atrophy of cerebellar Purkinje cells (PC), eventually leading to PC death. These mice are injected with adult subventricular zone stem cells at 24 weeks of age, right at the time when PC degeneration accelerates. In this SCA1 mouse model, it has been shown that transplanted NSCs are able to prevent PC death and to slow progression of ataxia, an effect we will term as rescue. The mechanism for this rescue remains undefined, although previous reports showed a requirement for connexin 43 (Cx43), which is a gap junction protein found primarily in astrocytes. Our goal is to determine what cell types are responsible for this rescue and how they change the properties of the host cells to slow their degeneration. Through these studies we will gain further understanding into how neural stem cell therapy can be used to treat patients with neural degeneration and neural injury.

Presenter: James Lederman
Title: *Sensory and motor encoding in the ventral pallidum*
Contributing Author(s): Lardeux S, Nicola SM

The ventral pallidum (VP) is essential for translating limbic sensory, value and motivation signals into motor output, but how it does so is unknown. In this study we ask how VP neurons fire in response to reward-predictive cues and how this firing relates to the motor response. Rats were food-restricted and trained on a discriminative stimulus (DS) task. The DS was an auditory cue, which directed the rat to approach and press a lever to obtain 10% sucrose reward. Trained animals were implanted with microelectrode arrays in VP allowing multi-unit recording of neuronal activity while video tracking of head-mounted LEDs enabled detection and measurement of locomotion. Approximately half of the neurons in the VP were excited by DS presentation, and a small number were inhibited. An overlapping population of neurons showed changes in activity highly correlated with initiation and cessation of spontaneous locomotor movements (i.e., movements during the inter-trial interval that were typically not directed towards the lever) in that neurons that showed inhibition during movement onset were

excited during movement cessation, and vice versa. These results show that VP neurons encode reward availability and may play a role in locomotor initiation and cessation. Further work aims to characterize the encoding of locomotor- and reward-related parameters in these neurons, and how this encoding is altered by drugs of abuse.

Presenter: Pablo Lituma
Title: *Presynaptic NMDA receptors contribute to short-term plasticity at hippocampal mossy fiber-CA3 synapses*
Contributing Author(s): Hyuangbae Kwon, Rafael Lujan, Pablo E. Castillo

Neurotransmitter release is a highly regulated process that controls the strength of neuronal communication. Presynaptic Ca^{2+} rise is a key component of this process not only for triggering action-potential driven transmitter release, but also for facilitating transmitter release during repetitive activity. Hippocampal mossy fiber (MF) synapses, which carry the main excitatory input to the hippocampus proper, express uniquely robust activity-dependent facilitation. Although the molecular mechanisms underlying this form of short-term plasticity remain poorly understood, there is evidence that glutamate autoreceptors may participate. Here, we test the hypothesis that preNMDARs likely due to their high Ca^{2+} permeability contribute to robust short-term plasticity at MF synapses. To identify and assess the functional role of preNMDARs we used immune-gold labeling electron microscopy, electrophysiology, selective pharmacology, and imaging in acute rat hippocampal slices. Together, our findings reveal that during repetitive activity preNMDARs facilitate glutamate release from MF boutons and thus, may contribute to dentate gyrus-CA3 information transfer.

Presenter: Stefano Lutzu
Title: *Molecular basis of activity-dependent bidirectional NMDA receptor plasticity*
Contributing Author(s): Karina Alvina, Pablo E. Castillo

NMDA receptors (NMDARs) are key mediators of synaptic plasticity and learning and memory. NMDARs have been shown to undergo activity-dependent bidirectional plasticity (i.e. NMDAR-LTP/LTD) at many central synapses but the molecular mechanisms underlying NMDAR plasticity remain poorly understood. At the hippocampal mossy fiber-to-CA3 pyramidal cell (MF-CA3) synapse, bidirectional NMDAR plasticity is elicited with physiological coincident pre/postsynaptic burst activity. While both NMDAR-LTP and LTD require postsynaptic calcium rise, the calcium sources differ, raising the possibility that different calcium dynamics determines the bidirectionality of NMDAR plasticity. To address this possibility, we measured postsynaptic calcium transients (CaTs) during the induction of NMDAR plasticity by combining 2 photon laser microscopy and electrophysiology in rat hippocampal slices. CaTs were significantly larger during the induction of NMDAR-LTP than NMDAR-LTD, and this difference was abolished by pharmacological blockade of specific calcium sources. Thus, distinct postsynaptic calcium dynamics likely underlies the sign of NMDAR plasticity.

Presenter: Mahfuzur Miah
Title: *Investigating Neurotoxicity Due to Dopamine Presence*
Contributing Author(s): Pan Chen, Aaron Bowman, Michael Aschner

Parkinson's disease (PD) is one of the most common progressive neurodegenerative disorders affecting Americans. Though PD etiology can be idiopathic, genetic, or toxicant related, the common thread is the marked degeneration of dopaminergic (DAergic) neurons. Though extensively studied, the mechanisms underlying PD remain elusive. A common perspective suggested in the literature proposes that dopamine is the culprit but this remains to be substantiated. Here we investigate the hypothesis that dopamine is intrinsically necessary and sufficient to render DAergic neurons susceptible to genetic and environmental risk factors of PD. To pursue this, we took advantage of the genetically tractable Caenorhabditis elegans (*C. elegans*) worm model and expressed green fluorescent protein (GFP), tyrosine hydroxylase (cat-2) and the dopamine reuptake transporter (dat-1) into ADF serotonergic neurons while removing native tryptophan hydroxylase (tph-1) and the serotonin reuptake transporter (mod-5). This novel approach allows us to investigate the role of DA on neurodegeneration in a completely different penotypic cell background in a live organism. We successfully stained for DA in these genetically altered ADF neurons, as well as native DAergic neurons, via formaldehyde induced fluorescence (FIF), representing our success in transforming these ADF neurons into pseudo-DAergic ADF neurons. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 1-methyl-4-phenylpyridinium (MPP+), 6-hydroxydopamine (6-OHDA), and manganese (Mn) are all well established toxicants used to model parkinsonian DAergic neurodegeneration. We verified that a 1 hr exposure to 2 mM MPTP at the first larval stage (L1) was sufficient to cause significant degeneration in native DAergic neurons in a wildtype strain ($p < .001$, by one-way ANOVA). Wildtype ADF neurons showed no significant degeneration, confirming that serotonergic neurons are not normally sensitive to this neurotoxicant. Interestingly however, subjecting our pseudo-DAergic ADF neuron expressing strain to 2 mM MPTP for 1 hr at L1 did cause significant ($p < .001$, by one-way ANOVA) degeneration in these altered neurons. These results suggest that the presence of DA and its transporter is sufficient to predispose a normally unsusceptible neuron to risk factors of neurodegeneration. Finally, we show ongoing work to investigate how genetic knockout of DA, DA transporter or both in *C. elegans* may protect against toxicant-induced DAergic neurodegeneration. Our current data shows significant protection ($p < .001$, by Tukey's multiple comparison's test) from DAergic neurodegeneration in worms lacking DA after 6-OHDA and MPP+ exposure when compared to WT worms, suggesting that DA presence is partially necessary for toxicant-induced DAergic neurodegeneration.

Presenter: Sophie Molholm
Title: *Multisensory processing in typically developing children and children with autism*
Contributing Author(s): Michael J Crosse, John Foxe

Autism spectrum disorders (ASDs) are characterized by impairments in social communication and by restricted, repetitive and stereotyped behavioral patterns. Unusual sensory symptoms have long been noted in individuals with ASDs. In fact both Kanner and Asperger noted sensory abnormalities in the first reports of this puzzling and complex disorder. Several of the longstanding as well as contemporary theories of ASD, such as *weak central coherence theory* of Frith and Happe and *enhanced perceptual functioning theory* proposed by Mottron reflect the notion that individuals with ASD do not process, and in particular do not integrate, sensory information in the same manner as those with typical development. Using a multimodal approach we set out to empirically test this thesis using well established metrics of multisensory integration. Here I will present related

behavioral and electrophysiological data that reveal marked differences in multisensory integration in autism.

Presenter: Hannah Monday
Title: *Molecular mechanisms underlying protein synthesis-dependent LTD of GABA release*
Contributing Author(s): Younts TJ, Klein ME, Castillo PE

The ability of synapses to undergo long-term changes in strength is critical for information storage in the brain. While postsynaptic changes have been well-studied, the molecular basis of long-term presynaptic alterations in neurotransmitter release remains poorly understood. Our lab recently discovered that local presynaptic translation is required for a form of long-term presynaptic plasticity of inhibitory transmission (iLTD) in the adult rodent hippocampus. iLTD is mediated by endocannabinoid retrograde signaling and activation of presynaptic type-1 cannabinoid receptor (CB1R). How exactly CB1Rs promote protein synthesis is unknown. To address this question, we performed electrophysiological recordings in acute hippocampal slices and used pharmacology to manipulate signaling cascades downstream of CB1Rs. We found that iLTD involves the Akt-GSK3-mTOR signaling pathway, but is independent of the Gβγ signaling arm of the CB1R. Our results may provide novel targets for diseases that involve disrupted endocannabinoid-mediated plasticity, like intellectual disability and addiction. Supported by R01 grants DA017392 and MH081935

Presenter: Kaoutsar Nasrallah
Title: *Firing a single dentate granule cell induces a presynaptic form of LTP at Mossy cell-dentate granule cell synapse*
Contributing Author(s): Pablo E. Castillo

The dentate gyrus, the major input area of the hippocampus, contains two types of excitatory neurons: dentate granule cells (GCs) and hilar mossy cells (MCs). MCs receive inputs from GCs and project back to GCs locally (intralamellar), contralaterally, and along the longitudinal (dorsoventral) axis of the hippocampus, thereby establishing an associative positive-feedback loop (GC-MC-GC). Such projections may be important to connect the dorsal hippocampus, primarily involved in spatial memory, with the ventral hippocampus, primarily involved in emotional memory. However, how MCs contribute to dentate gyrus function remains underexplored. Here, we studied the dynamic properties of MC-GC synapses using rodent hippocampal slices. We discovered that firing a single GC induces a presynaptic form of LTP at MC-GC synapses, but not other excitatory inputs onto GCs. MC-GC LTP is mediated by postsynaptic BDNF/TrkB and presynaptic cAMP/PKA signaling. This form of plasticity may play a critical role in memory formation and epilepsy. Supported by R01 grants DA017392, MH081935 to PEC and the Fondation pour la Recherche Médicale (Postdoctoral Fellowship for a research abroad) and the Fondation Bettencourt Schueller (Prix pour les jeunes chercheurs 2016) to KN.

Presenter: Saleem Nicola
Title: *Integrated control of cued approach by the nucleus accumbens*

One of the most adaptive behaviors in any animal's repertoire is approach to objects of value. For example, a hungry primate spying a patch of ripe red berries is likely to approach and pick the berries. A great deal of evidence indicates that the nucleus accumbens (NAc), in concert with its dopamine input from the midbrain, is an essential element of the neural circuitry that produces this behavior. NAc neurons fire in response to surprising reward-predictive cues, and this excitation both precedes the onset of approach and predicts the latency to initiate approach, with greater firing preceding shorter latencies to move. Moreover, the excitation is reduced by injection of dopamine receptor antagonists into the NAc, a manipulation that prevents cued approach by increasing the movement latency. These results indicate that NAc dopamine-dependent cue-evoked excitations drive the initiation of cued approach. Not surprisingly, the probability of cued approach to an object is influenced by several factors, including proximity to the object, satiety state, nutrient content of the food associated with the cue, and state of arousal. Our studies suggest that NAc neurons integrate information regarding each of these factors to set the probability of cued approach.

Presenter: Rodrigo Pavao
Title: *Reliability of spatial cues in human auditory processing*
Contributing Author(s): Brian Fischer, Elyse Sussman, Renee Symonds, Jose L Pena

Localizing sound requires detection of interaural differences in time and level (ITD and ILD). Analysis of head-filtered sound allows to compute statistics of these cues across frequency and location. Experiments in owls revealed midbrain neurons tuned to the frequencies that carry the least variable cues at each location, supporting a selection-by-reliability mechanism for sound localization. Our study searches for similar mechanisms in humans. We quantified mean and variance of ITD and ILD of sounds recorded in the ear canals. ITD in low frequencies are unambiguous and more reliable in central locations. ILDs are increasingly evident with high frequencies; central and peripheral locations are reliable, but not intermediate ones. We will employ psychophysics and electrophysiological experiments for testing whether reliability guides auditory processing in humans.

Presenter: Morgan Porch
Title: *PKA-dependent phosphorylation of GluN2B on hippocampal plasticity*
Contributing Author(s): Jee-Yeon Hwang, Andrés E. Chávez, R. Suzanne Zukin

NMDARs are glutamate-gated ion channels and Ca^{2+} influx through NMDARs is essential for synaptogenesis, plasticity of neural circuitry, and higher cognitive functions. Emerging evidence reveals that NMDAR-mediated Ca^{2+} influx can be modulated by PKA. We identified Ser1166 of GluN2B to be the target of PKA relevant to NMDAR Ca2+ permeability. To address its impact on NMDAR-dependent synaptic plasticity, we generated a mouse with a S1166A mutation knocked-in. We found that whereas synaptic plasticity in the form of HFS-LTP and LFS-LTD were normal in KI mice, TBS-LTP at the CA1 synapse was nearly abolished in slices from KI vs. WT. A potential mechanism underlying the difference in HFS and TBS-LTP is the incorporation of Ca^{2+}-permeable AMPARs. We next found hippocampal based memory is significantly impaired in these mice compared to wild-type controls. These findings indicate a novel role for PKA phosphorylation of the GluN2B subunit in the potentiation and cognition.

Presenter: Maisha Rahman
Title: *Uncovering interacting factors of Leukocyte Cell-Derived Chemotaxin 2 (lect-2) in dendritogenesis*
Contributing Author(s): Carlos A. Diaz-Balzac, Hannes E. Buelow

Abnormalities in dendrite morphology are associated with neurological disorders. We use the multi-dendritic *C. elegans* PVD neurons as a model to study genes involved in dendritogenesis. We found that the conserved gene, *lect-2/Chondromodulin II*, plays a role in patterning PVD dendrites. We propose that LECT-2 is a key player in the 'menorin' complex, comprised of MNR-1/Menorin, SAX-7/L1CAM, and DMA-1/LRR-TM. LECT-2 is diffusible and acts from the muscle to regulate PVD branching. We determined that LECT-2 is localized to the nervous system, acts in the same genetic pathway as *mnr-1*, *sax-7*, and *dma-1*, and its localization is fully dependent on SAX-7. Our studies reveal that the muscle is also involved in PVD development, and that LECT-2 may act as a co-factor to the 'menorin' complex. To elucidate other factors that function in concert with LECT-2, we are performing forward genetic screens to further isolate genes required for correct localization of LECT-2.

Presenter: Cindy Reyes
Title: *Exploring the mechanism by which optogenetic stimulation of ventral tegmental area dopamine neurons prevents extinction of cued approach behavior*
Contributing Author(s): Saleem Nicola

The nucleus accumbens (NAc) and its dopaminergic innervation from the ventral tegmental area (VTA) are involved in promoting reward-seeking behavior as well as strengthening cue-reward associations. Many NAc neurons exhibit cue-evoked excitations that are required for the subject to respond to the cue with approach to the sucrose reward. We hypothesize that dopamine neuronal activity at the predicted time of reward delivery is sufficient to reinforce the cued approach response by maintaining the magnitude of cue-evoked excitation of NAc neurons on subsequent trials. To test this hypothesis, we are using a reward omission paradigm in which the animal's probability of approach behavior declines when cued approach is not rewarded with sucrose. In recordings of NAc neurons during this paradigm, we observed a reduction in the magnitude of cue-evoked excitations of NAc neurons on trials subsequent to the reward omission. We found that the decline in behavioral responding was prevented when optogenetic stimulation of VTA dopamine neurons was delivered in lieu of sucrose reward. By recording from NAc neurons during optical stimulation at the time of reward omission we will be able to determine if the reduction in cue-evoked excitations is also prevented.

Presenter: Todd Rubin
Title: *Gender related differences in response to heading in amateur soccer players*
Contributing Author(s): Liane Hunter, Roman Fleysher, Namhee Kim, Michael Lipton

Head impacts and concussion in soccer are common. Although men may be exposed to a greater number and greater force of impacts, women tend to report more symptoms which also take longer to resolve. Much uncertainty thus surrounds the potential that women are biologically more sensitive to head trauma than men. Previous studies have applied diffusion tensor imaging MRI (DTI) to identify an association of heading with damage to white matter tract integrity (lower fractional anisotropy (FA)). In that study of 37 amateur athletes, biological sex was treated as a nuisance covariate. The present study explicitly characterizes the role of sex in the association of heading with microstructural changes (FA) in a cohort of amateur soccer players matched for age and prior 12-month heading. 49 men and 49 women from an ongoing longitudinal study met the inclusion and matching criteria. Subjects underwent 3.0T DTI imaging. FA was analyzed with a voxelwise linear model to

assess where the association of heading with FA was significant for men, for women, and for significant differences between men and women. We found 3 regions with an inverse association of heading with FA for men, and 8 regions with an inverse association of heading with FA for women. This accounted for 2,121mm3 of white matter where women exhibited lower FA associated with more heading, but only 408mm3 in men. These findings are the first to confirm, at the level of brain tissue microstructure, that women are more sensitive to brain injury in general and repetitive subconcussive injury in particular, compared to men.

Presenter: Amanda Schott
Title: *Cerebellar modulation of prefrontal cortex*
Contributing Author(s): Ilaria Carta, Christopher Chen

The cerebellum is canonically known for its role in coordinating movement. However, some cerebellar projections terminate in non-motor areas. Recent work in our laboratory has revealed a functional monosynaptic connection between the deep cerebellar nuclei (DCN) and ventral tegmental area (VTA), which is involved in reward and motivation. The VTA is known to project directly to the prefrontal cortex (PFC), an area implicated in complex cognitive processing. Here, we examine the putative connections between DCN, VTA, and PFC. We found that in mice, injection of anterograde, transsynaptic viral tracer H129-GFP into the DCN results in GFP-labeled cells in PFC. We also performed extracellular *in vivo* recordings in awake mice, and found that optogenetic stimulation of cerebellar axons in VTA robustly modulates firing rates of both VTA and PFC neurons. These data suggest that the cerebellum communicates with the prefrontal cortex, and may have a substantial role in cortical processing.

Presenter: Julie Secombe
Title: *KDM5: A histone demethylase with important neuronal functions*
Contributing Author(s): Sumaira Zamurrad, Helen Belalcazar, Coralie Drelon

Our work focuses on understanding the functions of the transcriptional regulator KDM5 (lysine demethylase 5). Mammalian cells encode four KDM5 paralogs, KDM5A-D, three of which are clinically important: overexpression of human KDM5A or KDM5B are associated with cancer, and mutations in KDM5A, KDM5B or KDM5C are found in patients with intellectual disability. Yet the basic mechanisms by which this family of proteins function in a physiological setting remain largely unknown. Taking advantage of the fact that Drosophila encodes a single, essential, KDM5 paralog, we have recently found that KDM5 regulates genes essential to mitochondrial function. This finding is significant because mitochondrial dysfunction is implicated in a large number of human diseases, including cognitive dysfunction. Importantly, KDM5 regulates mitochondrial function genes independently of its well-described JmjC domain-encoded histone demethylase activity. Instead, KDM5 requires its PHD motif that binds to histone H3 that is di- or trimethylated on lysine 4 (H3K4me2/3). Genome-wide, KDM5 binding overlapped with the active chromatin mark H3K4me3, and a fly strain specifically lacking H3K4me2/3 binding showed defective KDM5 promoter recruitment and gene activation. KDM5 therefore plays a central role in regulating mitochondrial function by utilizing its ability to recognize specific chromatin contexts.

Presenter: Selina Solomon
Title: *An optogenetic study of feedback in early visual cortex*
Contributing Author(s): Amir Aschner, Adam Kohn

Feedback pathways, which project from higher to lower cortex, make up roughly half the inter-areal connections in the cerebral cortex. These pathways have been proposed to mediate critical functions that include providing information about perceptual and cognitive context, relaying learned information and implementing attention. Although implicated in such diverse and important functions, studies that have inactivated feedback have found subtle and inconsistent effects on neural activity. All prior work investigating feedback has focused on spiking activity of single neurons recorded in isolation. We hypothesized that the primary role of feedback is to regulate coordinated activity of groups of neurons. Therefore, this effect would have been undetectable in previous work. Additionally, the effects of feedback may have been masked because feedback was inactivated by cooling, a technique which inactivates a large area of (higher) cortex and requires long delays between control and test measurements. To test our hypothesis, we used an optogenetic approach (that offers much improved spatial and temporal precision) to evaluate how feedback arising in area V2 influences neuronal populations recorded in primary visual cortex (V1) of anesthetized macaque monkeys. Optogenetic stimulation of V2 modulated the firing rates of a subset of neurons in V1; under most stimulus conditions, these neurons showed increased firing rates. While firing rates were only modulated in a subset of V1 neurons, V2 stimulation caused a substantial decrease in the co-variability of all V1 neurons. Interestingly, the subset of V1 neurons that showed modulated firing rates also showed greater co-variability. We conclude that stimulation of higher visual cortex can strongly affect network coordination in lower cortex.

Presenter: Marisol Soula
Title: *Synaptic activation of NMDA receptors induces Pannexin 1-mediated currents in CA3 pyramidal neurons*
Contributing Author(s): David L Hunt, Eliana Scemes, Pablo E. Castillo

Excitatory transmission at the hippocampal mossy fiber to CA3 pyramidal neuron synapse (MF-CA3) plays an important role in learning, memory, and epilepsy. While MF-CA3 synaptic currents are primarily mediated by ionotropic glutamatergic receptors (e.g. AMPA-, NMDA- and kainate receptor-types), we have evidence that synaptic activation of NMDARs induces a secondary inward current mediated by Pannexin 1 channels (Panx1). The Panx1-mediated secondary current is revealed at physiological temperature (35 °C) and probabilistically occurs following the peak of the NMDAR-mediated synaptic response. Calcium influx via NMDARs is necessary to elicit Panx1 currents. Exogenous activation of group I metabotropic glutamate receptors (mGluR1/5) strongly facilitates Panx1-mediated currents, whereas mGluR5 antagonism reduces the probability of these currents. Our findings indicate that Panx1-mediated currents are highly regulated, and can provide a mechanism for signal amplification in the CA3 area that may be relevant to memory formation and epilepsy. Supported by R01 grants DA017392, MH081935 and R25 GM104547

Presenter: Renee Symonds
Title: *Evidence for the organization and processing of unattended sounds during selective listening in complex auditory environments.*
Contributing Author(s): Elyse Sussman

Selective listening in noise requires discrimination of one sound source from the complex mixture that enters the ears. Attention can facilitate processing of attended sounds. However, the degree of processing of unattended stimuli during selective listening is debated. Our aim was to distinguish between two opposing theories that suggest that unattended sounds are (1) gated from further processing, or (2) processed automatically in parallel with task processing. We recorded EEG as a covert measure of ongoing stimulus processing and assessed behavior while we manipulated unattended target cues. Our previous work supports the hypothesis that unattended sounds are processed in parallel, thus we predicted that the unattended sounds would influence target processing and response. Results demonstrated automatic, parallel processing through brain responses to target and non-target pattern violations and facilitated processing in the cued condition. Unattended sounds are thus not gated and can influence target processing and performance in noisy environments.

Presenter: Ambika Tewari
Title: *Acute knockdown of ATM recapitulates the neurological phenotype of Ataxia-telangiectasia*
Contributing Author(s): Kamran Khodakhah

Ataxia-telangiectasia (A-T) is a multisystem disorder caused by an autosomal recessive mutation in the *Atm* gene. Even though the gene implicated in this disorder has been known for over two decades, the mechanisms underlying the dysfunction of ATM that causes A-T remains unknown. This has been hampered by lack of an animal model that recapitulates the major neurological symptom exhibited by A-T patients, ataxia. Several genetic mouse models have been made but they all fail to show this crucial feature of ataxia. For the first time we present a mouse model of A-T exhibiting ataxia and cerebellar atrophy. We show that acute knockdown of ATM in the adult mouse cerebellum is sufficient to induce ataxia. Furthermore, our results demonstrate that ataxia was associated with irregular cerebellar output caused by changes in the intrinsic activity of Purkinje cells (PC). Future studies will unravel how ATM maintains the normal activity of PCs.

Presenter: Vytas Verselis
Title: *Cx26 and Sensorineural Syndromic Deafness*
Contributing Author(s): Helmuth Sanchez, Thomas White

The prevalence of mutations in the *GJB2* gene encoding Cx26 in sensorineural deafness underscores the critical importance of this protein in cochlear function. We have focused on examining missense mutations with retained channel function that cause syndromes in which hearing loss is accompanied by serious and sometimes fatal cutaneous manifestations. Our prevailing hypothesis is that syndromic deafness is a gain-of-function disorder associated with aberrantly functioning Cx26 hemichannels. Biophysical examination of several mutants in exogenous expression systems have identified different aberrant functional properties that may underlie the phenotypic differences found among patients. Facilitation of Ca^{2+} influx is an example of one notable altered property and is now being examined in epithelial cells isolated from a transgenic mouse model and a patient afflicted with keratitis-ichthyosis-deafness syndrome. We are also pursuing the prospect of therapeutic

intervention using connexin channel inhibitors and the identification of novel inhibitors that provide specificity, which is currently lacking.

Presenter: Ariel Vitenzon
Title: *Activation of α1 adrenergic receptors is required and sufficient for stress-induced attacks of motor dysfunction in a mouse model of Episodic Ataxia Type 2*
Contributing Author(s): Esra Tara, Christopher Chen, Kamran Khodakhah

Episodic channelopathies are characterized by the expression of symptoms during discrete attacks superimposed on an unremarkable baseline phenotype. A common feature of these disorders is that attacks are induced by the same set of physical or psychological stressors. Understanding the mechanism by which the stressors trigger neurologic dysfunction, therefore, may identify potential intervention opportunities and therapeutic targets. Episodic ataxia type 2 (EA2) is one such disorder that arises from mutations in the *CACNA1A* gene encoding for the α1 pore forming subunit of P/Q-type voltage-gated calcium channels. In this disorder a mild baseline ataxia is interrupted by attacks of severe motor dysfunction triggered by physical or emotional stress or caffeine or alcohol consumption. The mechanism by which the stressors trigger the motor attacks is not known. We used the *tottering* mouse, a faithful model of EA2, to scrutinize the role of adrenergic transmission in triggering attacks of motor dysfunction. Using a combination of approaches, here we show that local noradrenergic transmission in the cerebellum of *tottering* mice is both sufficient and necessary to induce attacks. We further show that, at least at the receptor level, stress and caffeine do not seem to initiate attacks via the same mechanism.

Presenter: Jingqi Yan
Title: *Elevating autophagy corrects hippocampus-associated synaptic and cognition defects in Fragile X mice*
Contributing Author(s): Morgan W Porch, Brenda Court-Vazquez, Michael V.L. Bennett, and R. Suzanne Zukin

Fragile X syndrome (FXS) is the most common form of heritable intellectual disabilities and a leading genetic cause of autism. Autophagy is a process of programmed degradation and recycling of cellular components via the lysosomal pathway. The mammalian target of rapamycin complex 1 (mTORC1) is strategically positioned at pre- and post- synaptic sites of neurons, where it serves as a brake on autophagy. Here we show that autophagic flux, a functional readout of autophagy, and degradation of synaptic proteins via the lysosomal/autophagy pathway are impaired in hippocampal neurons of Fragile X mice. We further show that genetic inhibition of mTORC1 rescues aberrant spine morphology, synaptic function, and cognition behavior. Our findings establish a causal relation between impaired autophagy and cognitive defects in Fragile X and identify autophagy as a novel therapeutic target for Fragile X syndrome.

Presenter: Sumaira Zamurrad
Title: ***Defining the neuronal, behavioral and transcriptional defects of KDM5 mutations associated with Intellectual Disability***
Contributing Author(s): Xingyin Liu, Julie Secombe

KDM5 proteins are multi-domain transcriptional co-factors that function by recognizing and enzymatically altering specific histone modifications. They are most well known for their demethylase activity to-date. There are four KDM5 orthologs in mammalian cells (KDM5A-D) and a single KDM5 in Drosophila. KDM5A and KDM5B are over expressed in a number of metastatic cancer types, and KDM5A, B and C are mutated in patients with intellectual disability (ID). To-date, 39 mutations in A,B and C have been identified in patients. How mutations in KDM5 family genes result in cognitive phenotypes remains elusive. We defined direct KDM5 target genes in adults, as this is the stage used to model cognitive disorders. Using *Drosophila*, which encodes a single KDM5 protein, our lab carried out RNA-sequencing experiments using *kdm5* hypomorphic adult flies. This revealed that KDM5 is required for the activation of several genes previously implicated in intellectual disability disorders. Anti-KDM5 ChIP-seq experiments from wildtype flies demonstrate that many of these genes are direct KDM5 targets. We used a behavioral assay in flies and found that the $kdm5^{hypomorph}$ have impaired appetitive-olfactory associative learning. To complement our analyses of kdm5 hypmorphic mutant adults, we have generated eight fly strains harboring patient missense mutations in KDM5. All of the ID mutants generated thus far are expressed at wild type levels re-enforcing that these mutations affect function and not protein stability. ID mutant fly strain and our demethylase defective fly strain have a severe learning and memory defect. We are currently testing other ID allele fly strains for similar cognitive impairment using appetitive and aversive-odor association learning and memory assays. Mushroom body morphology is being tested with Fas II staining. Transcriptional analysis by RNA-seq is underway for the aforementioned ID mutant displaying a memory defect alongside the demethylase defective mutant strain. These studies will allow us to define whether similar or distinct target genes are affected by disease-associated alleles and allow us to define the mechanistic link between KDM5 dysfunction and intellectual disability.

Ethics Group Assignment (chairs in bold)

GROUP 1	**GROUP 2**	**GROUP 3**	**GROUP 4**	**GROUP 5**
VIGNETTES 3,6	**VIGNETTES 5,8**	**VIGNETTES 1,2**	**VIGNETTES 4,7**	**VIGNETTES 1,6**
J.Arezzo	P.Ballabh	G.Batista	R.Batista-Brito	M.Akabas
A.Aschner	T.Bargiello	S.Das	**R.Birnbaum**	M.Beckert
H.Belalcazar	L.Boudewyn	A.Davila	K.Brace	M.Bennett
S.Emmons	H.Buelow	A.Francesconi	I.Carta	A.Carbonell
D.Festa	K.Caref	M.Frechou	R.Coen-Cagli	M.Castillo
K.Fisher	**R.DeGregorio**	B.Galinski	S.Cook	B.Court-Vazquez
R.Jafari	P.DeSanctis	J.Garretson	M.Crosse	C.DeJesus
S.Kee	J.Frumkies	T.Goncalves	C.Crouse	K.Dobrenis
K.Khodakhah	D.Hall	J.Hebert	S.Duran	N.Hiroi
A.Krishna	K.Jensen	J.Hwang	D.Faber	R.K.B.
M.Miah	D.Klebe	**M.Kerner-Rossi**	C.Freire	**M.Kazmierczak**
H.Monday	J.Lederman	J.Krzyspiak	M.Gronska	H.Lachman
J.Pena	P.Lituma	**K.Nasrallah**	**A.Jasper**	S.Lutzu
H.Snell	M.Moreno-Escobar	R.Pavao	B.Jordan	**K.McDermott**
R.Symonds	A.Pereda	M.Porch	N.Kamatkar	S.Molholm
S.Walkley	**M.Rahman**	J.Secombe	A.Kohn	T.Rubin
Y.Yoon	C.Reyes	M.Soula	S.Nicola	S.Solomon
S.Zamurrad	S.Roudabush	E.Sussman	K.Palarz	L.Speranza
S.Zukin	S.Tikir	A.Tewari	V.Verselis	H.Tang
		A.Vitenzon		

Ethics Vignettes

Vignette 1: Animal Use

Kelly Kapoor is a postdoc in Dr. Meh's lab. She is working on a project looking at the role of serotonin (5-HT) on feeding behavior in mice using microinjections to the nucleus accumbens. She is using a selective 5-HT3 antagonist but believes that its effects do not last long enough to properly see a behavioral effect. She thinks a different 5-HT3 antagonist may have a longer effect and would be more appropriate for her experiments, but the lab does not have IACUC approval for use of this drug. She has already run experiments using the initial 5-HT3 drug and thus would either have to employ a new cohort of animals for the study or use the same animals for this experiment. She talks to Dr. Meh, and Dr. Meh decides that, due to it being a similar drug class and having been previously used in mice, she should go ahead and use it without submitting a change to protocol in a different cohort.

Questions for discussion:

1. Was it appropriate for Dr. Meh to give Kelly Kapoor the go ahead to use this new 5-HT3 antagonist?
2. Would these experiments duplicate previous experiments? What would be necessary to provide justification to using a new cohort of animals?
3. If this new cohort of animals is run and justified for a pilot experiment is there a point where it should be terminated and how will that be determined?
4. If these experiments were run in the same cohort would there be concerns about minimizing distress?
5. What information if any should Kelly Kapoor have provided Dr. Meh before beginning the pilot experiment of suggesting the new cohort of animals?
6. If this was a non-selective serotonin inhibitor would your answer change, why or why not? What if it was a different class of drug?

Vignette 2A: Authorship: Contribution Change

Student Furstyeer joins a lab and starts meeting with PI Hedhonchö, doing research, and eventually coming up with her thesis project that will be an fMRI study. Furstyeer writes this up for her Qualifying Exam. But after a while Hedhonchö decides that Furstyeer would be better off working on this other project they already started and hands off the thesis project idea to post-doc Täkscreddut who follows through with the project and writes it up as a paper with just Täkscreddut and Hedhonchö as authors.

1. Should Furstyeer be co-author on the paper?
2. In general, should conceptual contributions be worthy of authorship?
3. If Furstyeer should be an author, how should she handle this?
4. Should the PI discuss authorship with Furstyeer before the post-doc took over the project?

Vignette 2B: Collaborator Help

As Täkscreddut and Hedhonchö are editing the fMRI paper in preparation for submission, Hedhonchö thinks they really should apply a mixed model regression to the reaction time data that was collected during the fMRI study to be thorough in reporting all of their results. Taickscreddut tries to figure out how to do this in SPSS and cannot figure it out, so Hedhonchö suggests getting in contact with another Einstein PI Statsmart. Täkscreddut reaches out to Statsmart saying that Hedhonchö suggested reaching out and asking Statsmart if she is able to perform that kind of test on that data. After a short meeting discussing what needs to be done, Statsmart sets out to do this in R and sends the results to Täkscreddut by the end of the day.

Täkscreddut is excited this was apparently so easy but then becomes uneasy about how to handle "payment" for her services. Täkscreddut sends an email to both PIs Hedhonchö and Statsmart asking what should be done now. Statsmart replies that as a biostatician at Einstein, they normally give 5 free hours of work for projects before requiring payment of $125/hour, but that for any amount of work she should be listed as co-author, citing that authorship is based on 4 criteria which include "Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work". But Hedhonchö strongly feels that these stats results did not alter the results of the paper at all, they were just an add-on that didn't even take long to complete and thus Statsmart should only be acknowledged.

1. Should Statsmart be a co-author?
2. How can a disagreement like this be resolved?
3. Is it okay to not include the work that Statsmart did and not include her as an author?
4. How could this confusion have been avoided?

Vignette 3: Conflicts of Interest

Dr. Smith's lab is well-known for its work in developing and characterizing a rodent model of amyotrophic lateral sclerosis (ALS), a debilitating and fatal disorder. Due to Dr. Smith's renowned status in the field of ALS, he is approached by a pharmaceutical company to test some experimental drugs in his validated animal model. Dr. Smith's lab is awarded a large financial grant from the pharmaceutical company to pursue the drug study. The grant is renewable at the end of each year depending on the results of the study. Two years after the study begins in Dr. Smith's lab, Paul, a new graduate student is assigned to work on the project. As Paul is reviewing the past 2 years of data accumulated on the drug tests, gathered by a former technician, he finds that the technician was not blinded to the conditions of the experiments, several control experiments are missing and negative results were not reported in the grant renewal application. Paul approaches Dr. Smith and explains his concerns. Dr. Smith listens and explains that the grant from the pharmaceutical company will not be renewed if Paul's observations are correct. Dr. Smith further explains that the lab's finances rely highly on the grant, including Paul's stipend. Paul leaves Dr. Smith's office very disturbed from the conversation.

1. What is a conflict of interest? What aspect(s) of this scenario constitute(s) a conflict of interest?
2. Do you think that the conflict of interest reduces the credibility of the study? If yes, how?
3. Should Dr. Smith apply for or accept funding for a study that is only renewable depending on the success of the drug tests?
4. How can Dr. Smith design and conduct the study funded by the pharmaceutical company to ensure that it is carried out in an objective manner?
5. If you were in Paul's position, how will you proceed after the discussion with Dr. Smith?
6. Universities require conflict of interest disclosures from investigators but how can a university protect students like Paul?

Vignette 4: Data Management

George, a graduate student, and Sydney, a postdoc, are working on submitting a paper together. The project involved tracking a mouse cohort during a drug trial and making behavioral assessments over a period of one year. George worked on the behavioral data, while Sydney performed the tissue analysis. Given the large amount of data, George has been recording and compiling his behavioral data electronically to monitor his cohort with ease over time. George and Sydney are nearing the end of the study and their PI, Dr. Jones, organizes a meeting to go over the data. After each presentation, they find out that the mice on the drug do not appear to have improved tissue pathology based on Sydney's data, yet have a very improved performance on the behavioral tasks according to George's data. Sydney calls the data into question and believes that George, eager to publish the data, has made a mistake compiling the data or has compiled the wrong mice together to make the drug appear to have worked better than it did. George did not fabricate the data, but when asked to show his raw data does not have the original raw behavioral scores and only has his compiled data. Sydney talks to Dr. Jones about the issue and believes the study should be redone. George is sure he was careful during data compilation and ensures the data in his files was not modified, but is unsure how to prove this to his PI and Sydney.

1. What should George do? Can he confirm the data is sound with his current records?
2. When making corrections to compiled data, and during the compilation process, how do you make it clear what is original data vs modified data?
3. What are the pros and cons to hard copies of data vs electronic?

Follow up:

George and Sydney went through the data together and after replicating some of the experiments, Sydney trusts George's data again and they have since moved forward with publication. Following the study, George graduates and moves to another university. Three years later, a collaborator contacts Dr. Jones and asks to see the George's behavioral data as their lab is performing a study using a similar drug and have found a differing effect then what George published. The PI contacts George with a

question on the data, who says he has since gotten a new computer and no longer has the data in his possession.

1. Who should have a copy of this data? Whose responsibility is it to manage data?
2. How often should data be backed up? How long should the data be kept for following publication?
3. How should data be organized and whose responsivity is it to maintain lab records?

Vignette 5A: Human Subjects: Public Information

Hedhonchö is now running an fMRI study where he wants to see what kind of structural changes occur in the brain over the course of 6 months and recruits human subjects to come in for one scan every month. Participants are informed of the goal of the study and the expectation that if they sign up they will do their best to complete all fMRI sessions. Participants give consent and fill out a form with their name, contact information, and demographics information. As is typical, Hedhonchö recruits more subjects than they need for the study because there are always some drop-outs. But as more and more participants drop out and stop responding to emails about upcoming appointments, Hedhonchö feels desperate that if enough people don't complete all scans, there won't be a study anymore. One participant that only recently stopped responding to emails when he had only one more scan to go, originally seemed so enthusiastic to complete it and help the researchers. Since Hedhonchö knows the name of the participant, he googles it and finds their Facebook page and LinkedIn page. The profile pictures are public so Hedhonchö can tell this is the right person, and so he sends him a Facebook message and LinkedIn message again reaching out and asking him to come in and complete the study.

1. Is it ethical for a researcher to reach out using means that are not on the consent form?
2. Is the information found on the internet like that considered public information?
3. If a researcher wants to do a study looking at the effects of lead in water, could they just search for people on Facebook that were born in Flint, Michigan during a certain period and for people that were born in an otherwise-equal city during the same period? Is this targeting okay?

Vignette 5B: Human Subjects: Vulnerable Populations

Student Ivy Leeg is graduating from a prestigious university where she relied on a full academic scholarship. But she does not have a job lined up yet, and is worrying about how she will pay rent and keep herself afloat in expensive NYC before she can land a stable job. However, in the school newspaper and on the subway there are ads that she now takes notice of. These ads indicate that for women ages 21-30 who went to a top tier school could get paid up to $20,000 if they donate their eggs. Ivy reaches out to one of these companies because even $5,000 would make all the difference for her right now. She fills out an extensive form that goes through her health, family history, and physical description of herself. Then Ivy meets with a nurse who verifies this information, and takes her own notes of Ivy's physical characteristics. At the end, the nurse schedules an appointment with a doctor so Ivy can be examined. As Ivy walks out of the office she realizes that she doesn't even know what will happen at the

doctor's appointment. Feeling uneasy, Ivy goes home and Googles egg donation to find out that this process involves months of hormone treatment with surgery at the end for egg extraction. The surgery has caused many woman have a range of complications such as ovarian hyperstimulation (a condition involving enormous swelling and pain), cramping, infection, and life-threatening bleeding. On top of that, the long-term risks of egg donation to the woman's fertility and health are unknown.

1. Have there been any ethical issues in this scenario?
2. Is it okay for companies to advertise to particular populations (e.g. prestigious school newspapers, on the subway which can target lower-income people)?
3. Is it okay for advertisements not to mention health risks in medically invasive procedures?
4. Should the nurse have thoroughly discussed the risks and benefits with Ivy during this meeting even though Ivy has not yet been matched with a woman who wants her eggs?
5. Who is responsible for covering medical costs of possible post-surgery complications? The donor herself or the company that performed the surgery?

Vignette 6A: Lab Safety

It is the middle of July in NYC, and the air conditioning in the Pelham Center for Neuroscience Research is broken. Gary Stein, a graduate student working in the center, chooses to wear sandals on one particularly hot day. As he was not reprimanded by any of his superiors, he continues to wear sandals to the lab throughout the summer. One Saturday, Gary is diligently working in the lab when he spills concentrated HCl on the floor, splashing some onto his foot. He tries to quickly wash it off in the chemical shower, but it isn't working properly. He dashes out of the lab to the bathroom to wash his foot, and then makes his way to the emergency room. Thinking that no one else is likely to come into the lab on Saturday, he does not immediately report the spill nor clean it up. For Gary, the accident results in the loss of 3 of his toes.

1. What could Gary have done to avoid this?
2. Who is at fault? And how can this be avoided in the future?
3. What responsibility do lab members have to enforce safety protocols on fellow lab members?
4. What should you do when the workplace conditions are such that you need to make unsafe decisions to be comfortable?

Vignette 6B: Lab Safety

A little later on that same Saturday, Jill Johnson stops by the lab. She notices an odd smell and begins to have shortness of breath. She sees the spill and quickly leaves the lab to get some fresh air.

She contacts environmental health and safety to report the spill, though she doesn't exactly know the compound, and she places a note informing other lab members of the spill outside the door.

1. Gary failed to consider the effects of his spill on everyone else in the laboratory. How did Jill handle things differently?
2. Are there any further actions Gary or Jill should take?
3. Why is laboratory safety an *ethical* issue, and not merely a matter of procedural compliance?

Vignette 7A: Research Misconduct

Marvin McMaster, a graduate student in the lab of Dr. Bulltron at Lumpkin State University, recently published a first author paper on synaptic proteins in the Journal of Neuroscience. A year later, Marvin has prepared another manuscript that builds on the results of his first paper. Because he used many of the same experimental methods, Marvin copied several paragraphs from the Methods section of the published paper and included them in the Methods section of the new paper. Furthermore, because both papers are based on the same body of literature, he also included several identical sentences—amounting to a couple of paragraphs—from the Introduction of the original paper. The paper gets reviewed and accepted, but before it is published, the editor of the Journal of Neuroscience contacts Dr. Bulltron informing her that the paper has been red-flagged for redundancy by plagiarism-checking software. The Department Chair and the Dean of Lumpkin State are also informed of the incident.

1. Is Marvin's autoplagiarism defensible? Why or why not?
2. Which parties are culpable for this incident, and to what degree?
3. What should be the consequences for the parties involved?
4. Should the paper ultimately be published?
5. How can such an incident be avoided?

Vignette 7B: Research Misconduct

Rodd Button is an undergraduate student working with the post-doctoral fellow, Penelope Duran, in the laboratory of Page Ingram. The group is about to publish a very high-profile paper on a topic that several competing labs are also examining. This paper would help Penelope secure interviews for tenure-track research positions and would help Rodd secure a coveted place in a prestigious MD/PhD program. Dr. Ingram is really excited about the result, and as such has placed a lot of pressure on Rodd and Penelope to finish the last few experiments required by reviewers.

Rodd is charged with performing the last control experiment required by a reviewer to publish the paper. The goal was to examine levels of a novel protein, ETHC1, in sham-treated control and surgically-treated animals. The group had already shown a difference in ETHC1 expression in surgically-treated animals vs. untreated controls.

For the first cohort of animals that Rodd examined, the difference in ETHC1 was preserved, but not quite significant given the small number of animals and one outlier in which no difference was observed. However, for the second cohort of animals, there was no difference in ETHC1 between sham-treated and surgically-treated animals. This result could significantly delay the publication of the paper, and in the worst case may put its publication in jeopardy. Penelope looks at the data and decides not to use the second cohort of animals and to discard the outlier in the first set of experiments. The subsequent result was significant and consistent with what the group had previously seen. Penelope concluded that Rodd must have made an error, given his relative lack of experience in science. Despite Rodd's protestations that he had not in fact made a mistake, Penelope goes ahead and presents the results to Dr. Ingram, who ultimately submits the revisions to the journal.

1. What recourse does Rodd have? What should be his course of action?
2. Is Penelope justified in omitting the data? If not, under what circumstances might data omission be justified?
3. Assuming Dr. Ingram ultimately hears Rodd's side of the story, what action(s) should be taken?

Vignette 8: Research Ethics

Dr. Robertson runs a large laboratory studying synaptic vesicle trafficking in ACSF (American College of San Francisco). One of Dr. Robertson's postdocs, Richard, has discovered a novel protein involved in vesicle trafficking that he called Wnip (wnt-like insertion protein). Richard had been working on this project for several years, and the project shows promising results. Richard's story is almost complete, but he still needs one more crucial piece of data- a figure that illustrates that Wnip is regulating vesicle trafficking by binding to and inhibiting a protein called Dessert. With the publication of this high-profile paper, Richard is hoping to secure a post-doctoral position in a highly competitive lab. Recently, Richard has been busy writing his paper and thesis so he decided to put Veronica, a new student in the lab, on the project. Veronica is a diligent student, and she spends countless hours in the lab performing yeast-two hybrid and immunoprecipitation assays to show if Wnip is binding to Dessert. After a few weeks, Veronica finally obtains data suggesting that Wnip was in fact not interacting with Dessert. Richard is not convinced, however, and demands that she repeats the experiments. But alas, she obtains similar results. Richard frustratingly performs the experiments himself, and he too obtains the same results. Richard does not admit this to Veronica but instead tells her that some of the reagents must have expired and that's why the experiment wasn't working. Soon after, Richard gives her a new project and tells her that he will wrap up the work concerning Wnip and Dessert since he is almost done writing his paper. At the same time, Veronica became busy with her qualifying exam, and she lost interest in Richard's project. Several weeks later, after she successfully passed her qual, she notices that Richard's paper had been accepted to Nature. She reads the paper carefully and notices the figure of Wnip and Dessert does show that they interact with each other. She asks Richard to show her the raw data published in the article, but he says the data file is missing.

1. What ethical issue(s) are brought up in this scenario? What should Veronica do next?
2. Dr. Robertson runs a huge lab but what could he have done as a PI and mentor to both Richard and Veronica to prevent this situation?
3. What was Richard's responsibility in this situation? Data files should be stored for several years even after the completion of a project, if Richard cannot find the data file, what should be his next step?
4. Dr. Robertson tells Veronica that Richard is very experienced and therefore he trusts his data. What would you do if you were Veronica?
5. Veronica finds out that Richard redid the experiments with fresh reagents, and he obtained the same results as before – that Wnip and Dessert do not interact. How should she proceed? What institutional resources should be in place to help students like Veronica?

General Information

Edith Macy Conf. Center, 550 Chappaqua Road, Briarcliff Manor, NY 10510
Phone: (914) 945-8000

Guest Rooms
Guest Rooms are located behind the Conference Center in three buildings. The lower level includes Rooms 100 to 110, the main level includes Rooms 200 to 212, and the upper level includes Rooms 300 to 321.

Access to the Guest Rooms is through the Conference Center, past the meeting rooms to the rear. All walkways to the Guest Rooms are covered. Van service is available for all guests who require assistance.

Additional lodging is available at the Creedon Education Center, a short distance from the Main Center. Transportation and a map are available at the Front Desk.

Parking
Guest Parking is provided free of charge in our lower lot. Edith Macy courtesy vans will shuttle guests to and from the parking lots and the Conference Center. For your convenience, a telephone is located in the parking lot to call for pickup.

Rest Rooms
Rest Rooms are located in all sleeping rooms, in the Main Commons area behind the fireplace, in the Main Lobby near the Front Desk and adjacent to the outdoor pool.

Smoking Areas
Smoking is not permitted in any indoor location at Edith Macy Conference Center. Cigarette receptacles and ash trays are placed around the outdoor common areas for your convenience. Guests who violate this policy will be charged $295.00 for the cost incurred to clean and restore a smoke-free environment.

Telephone Messages/Faxes
Phone: Please direct calls through our Front Desk at (914) 945-8000. Messages will either be posted outside the conference room door, next to the break station in the commons on the message board, or left on an overnight guest's voicemail.

Telephones are also located throughout the property for your convenience. Please look for beige house phones.
Telephone dialing instructions are listed on a separate page in the back of the packet of information

Fax: The Conference Center Fax Number is (914) 945-8009. Faxes received will be also posted outside the conference room door.

Emergencies – Dial 333 Immediately from any house phone

The Edith Macy Staff has direct access to the local police department, local ambulance corp., a physician on call, the local hospital and local medical clinic. Contact the Front Desk immediately with any and all emergencies. Please don't hesitate! Emergency services need time to respond!

Check Out

Check out is at 10:00 AM. Please place your luggage outside the door to complete your checkout. Your luggage will be picked up and delivered to the Main Center for storage until your departure.

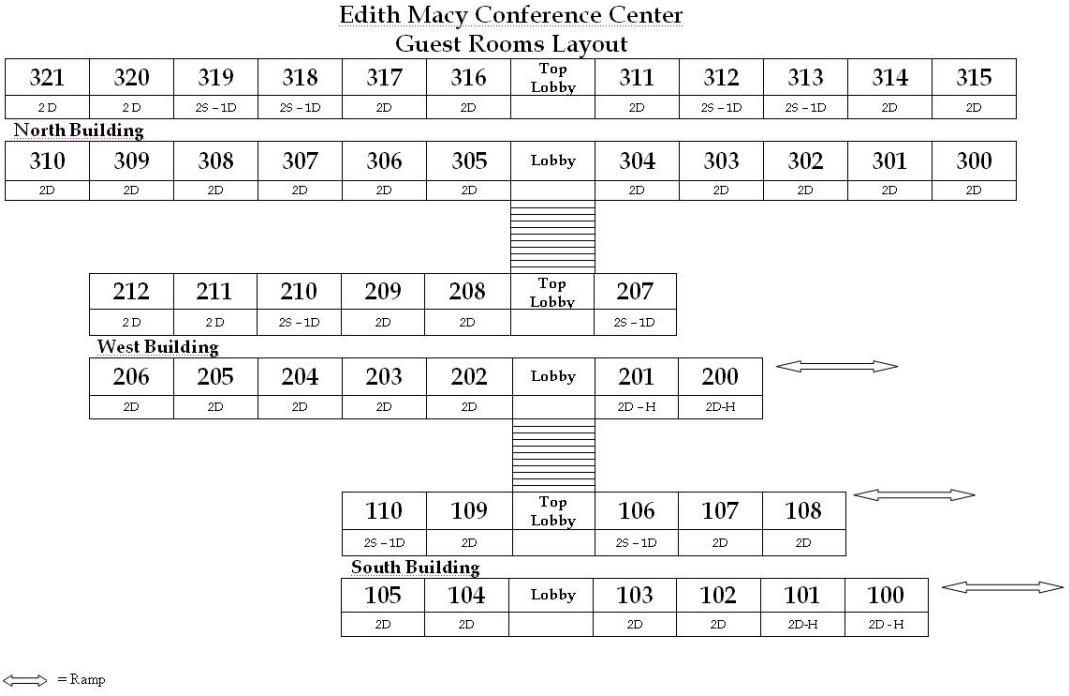
If you charged anything to your room, please check out at the Front Desk before 10:00 AM and be sure to settle any outstanding charges not being billed to the Master Account.

Further Assistance

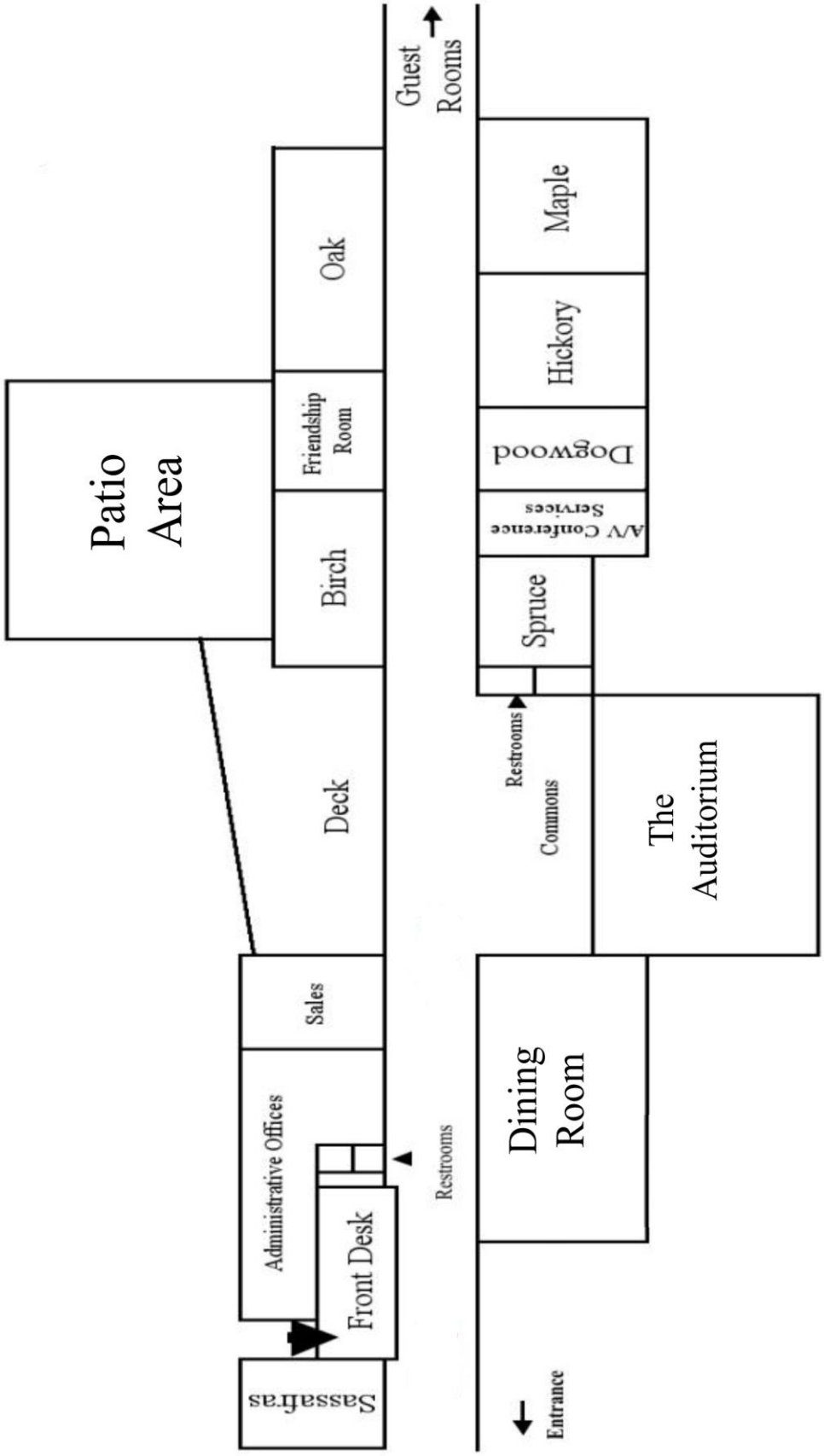
If you have any questions, please do not hesitate to call any one of the following extensions and someone will be happy to assist you.

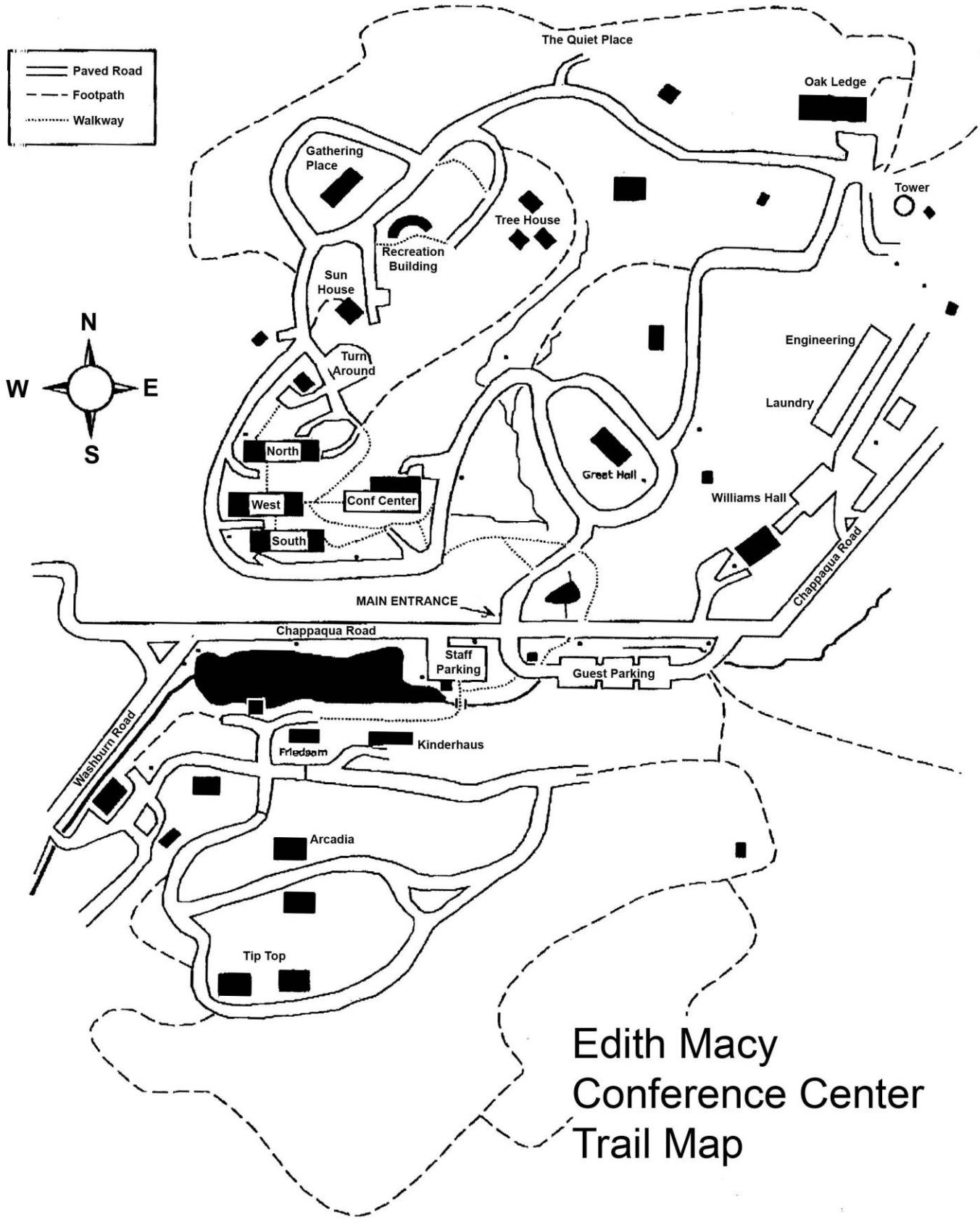
Front Desk	x0
Sales Department	x8097
Conference Planning Department	x8099
Audio/Visual Department	x8013

Maps and Floor Plans



Conference Center Map




Paved Road
Footpath
Walkway
The Quiet Place
Oak Ledge
Gathering Place
Tower
Tree House
Recreation Building
Sun House
N
W
E
S
Turn Around
Engineering
Laundry
North
Great Hall
West
Conf Center
Williams Hall
South
MAIN ENTRANCE
Chappaqua Road
Chappaqua Road
Staff Parking
Guest Parking
Washburn Road
Friedsam
Kinderhaus
Arcadia
Tip Top
Edith Macy
Conference Center
Trail Map

WINE TASTING EVENT

This year once again we have an eclectic selection of wines not likely to be found on most restaurant wine lists: our intention, to expand your exposure to less common varietals or to familiar grapes from unfamiliar terroirs. We start with a crisp yet supple refreshing white wine from Croatia made from the local Pošip grape. A second white, Borealis, from Oregon, features the highly aromatic Gewurztraminer grape classically associated with fine wines, often with higher residual sugar content, from Alsace and neighboring German territory. The Borealis is noteworthy for its unusually extensive content of three additional varietals. The third wine is a low-production rosé from Chateau Pradeaux, Bandol, France, featuring in part the Mourvèdre grape; a particularly robust and more complex wine for this category. A series of red wines begins with Gamay vines displaced south from Beaujolais towards the neighboring northern Rhone valley, and more importantly subjected to the wine-making of the latter to produce a more luscious wine. The second red comes from Hungary, blending indigenous varietals with doses of Merlot and Cabernet Franc. The last of our tastings is a Cabernet Sauvignon from South Africa, increasingly developing high quality wines.

As we did at our last retreat, we will have accompanying "small bites" at each station, two different food items for each wine. In some cases, they will provide an attractive contrast to each wine's nose and flavor, and in other cases, parallel particular notes in the wine. You are encouraged to first smell and taste the wine, evaluate; then take a bite and another sip, and reevaluate. Finally, new this year, you will find an additional table at which there will be a blind tasting of one white and one red wine. We welcome all of you to take a sip and see if you can identify the grapes that were used, the country of origin and other aspects. Your guesses will be recorded and the individuals with the most accurate information on each of the two wines will be announced at the end.

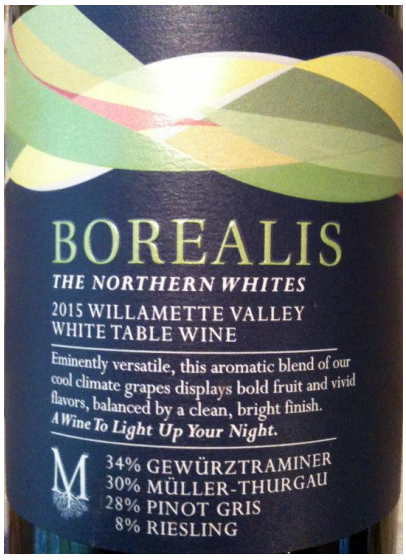
The wine committee worked together to select the final wines, develop ideas for pairings and contributed to each of the wine descriptions, as well as organizing and pouring at the tasting event.

Many thanks to all of you: Steven J Cook; Anna Francesconi; Sophie Molholm; Samantha Kee; Joanna Krzyspiak; Kristin Palarz; Alberto Pereda; Stacy Roudabush; Todd G Rubin; Heather Snell; Selina S Solomon; Luisa Speranza; Huizhen Tang; Ambika Tewari.

We wish you all a wonderful time.
K. Dobrenis

Croatian Dry White
Producer: Toreta
Grape: Pošip
Vintage: 2015
Selected Pairings: Roasted almonds; California sushi roll.

A wine of golden hue with hints of green, this fuller bodied, dry white Pošip has a crisp and fresh nose with the aroma of pear and other white fruits with floral notes. Slightly acidic, this wine has a well-balanced, complex and full structure and finishes cleanly. The Pošip grape is the signature white grape of Korčula, an island in the Dalmatian archipelago off the coast of Croatia in the Mediterranean Sea, and one of the few resistant to the pesky phyllexora. The wine comes from the Toreta winery in the village of Smokvica, where the Pošip first took root and is thought to give the best results. The wine can be enjoyed with seafood. (S. Kee)



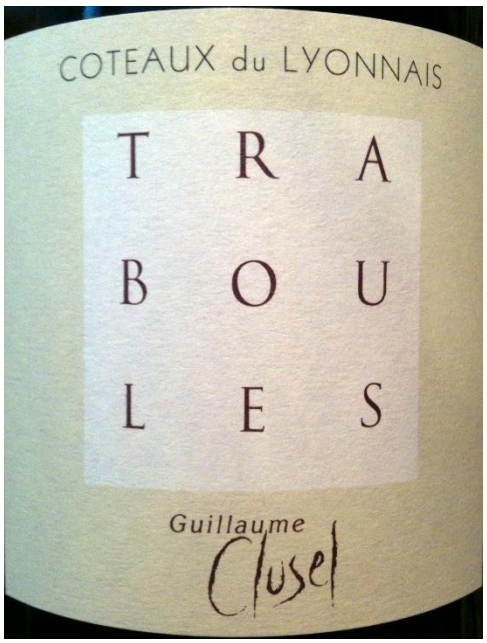
Oregon Off-Dry Blend
Producer: Montinore Estate
Grapes: Gewurztraminer, Muller-Thurgau, Pinot Grigio, Riesling
Vintage: 2015
Selected Pairings: Parmesan cheese; Spicy cashews.

The "Borealis" is summer in a glass. The wine comes from the Willamette valley in Oregon which has, for one, established a reputation for producing some outstanding Pinot Noir-based wines. The Borealis, led by the often otherwise unadulterated Gewrurztraminer, is made from a substantial mix of green and red-hued grapes, giving it a pale orange appearance and a vivid flavor. It smells fruity and floral, tastes of citrus and pear and is easy to drink. Although an off-dry wine, the Borealis is popular even among those who prefer red wines or dry flavors. Pairs well with cheese and nuts. (S. Solomon; K. Dobrenis)

French Provence Rosé
Producer: Chateaux Pradeaux
Grapes: Mourvèdre, Cinsault
Vintage: 2015
Selected Pairings: Mango; Tangerine slices.

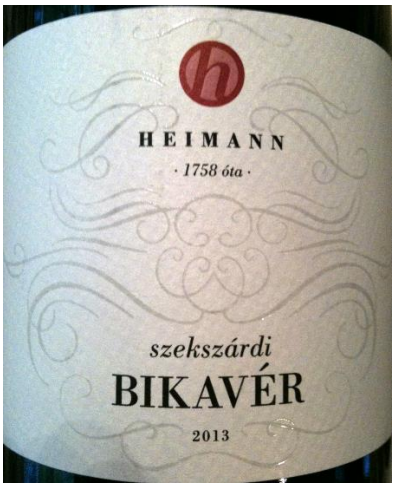
This Bandol comes from the Chateau Pradeaux winery in Saint Cyr-sur-Mer, Provence, southeast France, which was established in 1792. This winery has been family run and reestablished itself after being devastated by the French Revolution. Today, the winery tries to grow their grapes as natural as possible, even letting sheep graze the vineyards in the summer to provide natural herbicide and compost.

Chateau Pradeaux is known for making a rich and complex Bandol. This 2015 Bandol is made from a blend of Mourvèdre and Cinsault grapes. The Mourvèdre grape is a red wine grape that produces tannic wines. Wines made from this grape tend to have earthy tones and red fruit flavors. The Cinsault grape is a red wine grape that is generally low in tannins and used to blend with other varieties. It is typically used to add perfume and fruit, such as strawberry, to wines. This blend of grapes leads to a blood orange color with tones of pink, leaving a lighter color. The nose is a mix of floral, honey, and fruit. The palate has a nice roundness with hints of peach and apricot. The finish has a balanced acidity of pineapple, and raspberry. (K. Palarz, T. Rubin)



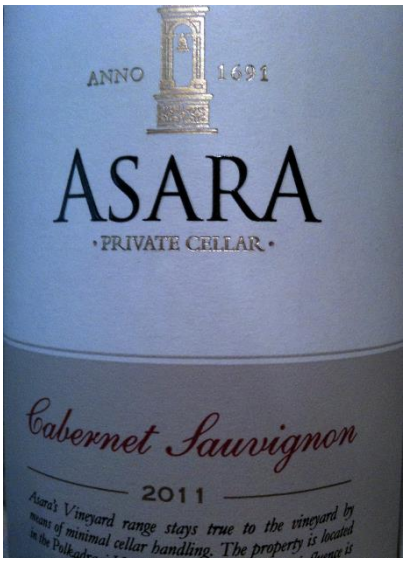
French Coteaux du Lyonnais Red
Producer: Guillames Clusel
Grape: Gamay
Vintage: 2015
Selected Pairings: Garlic salami; Triple crème brie.

The "Traboules" is made entirely from the Gamay grape variety which hails from the Beaujolais region in France. However, this particular wine was made from vines grown equidistant between Beaujolais and Rhone Valley, in the Coteaux du Lyonnais wine-growing appellation. This planting, and more significantly the use of the wine-making style that of the Northern Rhone produced a darker, deeper red wine. While still detectably "Gamay" and relatively light-bodied, this wine feels lusher and somewhat more complex in the mouth. On the nose, you may notice a hint of candied fruit with a musty remnant. There is a slight black pepper note on the finish, see if you notice it! The wine also pairs well with parmesan cheese as a snack, or perhaps with your favorite spicy meal, say paprika chicken. (S. Roudabush; K. Dobrenis.)



Hungarian Red Blend
Producer: Guillames Clusel
Grapes: Kékfrankos, Cabernet Franc, Merlot, Sagrantino, Kadarka
Vintage: 2013
Selected Pairings: Emmentaler; Roasted chestnuts.

Aptly named, Bikavér, literally translated as "Bulls Blood", describes the burgundy color, but also conveys the bold flavors of this medium-bodied, mildly acidic wine. Bikavér is made from a blend of at least three grapes and this 2013 Szekszárd version contains 41% Kékfrankos, 22% Cabernet Franc, 22% Merlot, 10% Sagrantino and 6% Kadarka. It is only made in two regions of Hungary; Eger and Szekszárd, which differ in their soil and climate adding dramatic distinctions to the weight, texture and aromatics. Szekszárd Bikavér is aged for at least one year in oak barrels; producing a musky tone on the palate reminiscent of old libraries filled with leather bound books. This deep woody flavor is further complemented by black pepper and sour cherry notes that linger on the tongue just long enough to make their presence known, but not to overstay their welcome. Thus, leaving a bold, but light aftertaste that, like a bull, continues the charge with the next sip. This is an elegant union of complex grape flavors that produces a warm-hearted red to enjoy. According to tastingtable.com "this wine pairs well with peppered steak, sausages, hearty stews, roast/grilled meats, duck or goose dishes, barbeques, and hard cheeses" (H.Snell, A.Tewari)



South African Red
Producer: Asara
Grape: Cabernet Suavignon
Vintage: 2011
Selected Pairings: Dark chocolate with sea salt; Roasted, salted pistachios.

This Cabernet Sauvignon, one of the world's most recognizable grape varieties, hails from the Stellenbosch valley in the Western Cape province of South Africa. The climate of the Stellenbosch is similar to the Mediterranean and favors viticulture - hot dry summers with cold wet winters. Since the end of apartheid, Cabernet Sauvignon is the most widely planted red grape in South Africa, which continues to produce full-bodied red wines. Asara, the winery producing this Cabernet, has existed since 2000 and sits on one of the largest estates in South Africa. The particular vines used to produce this wine come from a 19-year-old southwest facing vineyard on the estate and were planted in a combination of Tukulu and Oakleaf soils. The terroir and minimal cellar handling yield a balanced and integrated oak platform for the fruit of this wine. This cabernet needs a few minutes to breathe, but won't disappoint if you have the patience. On the nose, you may notice ripe fruit: red berries, blueberries, and cherries with a hint of oak. A substantive mouthfeel is accompanied by sweet and sour berries, pencil shavings, currants, and a tobacco undertone. This versatile wine would serve well with either vegetarian or meat dishes: ratatouille, venison, or steak. (S. Cook)