Morning Poster Session
Location: Row D
Poster #49

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Heather Acuff	Graduate	Phillips	Psychiatry

The Elucidation of Structural-Functional Relationships in Neural Circuitry Implicated in Youth at Risk for Bipolar Disorder

Background: Recent studies using diffusion tenor imaging (DTI) or functional magnetic resonance imaging (fMRI) have implicated white matter tracts and cortical regions in the pathophysiology of bipolar disorder (BD) and in healthy offspring of parents with BD. However the relationships between these structural and functional abnormalities have yet to be elucidated in offspring of parents with BD who are at high risk for developing BD themselves. In the present study we combined DTI and fMRI to identify biomarkers in neural circuitry that reflect the pathophysiology of youth at risk for BD. Methods: 30 healthy offspring of parents with BD (OBP) 30 healthy offspring of control parents with a non-BD diagnosis (OCP) and 30 healthy offspring of healthy parents (OHP) between the ages of 8 and 17 (matched for age gender and socioeconomic status) were scanned and performed a dynamic faces task. We used ANCOVAs multiple regression analyses and Least Absolute Shrinkage and Selection operator (LASSO) regressions to examine relationships among DTI and fMRI measures. Results: Compared to OCP OBP had decreased left amygdala activity in response to positive emotions but increased right ventrolateral prefrontal cortex (VLPFC) and dorsal anterior cingulate cortex (dACC) activity in response to negative emotions. In all groups right inferior longitudinal fasciculus (ILF) length predicted increased activity in the amygdala VLPFC and dACC in response to positive emotions while forceps minor volume predicted increased activity in the dACC in response to negative emotions. Group interactions also existed for the left ILF volume such that increased volume predicted increased activity in all regions for OBP but decreased activity for OCP. Conclusions: These findings suggest a pattern of emotion dysregulation caused by both abnormal neural connections and specific regional abnormalities. These structural and functional findings may serve as biomarkers for earlier diagnosis and treatment in youth at risk for BD.

Morning Poster Session
Location: Row D
Poster #45

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Gabriela Alarcon	Postdoctoral	Forbes	Psychiatry

Adolescent sex differences in default mode and cognitive control network functional coupling during cognitive control: a potential risk factor for major depressive disorder

Rates of depression increase sharply during adolescence particularly for girls who are twice as likely to experience a depressive episode compared to boys. The neural mechanisms mediating this sex difference in risk for depression have not been fully elucidated. The current functional magnetic resonance imaging study used an affective self-referential processing (SRP) induction capitalizing on the social re-structuring of identity that occurs during adolescence to measure sex differences in functional connectivity during a cognitive control task that immediately followed an SRP (Post-SRP Flanker) or Control (Post-Control Flanker) task. This approach was developed to examine the interaction between default mode and cognitive control networks (DMN and CCN) which support SRP and cognitive control respectively since aberrant interaction of these networks is implicated in major depressive disorder (MDD). Task activation was modeled and regressed; the residual time courses corresponding to the Flanker trials were used for functional connectivity analysis. Two-way ANOVA indicated a significant interaction between sex and task condition such that girls had stronger coupling between DMN and CCN during Post-SRP Flanker. CCN and DMN are generally de-coupled during cognitive control; thus the affective SRP task may have interfered with cognitive control processing in girls as has been shown in MDD.

Afternoon Poster Session
Location: Row E
Poster #64

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Ben Allen	Postdoctoral	Jennings	Psychiatry

Diffusion Imaging of the Superior Longitudinal Fasciculus and the Uncinate Fasciculus and Associations with Dimensions of Attention Deficit-Hyperactivity Disorder in Adults Diagnosed in Childhood

Alterations in white matter microstructure may play an important role in the pathophysiology of Attention Deficit-Hyperactivity Disorder (ADHD). However little is known about the extent to which ADHD symptom severity is associated with alterations in white matter tracts known to be involved in attention and emotional control processes. This study addresses this gap by using diffusion imaging (DI) to determine how differences in the superior longitudinal fasciculus (SLF) and the uncinate fasciculus (UF) relate to clinically relevant symptom dimensions in a sample of adults with or without a childhood diagnosis of ADHD. This sample is a subset from a longitudinal study of individuals diagnosed with ADHD as children based on standardized clinical interviews and parent/teacher ratings. For this study DSM-IV symptoms (based on self and parent report in adulthood) were averaged to create dimensions of inattention hyperactivity/impulsivity (H/I) and anger-irritability (A/I). Multi-shell diffusion weighted imaging data and T1 anatomical data were acquired in 46 adults (32 ADHD 14 nonADHD; mean age [SD]: 33 [3] years 44 males) on a 3T Siemens Trio MR scanner. Probabilistic tractography was used to reconstruct white matter tracts of interest(SLF; UF). Volume length and diffusivity metrics were extracted for each participant. Preliminary findings show that Smaller volumes for the UF ($p = .05$) and SLF ($p = .06$) in the right hemisphere in the ADHD vs nonADHD group. There were no significant group differences in diffusivity metrics for these tracts. In the ADHD group H/I symptoms were negatively correlated with length in the left and right SLF ($r = -.40$ $p = 0.01$ $r = -.40$ $p = 0.03$ respectively) and A/I symptoms were positively correlated with the volume of the right UF ($r = 0.40$; $p = 0.04$). The association between greater volume of the right UF and higher levels of A/I symptoms suggests greater connectivity between medial-temporal and orbitofrontal brain regions. Greater volume of the right UF may be indicative of more bottom-up processing in adults with high anger-irritability. Moreover diminished intra-cortical connectivity as evidenced by shorter length of the SLF may be a neurobiological substrate for higher levels of H/I symptoms in adults and represent a deficit in “cool” executive functions that enable flexible control over thought and action in pursuit of goal directed behavior. Future analyses will test whether these diffusion imaging characteristics are associated with prospectively gathered symptom trajectories from childhood.

Afternoon Poster Session
Location: Row C
Poster #33

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Flora M Antunes	Postdoctoral	Rubio	Otolaryngology

Lack of GluA3 AMPA receptor subunit alters synaptic transmission in the auditory nerve endbulb of Held synapse

Glutamate receptors of the AMPA type (AMPARs) which are tetrameric complexes assembled from combinations of four subunits (GluA1-A4) are primarily responsible for the fast excitatory transmission at central synapses. The subunit composition of AMPARs determines gating kinetics and thus shape the postsynaptic response (Cull-Candy et al. 2006; Yang et al. 2011). Fast gating GluA3- and GluA4-containing AMPARs mediate synaptic transmission at the endbulb of Held synapse on bushy cells (BCs; Gardner et al. 1999; Trussell 1999; Wang et al. 1998) one of the fastest synapses in the brain. Our preliminary data indicate prominent GluA3 expression at the endbulb-BC synapse when compared to synapses that receive auditory nerve input but exhibit slower kinetics. Thus we hypothesized that GluA3 plays a crucial role in fast synaptic transmission at the endbulb-BC synapse. We examined the kinetic properties of evoked and spontaneous EPSCs at the endbulb-BC synapse in slices prepared from GluR3-KO and wild type mice aged P17-P22. Our results show that the absence of GluA3 altered the kinetic properties of endbulb-elicited EPSCs and their short-term depression in BCs. In GluA3-lacking neurons endbulb-elicited EPSCs exhibited slower kinetics and stronger short-term depression. Our pharmacological studies indicate an increase in the expression of flip splice variants with slower desensitization kinetics in GluR3-KO mice which can explain the slower EPSC decay time. This finding suggests that GluA3 is needed for the normal insertion of flop splice variants in the endbulb synapse an important contributor to fast AMPAR kinetics in the mature endbulb synapse (Lawrence and Trussel 2000; Gardner et al. 2001; Schmid et al. 2001). We conclude that GluA3 plays a role in maintaining normal synaptic function at the endbulb-BC synapse.

Afternoon Poster Session
Location: Row F
Poster #70

Presenting Author:	Author Type:	Mentor/Lab:	Department:
William Ares	Postdoctoral		Department of Neurosurgery

A Comparison of CT Angiography and Digital Subtraction Angiography in the DIagnosis of Penetrating Cerebrovascular Injury

Authors: William J. Ares David M. Panczykowski Gregory M. Weiner Felix Nguyen Bradley Gross and Brian T. Jankowitz

INTRODUCTION: The current neurotrauma practice guidelines for the diagnosis and management of penetrating cerebrovascular injury (PCVI) give equal weight to CT angiography (CTA) and formal catheter based digital subtraction angiography (DSA) stating that there is no sufficient data to support one manner of imaging. It has been repeatedly shown in the literature that DSA outperforms CTA in the diagnosis of blunt cerebrovascular injury and as such we have hypothesized that catheter based angiography would also prove superior to CTA in the diagnosis of PCVI. METHODS: This population-based cohort study included all patients undergoing evaluation of penetrating cerebrovascular injury University of Pittsburgh Medical Center between October 2010 and June 2016. Clinical data was retrospectively collected and patients were excluded if information was missing or incomplete regarding imaging. All patients underwent radiographic evaluation consisting of both 16- or 64-slice multidetector row CT angiography (mCTA; 1.25mm slice thickness with coronal and sagittal reconstructions) and 4-vessel digital subtraction cerebral angiography DSA). Primary outcome was evidence of penetrating cerebrovascular injury on DSA. Injuries were defined according to Biffl et al. grading scale for BCVI since no universally accepted injury grading scale for PCVI exists. Agreement was assessed by Cohen's kappa coefficient; discriminatory power and calibration of these imaging modalities were assessed using multiple regression analyses and indicated by the area under the receiver operating characteristic curve (AUC). RESULTS: A sample of 21 patients was available for analysis. Agreement between diagnostic modalities was 76% (expected 57%) with a Kappa of 0.44 representing fair agreement (p=0.02). The sensitivity and specificity for mCTA for PCVI detection was 67% (95%CI 22-96%) and 80% (95%CI 52-96%) respectively. Multidetector CTA demonstrated adequate discriminatory ability for prediction of PCVI (AUC 0.73 95%CI 50-96%). The negative likelihood ratio of the patient suffering a PCVI despite having a negative mCTA for arterial injury was 0.42 (95%CI 0.13-1.3) while the negative predictive value of a normal mCTA was 86% (95%CI 57-98%). CONCLUSION: When compared to the gold standard of digital subtraction angiography CT angiography displays limited sensitivity and specificity for the diagnosis of PCVI. Patients who suffer penetrating neurotrauma may benefit from the definitive diagnosis offered by DSA if there is sufficient practitioner concern for PCVI.

Afternoon Poster Session
Location: Row B
Poster #15

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Justin Arnett	Graduate	Tyler-Kabara	Neurosurgery Physical Medicine and Rehabilitation

Clinical and Surgical Practices for Invasive Brain-Computer Interface Research

Background: Brain-Computer Interfaces (BCIs) are systems that record neural activity from the sensorimotor cortex and decode relevant activity patterns into control signals for prostheses such as computer cursors and robotic arms. While many animal studies have demonstrated successful BCI prosthesis control through microelectrode arrays (MEAs) and electrocorticographic (ECoG) arrays implanted in the sensorimotor cortex very few have demonstrated similar results in humans and to our knowledge there currently exists no literature describing in detail the clinical and surgical processes and techniques necessary for invasive human BCI research. Hypothesis: Here we describe our processes for subject selection and enrollment surgical implantation explantation and revision of electrodes postoperative management and our postoperative results and complications that had yielded successful BCI prosthetic control in all four of our subjects. Methods: From 2011 to the present day of this manuscript our group had implanted electrodes for the purposes of BCI testing in four subjects- three had received high-density ECoG arrays two had received MEAs and all five exhibited complete loss of upper extremity function prior to testing. Medical chart and study protocol review was conducted to enumerate the processes and results of subject selection screening examinations the processes and results of electrode implantation explantation or revision surgeries the postoperative findings medical complications and management thereof following surgical procedures the function and stability of implanted electrodes and briefly the success of our subjects in BCI performance. Results: Per the predefined inclusion/exclusion criteria all five subjects demonstrated significant sensorimotor cortex activation in response to attempted movement of their paralyzed upper extremity. All surgical procedures were uncomplicated with postoperative findings of only mild frontoparietal pneumocephalus in 3/5 subjects and mild mass effect in 2/5 subjects; one subject had developed symptoms related to psychiatric onset of Adjustment Disorder that persisted for 4 days following implantation and remitted with therapy. Electrode implantation was correctly targeted in all but two subjects- one in which an ECoG array shifted posteriorly to sensorimotor cortex but still resulted in stable successful BCI control; and one necessitating a revision surgery to reimplant MEAs anteriorly by one gyrus. MEA pedestal site skin retraction was observed in 2/6 total pedestal sites. Implanted arrays demonstrated stable recording performance in most electrodes throughout their implantation periods- greater than 28 days for three ECoG subjects 32 months for MEA subject 1 and greater than 12 months for MEA subject 2 (who at the time of writing this abstract is still implanted and undergoing BCI training); all subjects demonstrated successful BCI performance. Conclusions: We describe the clinical and surgical practices necessary for performing successful human invasive BCI research. We believe that this description of our methodology and findings will help standardize such practices within the BCI field as well as to serve as a basis from which future advancement in methodology can be made. References: 1) Wang W. et al. An Electrocorticographic Brain Interface in an Individual with Tetraplegia. PLoS ONE 8 (2013); 2) Collinger J. L. et al. High-performance neuroprosthetic control by an individual with tetraplegia. Lancet Lond. Engl. 381 557–564 (2013); 3) Wodlinger B. et al. Ten-

dimensional anthropomorphic arm control in a human brain-machine interface: difficulties solutions and limitations. J. Neural Eng. 12 016011 (2015);); 4) Degenhart A. D. Evaluation and Advancement of Electrocorticographic Brain-Machine Interfaces for Individuals with Upper-Limb Paralysis. (2015)

Afternoon Poster Session
Location: Row D
Poster #53

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Sertgei Baranov	Postdoctoral	Friedlander	Neurosurgery

Protecting mitochondria is a key to retain neuron synapses. Single-cell analysis.

Human studies reveal synaptic dysfunction decades before predicted clinical diagnosis in neurodegenerative diseases. Loss of synapses is a characteristic of Alzheimer's and Huntington's diseases. Normal synaptic activity is highly dependent on mitochondria because mitochondria is (i) the powerhouse (ii) a participant in the regulatory/signaling pathways and (iii) a critical player in the neuronal stress response cascades. Damage to synaptic mitochondria results in the impairment of the synaptic function and synaptic loss. The unique parameter characterizing mitochondrial status is mitochondrial membrane potential. Dissipation or prolonged decrease of the potential may lead to the reduction of number of mitochondria and/or triggering of apoptosis We hypothesized that Huntington's disease associated synaptic deregulation followed by neuronal cell death among other factors caused by a decreased mitochondrial membrane potential. Using single cell analysis approach we assessed mitochondrial membrane potential in the primary neurons from mouse model of Huntington's disease. We found that mitochondrial membrane potential was decreased with the distance from nucleus to the mitochondria. The decay in the membrane potential is more apparent in the neurons obtained from HD mouse model. We showed that found mitochondrial membrane potential decrease was also associated with an increased rate of the mitochondrial protein content oxidation and an increased production of reactive oxygen species by distant mitochondria. We explained our data in the framework of unique property of neurons to form very long processes (axons and dendrites) which results in delayed protein turnover in distal mitochondria and leads to the increased vulnerability of synaptic mitochondria to stress associated with the neurological disorder.

Afternoon Poster Session
Location: Row A
Poster #11

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Carl Beringer	Graduate	Gaunt	Bioengineering

Analysis of Intramuscular EMG Signals of the Extrinsic Hand Muscles During Single Degree of Freedom Movements

Myoelectric prosthetic hands (MPH) are motorized prosthetic devices which can use electromyography (EMG) signals as a control input to restore function and independence to upper limb amputees. Present MPH technology uses surface electrodes to collect EMG signals but are limited to muscles which are large or superficial. Intramuscular electrodes are an alternative method of capturing EMG activity directly from the muscle belly with a higher spatial resolution. Recent research has focused on development of control algorithms which use signals recorded by intramuscular electrodes placed within the extrinsic hand muscles including the compartments of the finger flexors and extensors. These algorithms often rely on a simple linear mapping which directly relates EMG activity to position or velocity. However there is a present lack in research which characterizes patterns of EMG activation in the extrinsic hand muscles. In order to address this gap in research we sought to characterize how wrist posture alters intramuscular EMG activation in the individual compartments of the extensor digitorum communis flexor digitorum superficialis and flexor digitorum profundus during single degree-of-freedom movements. We found that all assessed muscles show significant differences for peak EMG activation for different wrist postures. Our results suggest that future development of prosthetic control algorithms may require state information of the wrist in order to linearly translate EMG activity to kinematic output.

Morning Poster Session
Location: Row E
Poster #64

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Megan Bertholomey	Postdoctoral	Torregrossa	Psychiatry

Role of estradiol in ethanol-motivated behaviors

Recent epidemiological studies have shown that women but not men have demonstrated increased levels binge drinking and alcohol dependence compared to past cohorts. These findings are consistent with both clinical and preclinical data identifying females as a population that is particularly sensitive to predisposing factors leading to drug and alcohol abuse. For example it has been widely shown that female rodents show greater motivation to seek and take drugs compared to males. We have found that female rats maintain higher levels of ethanol self-administration and reinstatement of ethanol seeking following exposure to alcohol-paired cues and to the pharmacological stressor yohimbine especially when given in combination. However the mechanism underlying these sex differences is still unclear. Evidence suggests that estradiol is critical for the acquisition of cocaine self-administration and cocaine-primed reinstatement. However the effects of estradiol in ethanol-motivated behaviors are less consistent and few if any studies have determined estradiol-mediated changes in the reinstatement of ethanol seeking. To explore the role of estradiol in ethanol drinking and seeking gonadally intact and ovariectomized (OVX) female rats were trained to self-administer (SA) a 10% ethanol/0.1% saccharin solution paired with a light+tone cue on and FR1 schedule of reinforcement for 22 one-hour sessions. Rats then underwent ~10 extinction sessions and were tested for the effects of estrogen receptor modulation on cue+yohimbine-induced reinstatement of ethanol seeking. OVX rats were injected estradiol (E2) and intact rats were injected with either the selective estrogen receptor modulator (SERM) clomiphene to block the effects of estradiol or PHTPP an estrogen receptor β antagonist. As predicted E2 levels were positively related to ethanol drinking. OVX females showed reduced reinstatement compared to intact females and E2 did not rescue this effect. Rather activation of estrogen receptors with E2 tended to reduce reinstatement of ethanol seeking in OVX rats compared to vehicle while blockade of estrogen receptors with clomiphene or PHTPP tended to reduce reinstatement of ethanol seeking in intact rats. These findings suggest that estrogen signaling is important for ethanol-motivated behaviors though with paradoxical effects during ethanol seeking as a function of gonadal status. Current studies are aimed at further clarifying the role of E2 in ethanol-motivated behavior by determining the receptor and regional specificity of these effects in the brain. These findings will lead to a better understanding of the mechanisms underlying sex differences in alcohol-motivated behavior and guide potential treatment targets for alcohol dependent women.

Morning Poster Session
Location: Row D
Poster #52

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Brandon Bizup	Graduate	Ahmari	Psychiatry

Stress-induced Relapse in a Mouse Model of Obsessive Compulsive Disorder

Stress plays a role in many psychiatric disorders including those that are not necessarily classified as anxiety disorders. Stressful life events can be catalytic in the emergence of psychiatric illness and anxiety can play a role in relapse in individuals that are recovering from psychiatric episodes. Using a model of compulsive-like behavior induced by cortico-striatal hyperstimulation based on human imaging data in obsessive compulsive disorder patients we investigated whether stress was capable of causing mice to revert to a symptomatic state following a period of recovery. EMX-Cre mice (n=10 per group) were stereotactically inected in the medial orbitofrontal cortex with a channel rhodopsin virus (AAV5-DIO-hSyn-ChR2-eYFP ChR2) or an inert control virus (AAV5-DIO-hSyn-eYFP) and the mice were implanted with an optical fiber just dorsal to the nucleus accumbens core. Following recovery mice were stimulated with a 473nm wavelength laser for five minutes a day (10hz 10ms pulse width) for six days and grooming was assessed before during and immediately post stimulation. Following 6 days of stimulation ChR2-expressing mice were found to be grooming significantly more than control mice. Grooming levels of ChR2-expressing mice remained elevated from their own baseline until 4 weeks after cessation of stimulation. On the day of restraint stress ChR2 groomed significantly more than baseline though not significantly more than controls. Twenty-four hours following restraint stress ChR2-expressing mice were found to be grooming significantly more than controls at similar levels to the peak effect seen during the laser stimulation. By forty-eight hours both ChR2-expressing and control animals had returned to baseline grooming. Mice were then exposed to a second restraint stress. Strikingly following the second stressor ChR2-expressing mice did not return to baseline grooming levels forty-eight hours after restraint and maintained elevated grooming grooming until 5 weeks after the second stress event. This study demonstrates that stress in the cortico-straital hyperstimulation model of compulsive behavior can cause the overgrooming phenotype to return after recovery. Furthermore additional stress events are sufficient to reinduce a long lasting overgrooming phenotype.

Morning Poster Session
Location: Row A
Poster #13

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Meghan Bucher	Graduate	Hastings	Neuroscience

Dopaminergic degeneration following viral mediated dysregulation of dopamine: Implications for Parkinson's disease

Dopaminergic neuronal health is dependent upon the proper handling of dopamine (DA). Following synthesis in the cytosol DA is quickly packaged into acidic vesicles via the vesicular monoamine neurotransporter 2 (VMAT2). Disruptions in the packaging of DA can lead to increased cytosolic DA oxidation forming ROS and highly reactive DA quinone which can attack and covalently modify protein cysteinyl residues leading to detrimental downstream consequences. Cytosolic DA oxidation has been proposed to contribute to the neurodegenerative process in Parkinson's disease (PD). Previously it was shown that mice expressing only 5% of normal VMAT2 levels showed an age dependent loss of substantia nigra (SN) DA neurons and increased DA oxidation (Caudle et al. 2007). More recently Pifl et al. (2014) showed impaired VMAT2 function within the remaining dopaminergic terminals in PD patients suggesting that a dysregulation of DA storage can contribute to the pathogenesis of the disease. To investigate the effects of reduced VMAT2 expression in an adult animal an adeno-associated virus containing a plasmid coding for small-hairpin ribonucleic acid against VMAT2 was generated (AAV2-sh[VMAT2]). Rats were stereotactically injected unilaterally into the left SN with AAV2-sh[VMAT2]. Six weeks following the viral injection SN coronal sections were immunostained for VMAT2 tyrosine hydroxylase (TH) MAP2 and DAPI. Stereological counting of TH- and MAP2-positive neurons showed a significant loss of SN DA neurons on the AAV2-sh[VMAT2] injected side (-38.74%) compared to the contralateral non-injected SN (N=5 p<0.05). Likewise decreased density of striatal TH-immunoreactive terminals and the presence of dystrophic axons on the viral injected side also suggested neurodegeneration. In the remaining transduced TH-positive neurons VMAT2 protein levels were significantly decreased and there was an increase in insoluble alpha-synuclein. Consistent with the loss of DA neurons rats injected unilaterally into SN with AAV2-sh[VMAT2] showed significant asymmetric motor deficits as determined by the postural instability test and the cylinder test. These results show that a substantial reduction in the expression of VMAT2 within dopaminergic neurons is sufficient to cause neurotoxicity impairing proper VMAT2 functioning and DA sequestration in the maintenance of dopaminergic neuronal health.

Morning Poster Session
Location: Row F
Poster #69

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Ross Carson	Graduate	DeFranco	School of Medicine

Effects of Statins on the Proliferative Response of Neural Stem/Progenitor Cells

Although statins have proven to be safe and effective drugs in combating cardiovascular disease they are currently contraindicated in pregnancy due to potential teratogenic effects. Statins reduce serum cholesterol by inhibiting the rate-limiting enzyme of cholesterol synthesis HMG-CoA reductase (HMGR). In the developing neocortex products of the cholesterol biosynthesis pathway (CBP) including cholesterol and isoprenoids play essential roles in proliferation and differentiation of neural stem-progenitor cells (NSPCs); therefore we sought to investigate the effect of statins on the developing brain. To determine whether statins impact proliferation embryonic day 14.5 NSPCs were treated with pravastatin or simvastatin in vitro and cell viability was monitored over the course of 5 days. We found that both statins dose dependently decrease cell viability and neurosphere size. NSPCs treated with low doses of statins (1uM of Pravastatin or 0.1uM Simvastatin) were able to continue to grow but higher doses of statins (25uM Pravastatin or 5uM Simvastatin) caused a nearly complete inhibition of growth. In order to understand whether this phenotype was due to decreased proliferation or cell death we analyzed cell cycle phase and apoptosis by propidium iodide staining analyzed by flow cytometry. We found that while statins cause a dose dependent increase in cells progressing through the G1 phase of the cell cycle there is also a dose dependent increase in apoptosis. These findings were reinforced by significantly increased Cyclin D1 mRNA and protein and increased cleaved PARP protein in statin treated NSPCs. To understand how NSPCs respond to statins at a transcriptional level we treated NSPCs with pravastatin and examined global mRNA expression using RNA sequencing technology. Bioinformatics analysis revealed an upregulation of 17 CBP genes and a number of genes involved fatty acid and cholesterol metabolism. This upregulation was validated by qPCR in a handful of robustly upregulated CBP genes (HMGCS1 ACLY and DHCR24). To understand the regulation of this transcriptional phenotype we used our RNA-seq data to identify potential upstream regulators. We discovered that three of the top identified regulators (SCAP INSIG and SREBP2) form a complex known to regulate CBP genes in peripheral tissues. To validate this observation we measured activation of SREBP2 protein and found an increase in activation after treatment with either pravastatin or simvastatin. We found that SREBP2 activation occurs rapidly after treatment with statins and induces expression of CBP genes that plateaus around 24hr after treatment. Because NSPCs are able to continue to survive low doses of statin treatment we asked if statin induced transcription would be sufficient to rescue the cell growth phenotype. We found that a 24hr pretreatment with pravastatin not was able to rescue cell growth in NSPCs treated with statins compared to controls which indicates that the transcriptional response of NSPC's is not protective against statin induced cytotoxicity. This study suggests that chronic exposure to statins causes apoptosis in rapidly dividing NSPCs despite a robust compensatory upregulation of CBP genes. It remains to be elucidated whether statin induced cytotoxicity is due to decreases in cholesterol or other CBP end products.

Afternoon Poster Session
Location: Row E
Poster #63

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Pinar Celtikci	Postdoctoral	Fernandez-Miranda	Neurological Surgery

Revealing displacement and infiltration of fiber tracts in low-grade gliomas by advanced fiber tracking: novel imaging marker of fiber tract integrity

Background Low-grade gliomas (LGGs) originate from the supporting glial cells of the central nervous system (CNS) and comprise about 15% of the primary brain tumors in adults. LGGs are most common in third and fourth decades of life among patients with high quality of life and long survival expectancy 5 9 11. These are typically slow growing tumors characteristically located in the white matter that may demonstrate local growth invasion and malignant transformation6. Four patterns of white matter alteration by CNS tumors were defined in the literature: displacement infiltration edematous and disruption10. However which of the proposed patterns are characteristic to LGGs is a matter of controversy and has not been well established yet. Knowledge of how LGGs affect the white matter tracts around them is of significant importance especially for the neurosurgeon. The presence of any functional fibers in or around the tumor their position in relation to the lesion and the decision of which tracts could be sacrificed if needed in order to reach and resect the tumor are major surgical challenges3 8. High-definition fiber tractography (HDFT) is an advanced white matter imaging technique that has shown to be superior to diffusion tensor imaging2. HDFT provides an accurate evaluation of fiber tracts in vivo allowing determination of specific fiber tracts that are being compromised by a tumor mass and might be transgressed during surgical resection8. Objectives We aimed to demonstrate the patterns of white matter fiber tract alterations caused by WHO grade II LGGs using an advanced fiber tracking method. Furthermore our goal was to characterize and validate these qualitative patterns of fiber tract alteration via quantitative analysis in search for an objective imaging biomarker of fiber tract integrity. We finally investigated the correlation of these patterns with the neuropathological diagnosis. Methods Sixteen consecutive patients with preoperative HDFT and neuropathological diagnosis of LGG (WHO grade II) were enrolled. All patients were screened to rule out any contraindication to magnetic resonance imaging (MRI) and signed an informed consent as part of our IRB approved protocol. Diffusion data were acquired using a 3-Tesla Magnetom Verio® (Siemens Erlangen Germany) with a 32-channel coil. Total scan time was 34 minutes and included a 25-minute diffusion spectrum imaging (DSI) scan (repetition time = 3439 milliseconds echo time = 150 milliseconds multiband acceleration factor = 3 voxel size = 2.4 mm3 field of view = 231 × 231 mm) including 257 non-collinear gradient directions with a maximum b-value of 7000 s/mm2 followed by a 9-minute T1-weighted structural scan (repetition time = 2200 milliseconds echo time = 3.58 milliseconds voxel size = 1.0 mm3). The diffusion data were reconstructed using a generalized q-sampling imaging method to model an orientation distribution function in each brain voxel 12. Fiber tracking was performed with DSI Studio4. Peritumoral fiber tracts were determined based on their spatial relation with the tumor mass; once identified they underwent subsequent qualitative and quantitative evaluation. Their contralateral hemisphere counterparts were used for comparison. Qualitative evaluation classified peritumoral tracts as unaffected displaced infiltrated or displaced and infiltrated at the same time. Qualitatively affected tracts were further analyzed quantitatively. Quantitative anisotropy (QA) is a novel directionally-dependent measure of anisotropy that overcomes the limitations of fractional anisotropy (FA) in assessing fiber integrity12. Regarding displaced tracts QA

values were predicted to be higher or similar whereas with infiltrated tracts these values were hypothesized to be lower compared to the contralateral healthy side. For the quantitative analysis mean QA values of both whole tracts and peritumoral segments were obtained. Mean QA values of the contralateral healthy whole tract and anatomically equivalent segment of the peritumoral portion were also noted for comparison 1 7. In order to prevent disparity in comparison secondary to possible lateralization of fiber tracts perilesional segment mean QA (S) to whole tract mean QA (W) ratio (S/W) was calculated for both sides. Results Patient characteristics clinical information and qualitative evaluation are summarized in Table 1 (mean age: 38.1 years range; 17 – 63 years). There were 7 oligodendrogliomas 5 diffuse astrocytomas 2 gemistocytic astrocytomas one pleomorphic xanthoastrocytoma and one pilomyxoid astrocytoma. Qualitative analysis of 65 peritumoral tracts revealed 9 (13.8%) unaffected 24 (36.9%) displaced 13 (20%) infiltrated tracts and 19 (29.2%) tracts that demonstrated a combination of displacement and infiltration. There were no disrupted tracts. Partial infiltration of the perilesional tract was observed in 6 out of 13 tracts with pure infiltration and in 11 out of 19 tracts with the combination of displacement and infiltration. The most common pattern in oligodendrogliomas was displacement (41.9%) while in diffuse astrocytomas the combination of displacement and infiltration (53.3%) was the most frequent. When compared with the healthy side the quantitative analysis revealed that for displaced tracts there was an increase in the S/W S and W in 71.4% 61.9% 70.6% of the tracts respectively. For the infiltrated tracts there was a decrease in the S/W S and W in 63.6% 81.8% 66.6% of the tracts respectively. For tracts that were both displaced and infiltrated there was a decrease in the S/W and S in 64.7% and 58.8% of the tracts respectively (see Table 2). The increase of S/W ratio among displaced tracts and the decrease of S value in infiltrated tracts compared to the healthy side was statistically significant (p < 0.05). The p value for the decrease in S/W ratio in infiltrated tracts was not statistically significant (p=0.055). There was no statistically significant relationship between neuropathological diagnosis and qualitative alteration types or quantitative values. Conclusions WHO grade II LGGs might displace infiltrate or cause a combination of displacement and infiltration of white matter fiber tracts. Most common patterns were displacement and combination of displacement and infiltration. Infiltration (whether pure or with displacement) could be partial or include the whole diameter of the peritumoral segment of the tract. We found that the majority of S W values and S/W were increased in displaced tracts and decreased in infiltrated tracts compared to the healthy side and the increase of S/W ratio in displaced tracts and the decrease of S value in infiltrated tracts were statistically significant. Therefore we can conclude that QA changes correlate with the qualitative alterations and expected condition of the fiber integrity which may serve as an objective imaging biomarker of fiber integrity when altered by LGGs.

Afternoon Poster Session
Location: Row A
Poster #7

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Santosh Chandrasekaran	Postdoctoral	Santosh	Physical Medicine and Rehabilitation

Electrical stimulation of the cervical Dorsal Spinal Cord and Roots (DSCR) for sensory restoration in upper-limb amputees

A chief drawback of current prostheses is the lack of direct sensory feedback which leads to impaired prosthetic control and is associated with exacerbating phantom limb pain. Sensory feedback greatly enhances the embodiment acceptance and also the ease of use of a prosthetic device. Electrical stimulation of the peripheral and central nervous system is the focus of extensive research as a means to provide sensory feedback. In our approach we chose the dorsal spinal cord and roots (DSCR) as the site for such electrical stimulation. These structures are ideal targets for sensory electrical stimulation as they are well-isolated from motor pathways remain intact after most amputations and are accessible via minimally invasive procedures. Here we present observations from human psychophysics experiments performed in two upper-limb amputees using FDA-approved spinal cord stimulation (SCS; Boston Scientific) leads. Study participants were temporarily implanted with three 8 or 16-contact SCS leads in the lateral epidural space spanning the C5-C8 DSCRs. Multi-polar current-steering was used to improve the focality of sensory percepts. Feedback about the modality location and intensity of perceived sensations was provided by the subject through a structured reporting setup. Preliminary testing showed that sensory percepts in the form paresthesia can be evoked via selective stimulation through different SCS lead contacts. The sensations reported by the subjects include focal percepts localized to the amputated shoulder arm hand wrist palm and fingers consistent with the established dermatome maps corresponding to the respective spinal roots. These sensations were stable for more than two weeks of testing. A subset of electrodes generated naturalistic sensations of movement of the fingers on the missing hand in one of the subjects. Continuous modulation of stimulus amplitude was perceived as intensity changes and did not affect the overall location of the percepts. Psychophysical experiments that required subjects to distinguish between amplitudes of currents in a two-alternative forced choice task revealed a consistent threshold of detection (around 550 μA) across subjects. In conclusion we have established that sensory feedback can be provided to upper-limb prosthetic users using epidural dorsal spinal cord and roots stimulation.

Morning Poster Session
Location: Row C
Poster #36

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Daniel Charek	Postdoctoral	Collins	UPMC Sport Concussion Program

Additional Sport Exposure Following Concussion has Dose Response Effect on Recovery Time

Objective: Current guidelines suggest the immediate removal of athletes from contest after sustaining a sport-related concussion (SRC). However some athletes continue to play after sustaining a SRC due to lack of awareness of signs/symptoms sport culture and limited access to medical professionals. Concussed athletes who remain in play demonstrate worse outcomes including more severe acute cognitive impairment and longer recovery time. The goal of this study was to determine if there was a dose response of post-injury sport exposure (i.e. minutes remained in game/practice play after SRC) on athletes' severity of symptoms neurocognitive impairment and recovery time. Methods: Participants included 59 athletes aged 15.3+/-1.9 who reported remaining in play for 22.9+/-26.8 minutes (range=3-160) immediately following SRC. Participants were grouped by short duration (3-15 minutes [n=25]) or long duration (>15 minutes [n=34]) of continuous play following injury. A Mann-Whitney U test compared groups on recovery time and a series of t-tests compared groups on the Post-concussion Symptom Scale (PCSS) and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) 1-7 days following SRC. Results: Athletes in the long duration group took longer to recover (M=43.79 days SD=26.34) compared to those in the short duration group (M=29.08 days SD=12.90 p=.049) There were no significant differences on acute outcomes at 1-7 days post injury on ImPACT scores (p>.10) or PCSS score (p=.40). Conclusion: Additional exposure to sport immediately following SRC has a dose response effect on clinical outcomes. Further aerobic activity and exposure to additional contact are two potential mechanisms that may exacerbate injury.

Morning Poster Session
Location: Row A
Poster #14

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Jianming Chen	Postdoctoral	Burton	Neurology

Parkinson's disease-related protein α-synuclein modulates dynamic RedOx responses in CNS dopaminergic neurons in vivo

Parkinson's disease (PD) is characterized pathologically by death of specific neuronal groups (most prominently dopaminergic neurons of the substantia nigra) and accumulation of the presynaptic protein α-synuclein in cytoplasmic and axonal aggregates. Oxidative damage and mitochondrial dysfunction are thought to be central to the events leading to degeneration of dopaminergic neurons in PD. It is known that α-synuclein can influence both mitochondrial physiology and cellular oxidative biochemistry; however it is not known how α-synuclein modulates the production of ROS or physiologic maintenance of the RedOx potential in disease-vulnerable neurons. In order to address this question in CNS dopaminergic neurons in vivo we generated novel transgenic zebrafish expressing ratiometric reporters to allow measurement of dynamic RedOx responses in by direct intravital imaging. roGFP2-Orp1 is a sensitive detector of peroxide and is therefore a reporter of ROS generation. Grx1-roGFP2 senses changes in the oxidation status of the glutathione 2GSH/GSSG RedOx couple and is a reporter of oxidative stress. Our initial data using these novel transgenic reporters indicate that we can measure levels of ROS production and oxidative stress in vivo including dynamic responses after application of an oxidative challenge. By crossing these lines with further novel transgenic zebrafish expressing human α-synuclein we have shown that α-synuclein causes increased ROS production and disrupts RedOx homeostasis following a sub-lethal oxidative insult. The effect appears to be specific to dopaminergic neurons. These results are important since the direct measurement of these proximate pathogenic events for the first time in disease-relevant neuronal groups in vivo will allow us to exploit the genetic and chemical approaches possible in zebrafish to dissect the underlying biochemical mechanisms and to identify novel therapeutic targets.

Morning Poster Session
Location: Row B
Poster #20

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Mary Cheng	Faculty	Cheng	Departments of Computational & Systems Biology

Human dopamine transporter: transport and modulation mechanism

Human dopamine transporter: transport and modulation mechanism Mary H Chenga E Blockb J Pinoc G Torresc A. Sorkinb and Ivet Bahara Departments of Computational & Systems Biology a cell Biology b University of Pittsburgh School of Medicine Pittsburgh PA 15261; and c Department of Pharmacology and Therapeutics University of Florida Gainesville FL 32610 Dopamine transporters (DATs) control neurotransmitter dopamine (DA) homeostasis by reuptake of excess DA assisted by sodium and chloride ions. The recent resolution of DAT structures (dDAT)1 from Drosophila permits us for the first time to directly view the sequence of events involved in DA re-uptake in human DAT (hDAT) using homology modeling and full-atomic microseconds accelerated simulations. Major observations are2: spontaneous closure of extracellular (EC) gates prompted by DA binding; stabilization of a holo-occluded intermediate; disruption of N82-N353 hydrogen bond and exposure to intracellular (IC) water triggered by Na2 dislocation; redistribution of a network of salt bridges at the IC surface in the inward-facing state; concerted tilting of IC-exposed helices to enable the release of Na+ and Cl- ions; and DA release after protonation of D79. The observed time-resolved interactions confirm the conserved dynamics of LeuT-fold family while providing insights into the mechanistic role of specific residues in hDAT.2 The model provides excellent structural basis for understanding hDAT interactions with regulatory proteins and drug molecules. Further simulations show the ability of DAT to readily translocate DA and amphetamine; whereas orphenadrine (our predicted re-purposable drug) acts as a blocker like cocaine.3 We also note the propensity of DAT C-terminal end to bind Gβ consistent with experiments. Currently the potential mechanism of DA efflux induced by either Gβ or AMPH binding is being investigated. Acknowledgement: NIH grants P30DA035778 and P41GM103712 (I.B.) R01DA014204 (to A.S.) and R01DA038598 (G.T.) References: 1.\tKH Wang A. Penmatsa E. Gouaux. Nature (2015) 521 (7552): 322-7. 2.\tMH Cheng and I Bahar (2015) Structure; 23: 2171-81 3.\tMH Cheng E Block F Hu M Cobanoglu A Sorkin and I Bahar (2015) Frontiers Neurol 6:134

Afternoon Poster Session
Location: Row C
Poster #37

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Michael Chiang	Graduate	Ross	Neurobiology

Optogenetic dissection of central pain pathways

Pathological pain is a widespread condition that affects one in four Americans. Although opioids have long been used for their analgesic effects in pain management these drugs have severe adverse effects. An alternative approach with reduced adverse effects is delivering pain therapeutics to modulate neural circuitry within the brain responsible for contributing to the affective component of pain perception. Pain affect is believed to arise from the spino-parabrachial pathway via the lateral parabrachial nucleus (LPBN). However the role of distinct projections from the LPBN in the pain response is poorly understood. Here we show that the LPBN projects to six major targets in the brain: the insular cortex bed nucleus stria terminalis central amygdala hypothalamus ventral thalamus and periaquedutal gray. Using optogenetic approaches to target specific pathways we find that the two amygdala targets (central amygdala and dorsolateral bed nucleus stria terminals) are highly aversive as measured in a real time place preference assay. In contrast projections from the LPBN to the ventromedial hypothalamus mediate changes in heart and respiratory rates. Finally projections from the LBPN to the periaqueductal gray mediate the descending modulation of pain as measured by response latency to heat stimuli. These findings suggest that different components of a pain response are encoded within distinct pathways arising from the LPBN. Interestingly anatomical tracing of LPBN pathways indicate that distinct subpopulations of LPBN neurons differentially project to subsets of recipient brain regions suggesting that certain LPBN subsets mediate different aspects of pain perception. Identifying these will provide insight in our understanding of how the brain integrates nociceptive stimuli to generate pain perception. Furthermore this understanding can potentially contribute to the development of novel therapeutic agents that target a specific neural pathway mediating clinically relevant aspects of pain such as those neural pathways conveying the unpleasantness of pain.

Afternoon Poster Session
Location: Row A
Poster #5

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Patrick Cody	Graduate	Cui	Bioengineering

Evaluation of neural cell adhesion molecule L1 coating for improved chronic recordings

Neural probes are used in brain-machine interface based prosthetics to restore movement to paralyzed individuals. Intracortical neural electrodes provide the greatest spatiotemporal resolution compared to other recording approaches to enable optimal decoding of neural activity for prosthetic control. Inflammatory brain responses including glial scarring and neural degeneration degrade and limit the longevity of recordings thereby severely hindering the clinical potential of neural probes. Our lab has demonstrated that the neural cell adhesion protein L1 may be covalently conjugated to silicon and parylene based neural probe surfaces to reduce inflammatory glial activation improve neuron survival and enhance neurite outgrowth throughout a chronic period in a rat model as verified with quantitative histological measures. Chronic electrophysiological recordings from L1 coated and uncoated parylene-C insulated Utah arrays were compared in male Rhesus monkeys and rats up to 72 and 12 months respectively. Each monkey was implanted in the motor cortex with both a coated and uncoated 96 channel Utah array while each rat was implanted in the primary monocular visual cortex with either a coated or uncoated 4x4 Utah array. Coated monkey arrays exhibit significantly greater number of units than uncoated. For rats a repeatable and established visual stimulation paradigm was used to compare evoked activity between array treatments. In addition to a battery of histological analyses laser capture micro-dissection to assay RNA expression changes in the immediate micro vicinity of the probe is developed and combined with immunohistochemical staining to better elucidate the mechanism of L1's benefits. Recording performance from rat implants is quantified with single-unit yield (percent of electrode sites recording single-units) single-unit signal-to-noise amplitude ratios and multi-unit signal-to-noise firing rate ratios. Understanding the effect and mechanism by which L1 improves neural probe performance will inform approaches to better realize the full clinical potential of neural prosthetics for treating paralysis.

Morning Poster Session
Location: Row C
Poster #39

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Paul Cohen	Postdoctoral	Kontos	Orthopaedic Surgery

Do Initial Symptom Factor Scores Predict Subsequent Impairment following Concussion?

Objective: High symptom scores at initial visit (Meehan et al. 2013) and at baseline (Custer et al. 2016) are predictive of impairment and protracted recovery following concussion. However the predictive value of symptom factors (e.g. Kontos et al. 2012) on subsequent impairment is unknown. The purpose of this study was to examine the ability of patients' symptom factor scores at their initial clinic visit to predict neurocognitive and vestibular/oculomotor impairment at their second clinic visit. Participants and Methods: Participants included 72 athletes aged 13-22 with a sport-related concussion. Participants completed the Post-Concussion Symptom Scale (PCSS) Immediate Post-concussion Assessment and Cognitive Testing (ImPACT) and Vestibular/Ocular Motor Screening (VOMS) at 1 week post-injury and again approximately 2-4 weeks post-injury. PCSS scores were aggregated into symptom factors per Kontos et al. (2012). Multiple regressions were conducted with symptom factors at <1 week as predictors of ImPACT and VOMS scores at 2-4 weeks and recovery time. Results: The cognitive fatigue/migraine symptom factor predicted impairment on visual memory (β=-.348 p=.033) and reaction time (β=.003 p=.029). The affective symptom factor predicted higher scores on the horizontal (β=.398 p=.019) and vertical saccades (β=.390 p=.031) and vertical (β=.571 p=.013) and horizontal vestibular ocular reflex (VOR) (β=.471 p=.030). Symptom factor scores did not significantly predict recovery time. Conclusions: Clinicians can utilize patient's initial symptom factor scores to better predict subsequent impairment and identify patients for earlier targeted treatment. Patients with anxiety/mood symptoms following concussion may experience increased vestibular impairment following concussion.

Morning Poster Session
Location: Row E
Poster #56

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Victoria Corbit	Graduate	Gittis	Neurobiology

Circuit-specific corticostriatal dysfunction in a mouse model of Obsessive-Compulsive Disorder

Obsessive-Compulsive Disorder (OCD) is a psychiatric disorder associated with an inability to suppress intrusive thoughts and/or compulsive behaviors. Supplementary motor cortex (SMA/pre-SMA) and lateral orbitofrontal cortex (lOFC) have been implicated in OCD because they are hyperactive in OCD patients and they are involved in response inhibition and behavioral flexibility which have been found to be abnormal in OCD. In addition studies have demonstrated efficacy of SMA/pre-SMA transcranial magnetic stimulation (rTMS) treatment for OCD. More specifically dysfunction in the projections from these cortical areas to the striatum has been implicated in OCD. We therefore used optogenetics and acute slice physiology to investigate corticostriatal synaptic dysfunction in in an OCD-relevant mouse model the Sapap3-KO mouse. Our studies focused on the centromedial region of striatum (CMS) because 1) CMS is the projection target of the mouse homologues of these cortical regions and 2) a prior study in Sapap3-KOs has shown deficient inhibition of striatal output neurons (MSNs) by fast-spiking interneurons (FSIs) in the CMS. Intrastriatal stimulation showed that KO mice exhibit selectively increased overall excitatory drive onto CMS FSIs but not MSNs. To determine which specific cortical inputs were contributing to the increased drive of interneurons we injected channelrhodopsin2 (ChR2) and recorded 470nm light-evoked excitatory post-synaptic currents (EPSCs). We first examined inputs from lOFC (the primary input to CMS) and observed that EPSCs in FSIs were no different in KOs compared to WTs. This demonstrates that lOFC inputs are not the source of overall increased excitatory drive to FSIs in Sapap3-KOs. Furthermore lOFC EPSCs onto MSNs were weaker in KO mice in contrast to the unchanged overall excitatory drive to MSNs. These results suggested that another input played a role in CMS microcircuit changes we observe in the Sapap3-KO mice. We therefore virally injected ChR2 into M2 to investigate corticostriatal synapses from this region. Light-evoked EPSCs from M2 were increased onto both MSNs and FSIs in KO mice relative to WTs. Combined with the results from LOFC inputs the increase in M2 inputs onto both cell types can explain the selective differences in overall excitatory drive. Furthermore these data suggest that M2 corticostriatal circuits may be overactive in this OCD mouse model which supports literature demonstrating hyperactive corticostriatal circuits and hyperactive SMA/pre-SMA in OCD patients. To mimic the inhibitory effects of rTMS treatment in the SMA/pre-SMA our future experiments will inhibit the hyperactive M2 corticostriatal projections in the Sapap3-KO and determine the impact OCD-relevant repetitive grooming behavior. These results in combination with our synaptic physiology data will bring new focus to the role of supplementary motor cortical regions in the pathology of OCD and will contribute valuable information towards optimizing rTMS treatments for OCD.

Afternoon Poster Session
Location: Row C
Poster #34

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Marc Coutanche	Faculty	Coutanche	Psychology

The influence of recent semantic learning on human visual cortex

Humans are frequently exposed to information about the many objects, animals and people we that encounter in our environments. In addition to a suite of perceptual processes that can extract information from observed items, humans have the unique ability to discover the properties of objects through abstract communication. We have investigated how the introduction of visually relevant information –the real-world size of recently introduced animals– impacts the patterns of neural activity observed in a person's visual cortex. We scanned human participants with functional Magnetic Resonance Imaging (fMRI) while we introduced them to novel and known animals and tools. At the start of the experiment, participants were exposed to images of these items through a simple 1-back task. Participants were next presented with, and tested on, new factual information about each new concept. Finally, a post-learning 1-back task was administered. We used multivariate pattern analysis (MVPA) to decode the neural patterns underlying the processing of the new and known animals and tools, in order to compare activity patterns before and after learning. We find that after introducing people to new information about items' real-world size, visual activity patterns for the newly introduced animals more closely resemble the activity patterns observed for similarly sized known animals. In contrast, learning semantic information about the intended motor manipulation of a new tool did not affect future visually generated activity patterns. Our findings suggest that learning information about a new visual concept might rapidly influence visual cortex neural activity.

Morning Poster Session
Location: Row B
Poster #26

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Sabya Das	Postdoctoral		Pharmacology & Chemical Biology

WNK kinase-mediated changes in GABAA receptor neurotransmission after ischemic stroke

Synaptic and extrasynaptic γ-aminobutyric acid type A receptors (GABAARs) generate inhibitory neurotransmission in the healthy adult brain through hyperpolarizing chloride ion influx and are essential in regulating brain function. Ischemic brain injury results in severe damage and death of brain tissue due to disruption of intracellular and extracellular ion homeostasis and an imbalance between excitatory/inhibitory neurotransmission. In particular ischemic injury is associated with reduced GABAAR inhibition; however the underlying mechanisms are not understood. The strength and polarity of GABAAR neurotransmission (inhibitory or excitatory) depends on the intracellular chloride concentration ($[Cl^-]i$) set by the activity of two cation-chloride transporters: chloride importer Na+-K+-Cl- cotransporter (NKCC1) and neuronal chloride extruder K+-Cl- cotransporter (KCC2). The Cl- transporters are reciprocally regulated by the chloride sensitive WNK3 kinase; WNK3 stimulates NKCC1 but inhibits KCC2 activity through phosphorylation. Recent studies show that GABAAR subtype expression depends on $[Cl^-]i$ during development but effects of ischemic stroke on altering GABAAR plasticity have not been investigated. WNK3 knockout (KO) mice exhibit smaller ischemic infarct and improved neurological function recovery after focal ischemic stroke (middle cerebral artery occlusion MCAO) in association with reduced phosphorylation and activation of NKCC1. However whether improved post-stroke recovery in WNK3 KO mice in part results from maintenance of inhibitory GABAergic neurotransmission remains unknown. Our pilot study shows that in vitro ischemia [an oxygen-glucose deprivation (OGD) model] leads to loss of KCC2 and downregulation of α1 GABAAR protein expression in cortical neurons. Furthermore initial in vivo data reveal a decrease in α1/α2 GABAAR ratio extrasynaptic α4δ GABAAR and KCC2 expression in WNK3 wild type (WT) mice at 48 h post-stroke. Importantly WNK3 KO mice exhibit an absence of ischemic stroke-induced GABAAR plasticity that could be neuroprotective. Biochemical calcium imaging and electrophysiological methods are being used to investigate WNK3 dependent mechanisms leading to ischemic alteration of KCC2 activity and GABAAR subunit composition and localization. These studies will provide critical insight into GABAergic signaling following ischemic injury and identify new therapeutic targets for stroke treatment.

Afternoon Poster Session
Location: Row A
Poster #2

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Alan Degenhart	Postdoctoral	Batista	Systems Neuroscience Institute

Self-recalribrating brain computer interfaces based on population subspace alignment

A key problem limiting the clinical translation of intracortical brain-computer interface (BCI) technology is that of stability. Over time neural signals recorded by penetrating microelectrode arrays can change due to a number of factors including glial scarring electrode micro-motion and mechanical failure. To combat these changes BCI systems typically rely on explicit daily recalibration of their decoding algorithms to recover satisfactory control. Recalibration procedures require the user's participation and may be burdensome in a clinical setting. To overcome this shortcoming we present an algorithm for decoding a continuous control signal which performs automatic recalibration by leveraging the low dimensional structure found in neural population activity. We make the assumption that the day to day relationship between a low-dimensional representation of neural activity and intended BCI movements is constant even if the set of neurons recorded and the characteristics of the signals vary from day to day. By finding the alignment between low-dimensional spaces of the population activity estimated at different points in time decoding parameters can be automatically updated based only on observation of new neural activity and without knowledge of intended movement kinematics. This allows recalibration to occur in the background and requires no time or effort on the part of the user. We assessed performance of the self-recalibrating algorithm in a series of closed-loop BCI experiments with a Rhesus macaque implanted with a Blackrock array in primary motor cortex (M1). Experiments began with the calibration of a well-controlled "baseline" decoder. As the neural activity within a single experimental session is often stable we simulated recording instability by perturbing the neural activity using: (1) baseline shifts where a random constant offset was added to the firing rate of each neuron (2) silencing where the firing rates of a subset of neurons was set to zero (3) swaps where the activity of a subset of neurons was replaced with that of held-out neurons or (4) combinations of baseline shifts silencing and swaps which might mimic clinically severe recording instabilities. In 30 of 32 experiments we find that the self-recalibrated decoder was able to significantly improve performance in the presence of the perturbation returning control to pre-perturbation levels or better in 11 of these sessions. Furthermore we found that use of the algorithm in the absence of artificially-generated neural instabilities did not adversely alter performance. This work has the potential to increase the viability of BCI systems for clinical use.

Afternoon Poster Session
Location: Row A
Poster #4

Presenting Author:	Author Type:	Mentor/Lab:	Department:
John Downey	Graduate	Collinger	Bioengineering

Encoding of intended grasp force in primary motor cortex during brain-computer interface controlled robotic arm use

Brain-computer interfaces (BCIs) for neuroprosthetic arm control are being developed as assistive devices for people with tetraplegia. Often signals from primary motor cortex (M1) are used to decode endpoint velocity but M1 is also known to encode force. For BCI-controlled grasping it is important to be able to modulate force in order to grasp objects of varying weights and fragility. We sought to determine if we could decode a BCI user's representation of grasp force during attempted grasping of virtual objects. Under an Investigational Device Exemption a 28 year-old male participant with chronic C5 motor and C6 sensory AIS B spinal cord injury was implanted with two microelectrode arrays in M1 and two microelectrode arrays in S1. Neural data was recorded while the participant watched a virtual prosthetic arm grasp a spherical object. Trials started with an auditory cue naming a graspable object (marshmallow tomato can of soup) chosen to span the range of possible grasp force representations. After a 2 s planning period he attempted to grasp with "the minimum force required to grasp and lift the cued object". He then attempted to hold the object with the appropriate amount of force for 2 s before being cued to release it. The virtual arm automatically grasped and released the object regardless of the participant's actions. To determine whether the intended grasp force was encoded in the recorded neural activity each channel's firing rate was averaged over a 1 s sliding window (0.2 s step size). Each window was used to train and test a naïve-Bayes classifier using leave-one-out cross validation to create a time series of classification accuracy. Classification accuracy of the 3 objects using firing rates in M1 peaked at 88% for the 1 s window starting 0.2 ms in to the 2 s hold time and remained above 85% for the rest of the hold time. The accuracy did not diverge from chance level until the participant began attempting to grasp the object. When the object was released the classification accuracy fell to 62% at the end of the trial. Classification accuracy using S1 firing rates followed a similar trend but increased later than M1 accuracy by approximately 0.5 s and peaked at only 67%. This study shows that graspable objects requiring a variety of forces (the participant reported relative force ratings of 1 2 and 4) can be well classified from M1 and to a lesser extent S1 in a BCI user with tetraplegia. Future work will integrate this decoded information into closed-loop BCI arm control to attempt to improve the users' ability to grasp and manipulate a variety of objects.

Afternoon Poster Session
Location: Row C
Poster #42

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Haley Dresang Chia-Ming Lei	Graduate	Dickey	Communication Science and Disorders

Neural bases of semantic-memory deficits for events

This study investigated the neural bases of event-related semantic-memory deficits among people with aphasia due to left-hemisphere (LH) stroke. A novel task using naturalistic photographic stimuli and patient-friendly procedures was used to test event-related semantic knowledge. In the task participants decided whether depicted events were normal (represented in semantic memory) or were abnormal (not represented in semantic memory). Performance on this Event task was correlated with deficits in action- and object-concept processing and on standardized language measures especially action- and verb-processing deficits. Logistic regression analyses examined lesion correlates of patient performance on the Event task. Surprisingly increasing LH lesion size in action ROIs was associated with improved performance on the event-knowledge task. These findings suggest that action processing may play a special role in event-related semantic memory representations. Furthermore they are consistent with recent claims that the right hemisphere may be especially important for activation of event-related knowledge.

Morning Poster Session
Location: Row B
Poster #15

Presenting Author:	Author Type:	Mentor/Lab:	Department:
April Dukes	Postdoctoral	Burton	Pittsburgh Institute for Neurodegenerative Diseases and Neurology

Role of Parkinson's disease-related protein α-synuclein in mitochondrial transport and degradation in CNS dopaminergic neurons in vivo

Parkinson's disease (PD) is characterized pathologically by neuronal loss and accumulation of α-synuclein in large protein aggregates (Lewy bodies) in surviving neurons. Extensive oxidative damage and loss of mitochondrial respiratory function has been found in PD autopsy material suggesting that mitochondrial dysfunction is a key pathogenic mechanism. Maintenance of a healthy mitochondrial population requires a delicate balance of biogenesis fission fusion transport and degradation by mitophagy. Rare Mendelian Parkinsonism phenocopies are associated with loss of function in proteins that are centrally involved in mitochondrial quality control; however little is known about the role of mitochondrial transport and degradation in sporadic PD or how these processes are influenced by α-synuclein. We previously developed a method for measuring mitochondrial transport in dopaminergic neurons in the intact CNS of live transgenic zebrafish lines expressing fluorescent reporters within their mitochondria. In this model low sublethal concentrations of a mitochondrial inhibitor previously implicated in PD pathogenesis (MPP+) caused a dramatic 3-fold increase in retrograde mitochondrial transport in dopaminergic axons (Dukes et al. Neurobiology of Disease 2016:95:238). We now aim to determine (i) whether the large increase we observed in retrograde transport following MPP+ exposure is part of a compensatory cellular response encompassing mitophagy within the cell body of irrevocably damaged presynaptic mitochondria; and (ii) how this process is influenced by α-synuclein. In order to directly address these questions in dopaminergic neurons in vivo we have generated additional novel transgenic lines including zebrafish that express an LC3-GFP fusion protein that labels autophagosomes in living cells and zebrafish that express human α-synuclein in dopaminergic neurons. By a combination of genetic crosses and high-end in vivo imaging we now have the tools to observe mitophagy in CNS dopaminergic neurons in vivo and to determine how this is modulated by mitochondrial inhibitors and α-synuclein. These unique reagents and approaches will elucidate how α-synuclein and mitochondrial quality control intersect in the pathogenesis of PD.

Afternoon Poster Session
Location: Row E
Poster #55

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Jeff Dunworth	Graduate	Doiron	Mathematics

Finite Size Effects and Rare Events in Balanced Networks

Cortical neuron spiking activity is broadly classified as temporally irregular and asynchronous. Networks with a balance between large recurrent excitation and inhibition capture these two key features making them a popular framework for relating circuit structure and network dynamics. Balanced networks stabilize the asynchronous state through reciprocal tracking by the inhibitory and excitatory population activity leading to a cancellation of total current correlations driving neurons within the network. Analysis of recent data from spontaneously active mouse auditory cortex slices show balanced network activity except for intermittent periods when the network experiences macroscopic synchronous events. These data suggest that while the core mechanics of balanced activity are important we require new theories capturing these brief but powerful periods when balance fails. Traditional balanced networks with linear firing rate dynamics have a single attractor and fail to exhibit macroscopic synchronous events. Mongillo et. al. (2012) showed that balanced networks with short-term synaptic plasticity can depart from strict linear dynamics through the emergence of multiple attractors. We extend this model by incorporating finite network size and introducing strong nonlinearities in the firing rate dynamics which allows finite size induced noise to elicit large scale yet infrequent synchronous events. We carry out a principled finite size expansion of an associated Markovian birth-death process and identify core requirements for system size and network plasticity to capture the transient synchronous activity observed in our experimental data set. Our model properly mediates between the asynchrony of balanced activity and the tendency for strong recurrence to promote macroscopic population dynamics.

Afternoon Poster Session
Location: Row E
Poster #66

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Kristen Eckstrand	Postdoctoral	Forbes	Psychiatry

Heightened Activity in Social Reward Networks is Associated with Adolescents' Risky Sexual Behaviors

BACKGROUND: Compared with both adults and children adolescents have an enhanced propensity to engage in rewarding risky behavior. While sexual behavior in adolescence is a normative part of development risky sexual behavior is particularly important as it involves decisions to engage in potentially highly rewarding experiences that can lead to serious health consequences. The neural circuits underlying risky sexual behavior are largely unstudied; however it is believed that increased reward responsiveness – particularly social reward – contributes to risky sexual behavior. Using a social reward fMRI paradigm we hypothesized that adolescents engaging in higher risk sexual behaviors would exhibit increased activity and functional connectivity in response to social reward. METHODS: 47 typically developing adolescents (18M 29F [16.3±1.4 yrs]) underwent fMRI on a 3T scanner using a task in which they received rewarding or neutral feedback from peers. Adolescents completed the Youth Risk Behavior Survey including sexual health risk behaviors. Based on these responses individuals were classified into higher and lower sexual risk. Activation and functional connectivity analyses comparing higher and lower sexual risk adolescents were conducted in SPM12. RESULTS: Twenty individuals had engaged in sexual intercourse; male and female participants did not differ in risky sexual behaviors. Adolescents with higher risk sexual behaviors demonstrated increased activation in the right precuneus and the right temporoparietal junction (TPJ) during receipt of social reward compared with adolescents with lower risk sexual behaviors (see Figure 1). Further, adolescents with higher sexual risk demonstrated greater functional connectivity between the precuneus and both the temporoparietal junction bilaterally as well as frontal regions including one cluster involving the dorsal mPFC and anterior cingulate cortex and another involving the left ventrolateral PFC and anterior insula (see Figure 2). DISCUSSION: In response to social reward adolescents engaging higher risk sexual behaviors exhibited greater activation and functional connectivity in social reward networks. Heightened activation in these reward- self- and social-processing regions could reflect a combination of tendencies toward reward seeking and enjoyment sensitivity to socially rewarding stimuli and orientation toward social rewards among youth engaging in higher risk sexual behavior. Given the limited neurodevelopmental literature on emerging adolescent sexual behavior these results provide evidence for the particular importance of social influence on neural circuits underlying sexual risk behaviors.

Afternoon Poster Session
Location: Row A
Poster #3

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Sharlene Flesher	Graduate	Gaunt	Bioengineering

Intracortical microstimulation of human somatosensory cortex elicits cutaneous percepts

Dexterous object manipulation requires cutaneous sensory feedback. In its absence, simple tasks are very difficult. In prosthetic limbs controlled through brain-computer interfaces (BCIs), providing somatosensory feedback could be an important step to improving function as vision provides impoverished cues about object interactions. Intracortical microstimulation (ICMS) of primary somatosensory cortex (S1) is a potential method to restore this sensory channel, particularly in people that cannot benefit from stimulation of the peripheral nervous system. Under an Investigational Device Exemption, a 28 year old participant with a chronic spinal cord injury was implanted with 2 intracortical microelectrode arrays (MEAs) in motor cortex and 2 MEAs in area 1 of S1. Locations of the S1 MEAs were based on presurgical imaging with the goal of eliciting percepts that project to the fingers of the right hand. Electrodes were stimulated at supraliminal intensities and the participant described the locations and qualities of evoked percepts. Projected fields were located on the proximal pads of digits 2-5. Sensations were evoked on 59 of 64 electrodes, and no painful sensations or paresthesias were reported. We tested whether the subject could use this spatial information to identify which of four fingers on a robotic limb was touched by converting robot finger torque to stimulus intensity. The load-bearing finger was identified with 84.3% accuracy (54 trials). We measured detection thresholds using a two-alternative forced choice task and found the median detection threshold to be 34.9μA, with upper and lower quartiles at 60.0 and 24.8μA, respectively. Thresholds were generally stable over 11 months. Of the 32 electrodes with 3 or more measured thresholds 7 changed significantly over time, 3 of which had a negative slope, suggesting thresholds were not globally increasing. We measured the discriminability of ICMS trains differing in amplitude and found the just noticeable differences to be 15.4 ± 3.9 μA (mean ± s.d.) and independent of the magnitude of the reference stimulus. In magnitude estimation experiments, we found that perceived intensity increased linearly with stimulation amplitude (R2 = 0.98) for 5 electrodes tested. In summary, percepts were evoked at somatotopically appropriate locations with intensities that scaled linearly with amplitude over a wide range. These properties of evoked percepts can be used to convey location and intensity of object contact, key types of information for guiding interactions with objects. Providing artificial somatosensory feedback to BCI users could improve the user's control and experience with the prosthetic device

Afternoon Poster Session
Location: Row B
Poster #21

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Gurpreet Gandhoke	Graduate	Jankowitz	Neurological Surgery

Uniform pricing of coils used to treat intracranial aneurysms - A pilot Cost-Minimization Study

Introduction: The literature has ample evidence on endovascular coiling being more expensive than surgical clipping of intracranial aneurysms. Clinical effectiveness of endovascular coiling has been universally accepted however studies with long-term follow up have failed to demonstrate cost-benefit with endovascular treatment in comparison to open clipping. We hypothesize that this is due to the ever-increasing price of the coils required to accomplish the task. We believe that a very important contributor to coil cost escalation is that physicians are not affected by device pricing since their reimbursements have not been directly related to hospital costs. We decided to test our hypothesis by switching to a capped price for coils. The question was 'If all other parameters remain the same will paying the same lump sum amount irrespective of the number of coils used to treat a particular aneurysm make any difference to the overall cost' Methods: The endovascular surgeons at our institution negotiated an agreement with company 'X' to use a capped amount of $4000 for coil cost irrespective of the number of coils used to embolize an intra-cranial aneurysm. We retrospectively reviewed the coil and cost data on 12 patients who underwent coil embolization using coils from company 'X' during the period of September 2015- June 2016. The characteristics (length diameters) and number of coils used in every patient were analyzed. For the same patients we calculated the costs to use the same number of company 'Y' coils with similar dimensions and characteristics. Company 'Y' is the highest priced company within our system. We have withheld the names of companies 'X' and 'Y' on their request. Results: Total number of coils used for the twelve patients was 67 with a mean 5.6 coils per patient. The total cost of coils for twelve patients under the new-capped policy using coils from company 'X' was $48 000. The mean cost for each coil using company 'Y' was $1727 with a range of $951 to $2420. The total cost to use similar dimensions and same number of company 'Y' coils for the 12 patients was $106 905 resulting in a potential cost saving of $58 905. Thirty-eight different types of coils with varying diameters and lengths were used for the treatment of the 12 patients. The mean cost saving (using the capped policy) per patient was $4909 (p=0.01) with a range from -$395 to $14 860. Conclusion: This preliminary analysis is an impetus to explore coil cost capitation as a potential cost minimization strategy in endovascular surgery for coiling intracranial aneurysms. We are now exploring our own database to compare 1-year pre and post coil cost capitation differences in coiling aneurysms.

Afternoon Poster Session
Location: Row C
Poster #31

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Sofia Garcia-Hernandez	Postdoctoral	Rubio	Otolaryngology

Impaired auditory processing and altered synaptic structure in mice lacking the GluA3 subunit of AMPA receptors

AMPA glutamate receptor complexes with fast kinetics subunits -GluA3 and GluA4- are essential for temporal precision in the auditory system. We evaluated the role of the GluA3 subunit in auditory processing using auditory brainstem responses (ABR) to assess auditory function and electron microscopy to evaluate the ultrastructure of the auditory nerve synapse on bushy cells (AN-BC synapse) in wild type mice (WT) and mice lacking GluA3 (GluA3-KO). Since GluA3 subunit localization increases on auditory nerve synapses within the cochlear nucleus in response to transient sound reduction we investigated the role of GluA3 in experience-dependent changes in auditory processing; we induced transient sound reduction by ear plugging one ear and evaluated ABR threshold recovery for 60 days after ear plug removal in WT and GluA3-KO mice. We found that the deletion of GluA3 leads to impaired auditory signaling that is reflected in decreased ABR peak amplitudes increased latency of peak 2 premature hearing loss and ultrastuctural changes in the AN-BC synapse. Additionally the lack of GluA3 hampers ABR threshold recovery after transient ear plugging. We conclude that GluA3 is required for normal auditory signaling normal adaptive plastic changes after transient sound reduction and normal ultrastructure of AN-BC synapses in the cochlear nucleus.

Afternoon Poster Session
Location: Row D
Poster #43

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Rebecca Gerth	Graduate	Colby	Bioengineering

Coherence between PFC and PPC local field potentials in monkeys during the memory guided saccade task

The dorsolateral prefrontal cortex (PFC) and the posterior parietal cortex (PPC) of the macaque monkey are linked to each other by dense reciprocal axonal projections. Both areas contain neurons that exhibit spatially selective cue-period delay-period and saccade-period activity during performance of a memory guided saccade task. How interconnections between the two areas contribute to their function is not yet well understood. To explore this issue we have analyzed the coherence of local field potential (LFP) signals monitored simultaneously in PFC and PPC during performance of a memory guided saccade task. During each experimental session we recorded with an eight-channel linear electrode array in each area. This approach permitted comparing signals recorded from multiple pairs of sites within a single session. However it prevented systematic placement of the saccade target relative to the response field because neurons at different sites had different patterns of spatial selectivity. We presented targets at two widely separated contralateral sites during each session and characterized spatial selectivity at each site post hoc on the basis of differential neuronal responses on trials involving the two targets. We analyzed coherence of LFPs recorded at pairs of sites one in PFC and the other in PPC. We focused on oscillations in the beta and gamma ranges (15-30 and 30-80 Hz respectively). The degree of coherence depended on time during the trial and also on whether the target was at the preferred or non-preferred location. There were modulations in the degree of coherence during the visual epoch the delay epoch and the peri-saccadic epoch. Each effect was most pronounced during trials in which the target was at the preferred location.

Morning Poster Session
Location: Row C
Poster #41

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Brandon Gillie	Postdoctoral	Kontos	UPMC Sports Medicine Concussion Program

Comparison of Adolescents with Vestibular and Anxiety Clinical Profiles following Concussion

Comparison of Adolescents with Vestibular and Anxiety Clinical Profiles following Concussion Brandon L. Gillie PhD Anthony P. Kontos PhD Erin Reynolds PsyD Alicia Sufrinko PhD Valerie L. Reeves PhD Cyndi L. Holland MPH & Michael W. Collins PhD Objective: Concussed patients present with clinical profiles including vestibular and anxiety (Collins et al. 2014; in press). However there is no research on outcomes in patients with different clinical profiles. The purpose of this study was to compare clinical outcomes among concussed adolescents with vestibular anxiety and neither-vestibular nor anxiety (NVA) clinical profiles. Participants and Methods: A vestibular group (n= 11; i.e. presence of vestibular dysfunction/symptoms) an anxiety group (n= 10; i.e. presence of anxiety symptoms with or without vestibular dysfunction/symptoms) and a NVA (neither anxiety nor vestibular) group (n=12) were derived from a sample of 33 adolescents aged 12-20 (M= 15.0 SD= 1.9) with a diagnosed concussion. Participants completed the Post-concussion Symptom Scale (PCSS) Immediate Post-concussion Assessment and Cognitive Testing (ImPACT) Vestibular/Ocular Motor Screening (VOMS) Balance Error Scoring System (BESS) 2-10 days post-concussion. Univariate ANOVAs with Bonferroni corrections were used to compare the groups. Results: The anxiety group took longer to recover ($F=2.8$ $p=0.05$ $\eta2=.21$; M= 63.9 SD= 68.6 days) than both the vestibular group (M= 36.6 SD= 11.9) and the NVA group (M= 19.9 SD= 12.3). The anxiety group reported higher symptoms ($F=3.2$ $p=0.05$ $\eta2=0.18$) and lower processing speed scores ($F=5.6$ $p=0.009$ $\eta2=0.21$) than the other groups. The vestibular and anxiety groups scored worse on vestibular ($F=4.3$ $p=0.02$ $\eta2=0.23$) and ocular motor ($F=43.5$ $p=0.04$ $\eta2=0.20$) outcomes than the NVA group. Conclusions: Clinicians should employ multimodal comprehensive assessments to identify patients with clinical profiles such as anxiety that may be linked to worse clinical outcomes and longer recovery times.

Morning Poster Session
Location: Row A
Poster #4

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Amanda Gleixner	Postdoctoral	Donnelly	Neurobiology

Assessment of FG Nup function in C9ORF72 ALS

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease characterized by the degeneration of the motor neurons and interneurons in the brain and spinal cord. The majority of ALS occurs sporadically (sALS; 90%) with no family history. Genetic studies of patients with a family history of ALS familial ALS (fALS; 10%) have been studied to identify ALS-causing mutations within the human genome. Despite 31 known ALS-causing mutations a G4C2 repeat expansion in the first intron of the C9orf72 gene has been identified as the most common known genetic cause of both fALS and sALS comprising 30% and 8% of cases respectively (Renton et al. 2013; DeJesus-Hernandez et al. 2013). A molecular mechanism conferring neurotoxicity for the repeat expansion mutation is the generation of toxic G4C2 RNAs that sequester RNA binding proteins and the accumulation of dipeptide repeat proteins (DPRs) through the non-canonical repeat associated non-ATG translation (RANT) pathway (Donnelly et al 2013; Wen et al 2014; Ash et al 2013). Recent studies show that the expression of G4C2 or arginine-rich DPRs products of the C9orf72 repeat expansion dramatically alter the nucleocytoplasmic transport pathway (Zhang et al 2015; Freidbaum et al 2015; Jovičić A). This results in the nuclear retention of RNAs and the reduction in the rate of nuclear import of proteins that contain a classical nuclear localization sequence (NLS) and the cytoplasmic enrichment of TDP-43 (Freidbaum et al 2015; Zhang et al 2015). Moreover components of the nuclear pore complex (NPC) were identified as potent modifiers of both nuclear transport defects and neurodegeneration in C9orf72 ALS Drosophila models (Freidbaum et al 2015; Boeynaems et al 2016). The NPC functions to regulate passive transport of molecules >40kDa across the nuclear membrane. It is comprised of thirty different nucleoporins and approximately half of the nucleoporins contain intrinsically disordered phenylalanine-glycine repeat domains (FG domains). FG Nups comprise the selective barrier of the NPC and their dysfunction alters the compartmentalization of nuclear and cytoplasmic proteins. Loss of some FG nucleoporins (FG nups) have been shown to modulate degeneration in C9ORF72 ALS Drosophila models. In this work we begin to address the role of FG Nups in C9orf72 ALS pathobiology. Here we employed a genetic screen in RNA and DPR Drosophila models of C9orf72 ALS and iPSC motor neurons to determine FG Nups important for C9orf72 mediated neurodegeneration. Next we assessed how C9orf72 RNA and/or DPR products alter FG Nup biology including stability and post-translational status. Finally we determine if modulating FG Nup function and contributes to or rescues nucleocytoplasmic trafficking deficits in C9ORF72 ALS.

Afternoon Poster Session
Location: Row B
Poster #25

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Asiyeh Golabchi	Postdoctoral	Cui	Bioengineering department University of Pittsburgh

Long term performance of PEDOT/MWCNT/Dexamethasone coated electrodes implanted in visual cortex of rats

In chronic neural recording studies the temporal degradation in signal quality such as single-unit yield and signal-to-noise ratio due to electrode material failure and development of glial scar and neuronal death has been reported. These limitations can be addressed by using organic electrode coatings which provide a combination of recording and stimulation advantages including lowered impedance and increased charge transfer and ability to incorporate and release anti-inflammatory and neuroprotective drugs. Multi-walled carbon nanotubes (MWCNTs) loaded with dexamethasone can be incorporated into poly (3 4-ethylendioxythiophene) (PEDOT) as electrode coatings. Previously we have reported that dexamethasone-loaded PEDOT/MWCNT-coated microelectrodes showed lowered impedance and reduced inflammation after 14 days of implantation and stimulation in rat dorsal root ganglion compared to uncoated electrodes. Here we further evaluate the electrode/tissue interface and recording performance during prolonged implantation period (>12 months). The coated electrodes performed very well in recording visually evoked neural response from rat visual cortex even at the chronic time points showing great promise in advancing the quality and stability of chronic neural recording.

Morning Poster Session
Location: Row E
Poster #60

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Felipe Gomes	Postdoctoral	Grace	Neuroscience

Prefrontal cortex dysfunction increases susceptibility to schizophrenia-like changes induced by adolescent stress exposure

Adolescence is a developmental period of complex neurobiological changes and heightened vulnerability to psychiatric disorders. In particular evidence suggests that stress during adolescence is an important risk factor in the etiology of schizophrenia a developmental disorder that typically manifests in late adolescence or early adulthood. Indeed the emergence of psychosis is often associated with stressful life events and adolescents that are at high risk for schizophrenia experience abnormally high reactivity to stress. A dysfunction of the medial prefrontal cortex (mPFC) is proposed to interfere with stress control increasing the susceptibility to stress and consequently contributing to the emergence of psychiatric disorders including schizophrenia. Thus we evaluated the impact of single and combined stressful events during adolescence on schizophrenia-like signs in rats as adults and whether disruption of prelimbic (pl) PFC during adolescence affects stress-induced pathology that emerges in adulthood. Adolescent male rats were submitted to different stressful events [restraint stress (RS; 1 h session at postnatal day (PD) 31 PD32 and PD40); footshock (FS; 25 footshocks of 1.0 mA/2s/session daily through PD31-40); or a combination of FS and RS]. At adulthood animals were tested for anxiety responses (elevated plus-maze EPM) cognitive function (novel-object recognition test NOR) and locomotor response to amphetamine. One week after the behavioral experiments the activity of VTA DA neurons was evaluated using in vivo electrophysiology. Three parameters were measured: population activity ie the number of spontaneously active DA neurons per electrode track; average firing rate; and the percentage of action potentials occurring in bursts. We also evaluated whether the exposure to the combination of FS and RS in adulthood produced behavioral and electrophysiological changes similar to the adolescent stressors. In another experiment we sought to determine if a lesion within the plPFC would increase the vulnerability to FS exposure during adolescence in the DA system activity in rats as adults. The plPFC lesion was induced by infusing ibotenic acid bilaterally into the plPFC in rats at PD25. Six days after surgery rats were submitted to FS (daily through PD31-40). At adulthood they were tested in the EPM NOR test locomotor response to amphetamine and activity patterns of VTA DA neurons. All stressors induced anxiety-like responses in the EPM. FS and FS+RS also disrupted cognitive function as assessed by the NOR test. Additionally only animals exposed to the combination of FS+RS showed a dopaminergic hyper-responsivity in terms of amphetamine hyperlocomotion and increased VTA DA population activity resembling that observed in animal models of schizophrenia. Interestingly the increased number of spontaneously active DA neurons was confined exclusively to the lateral VTA which project to associative striatal regions analogous to those found to be hyper-responsive in schizophrenia patients. In contrast no change was observed when rats were exposed to the combination of FS+RS during adulthood underscoring that adolescence is a developmental period of particular susceptibility. Unlike intact rats animals with a plPFC lesion exposed only to the FS during adolescence showed DA hyper-responsivity. However plPFC lesioned animals exposed to FS displayed a more widespread increase in DA neuron activity with significant differences in both medial and lateral VTA regions. Given that the medial and central parts of the VTA send projections to the mPFC and amygdala and these projections play a role in emotional

states an increased DA activity in these VTA subregions may reflect a mechanism related to a disruption of the plPFC control of amygdala reactivity to stress. Our results are in agreement with previous studies showing long-lasting changes induced by stressful life events during adolescence. The impact on DA system activity however seems to depend on higher-level multiple stressors. Furthermore a failure of the plPFC to regulate the impact of stress which may be present in at-risk individuals increases the vulnerability to stress consequences. Thus predisposition to stress hyper-responsivity or exposure to substantial stressors during adolescence can initiate a cascade of events that result in a schizophrenia-like profile in adults. This data can provide information with respect to identifying markers for schizophrenia vulnerability early in life and by mitigating the impact of stressors prevent the transition to psychosis in susceptible individuals. Financial Support: NIH MH57440.

Morning Poster Session
Location: Row E
Poster #57

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Melanie Grubisha	Postdoctoral	Sweet	Psychiatry

A Schizophrenia-Associated Missense Mutation in KAL9 Influences Dendritic Morphology Pathways in a Mouse Model

Background: Kalirin (Kal) is a Rho GEF that is highly involved in regulation of the cytoskeleton within dendrites a pathway that is the site of convergence of multiple genetic risk factors in schizophrenia. There are several isoforms of Kal that arise from differential splicing of its 66 exons. A missense mutation located within a region shared by the two longer Kal9 and Kal12 isoforms (P2255T PTKAL9/12) has been associated with schizophrenia. When this mutation is overexpressed on the Kal9 background in vitro it results in increased activation of RhoA and reduced branching of basilar dendrites. We sought to determine the biological effects of this mutation when expressed at the endogenous locus in a mouse model. Methods: Using CRISPR/Cas9 genome editing we introduced the PTKAL9/12 mutation at the endogenous gene locus in C57/BL6 mice. Absence of off-target effects as well as confirmatory sequence analysis was done with both PCR and Sanger sequencing. Cortical tissue homogenates were prepared from 4 wildtype and 4 homozygous PTKAL9/12 mutant mice. They were subject to either RNA extraction /qPCR protein isolation/ western blotting or trypsin digestion. The resulting peptides from digestion were enriched for phospho-peptides and analyzed by differential mass spectrometry. Peptide intensities were first calculated in Chorus and MaxQuant select phospho-peptides were then manually evaluated in Skyline. Ingenuity Pathway Analysis (IPA) was used to perform functional enrichment of cellular processes most affected by changes in peptide phosphorylation in PTKAL9/12 mice. Results: A homozygous male mouse free of any off-target effects was successfully generated via CRISPR/Cas9. Selective breeding produced multiple generations of mice with the PTKAL9/12 mutation. Transcript and protein levels of Kal isoforms in PTKAL9/12 cortical homogenate did not differ from WT. Mass spectrometry analysis of cortical homogenate phospho-peptide enrichments observed >4000 phospho-peptides. Of these 589 were confidently quantified in all 8 mice. Phospho-peptides with evidence of altered levels in PTKAL9/12 mice were enriched for genes affecting neuronal morphology and microtubule assembly. MECP2 a gene known to be involved in intellectual disability and correlated with dendritic tree and spine deficits was among the most significant phospho-peptides altered in PTKAL9/12 homogenates. Conclusions: We have successfully created a mouse model of a rare schizophrenia-associated point mutation within KAL9/12. Confirming our in vitro observations of functional effects of this mutation we have identified perturbed phosphorylation of proteins involved in neuronal morphology and microtubule dynamics pathways known to be affected by kalirin. Additional analyses of pyramidal neuron morphology and electrophysiology are ongoing and will be presented. This model will facilitate developmental studies of the downstream signaling alterations due to PTKAL9/12. A better understanding of these changes in signaling will provide insight into upstream causes of the impaired dendritic morphology that has been observed in schizophrenia and ultimately how this alters neuronal function.

Afternoon Poster Session
Location: Row C
Poster #39

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Junichi Hachisuka	Postdoctoral		Neurobiology

Neural circuit for inhibition of itch by scratching

Counter stimuli such as scratching and cooling are known to reduce itch. However, the neural circuit mechanisms underlying this phenomenon remain unclear. To address this question, we developed a novel semi-intact preparation that allows us, for the first time, to record from lamina I spinal output neurons while controlling somatosensory input though natural stimulation of the skin and manipulating the activity of spinal interneurons though optogenetic approaches. We identify spinal projection neurons that are tuned for itch, and show that scratching the receptive field of these cells reduces itch-related responses. Moreover, we reveal that nNOS inhibitory interneurons provide strong feed forward inhibition onto these spinal projection neurons. Thus, nNOS inhibitory interneurons provide a feed forward mechanism through which counter stimuli inhibit itch.

Morning Poster Session
Location: Row D
Poster #44

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Jamie Hanson	Faculty	Hanson	Psychology & LRDC

The experience of childhood trauma and recent stress interact to influence functional connectivity of the ventral striatum and medial prefrontal cortex associated with depression

The experience of childhood maltreatment is a significant risk factor for the development of depression. This risk is particularly heightened after exposure to additional more contemporaneous stress. While behavioral evidence exists for such “stress sensitization ” little is known about biological correlates of this putative process. Identifying such correlates may not only substantiate the “stress sensitization” model but also provide biomarkers of risk for later depression. Suggestive clues have emerged from targeted neurobiological investigations that experiences of early life stress such as childhood maltreatment may influence the structure and function of a corticostriatal circuit supporting motivation and action. Moreover dysfunction of this circuit has been implicated in the pathophysiology of depression. The limited available research though informative has not investigated whether differences in reward-related corticostriatal circuit function may be associated with “stress sensitization ” or if any circuit-level effects explain subsequent risk for depression. To begin to fill in these important gaps we turned to the Duke Neurogenetics Study (DNS) an ongoing project assessing a wide range of behavioral and biological traits in a large cohort of non-patient 18-22 year-old university students. Investigating reward-related functional connectivity within the corticostriatal circuit of 926 participants we found evidence for increased connectivity between the ventral striatum and the medial prefrontal cortex (Interaction β=0.199 p<.005) in individuals exposed to greater levels of childhood maltreatment who also experienced greater levels of recent life stress. We also found that this aberrant pattern of connectivity was associated with elevated symptoms of depression specifically reduced positive affect (β=0.089 p<.005). These findings suggest a novel neurobiological mechanism linking cumulative stress exposure with later depressive symptoms and provide support to the “stress sensitization” model of depression.

Afternoon Poster Session
Location: Row B
Poster #28

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Angelica Herrera	Graduate	Collinger	Bioengineering

Neural tuning properties of the primary motor and somatosensory cortices during cursor and hand tasks

Research has shown that brain-computer interfaces (BCIs) can restore lost limb function by allowing control of a prosthetic arm via signals from motor cortex (M1). However we recently reported that in addition to M1 neurons in somatosensory cortex (S1) were also tuned to cursor and hand movements. M1 showed stronger tuning than S1 in general but S1 was more strongly tuned to hand rather than cursor movements. Here we examined the temporal aspects in tuning hypothesizing that M1 would lead kinematics while S1 would lag kinematics. Two 88-channel and two 32-channel intracortical microelectrode arrays were implanted in a human subject with tetraplegia in M1 and S1 respectively. Neural data was collected during 5 test sessions while the subject performed a 2D cursor control and a 2D robotic hand-shaping task. Data was collected under 2 conditions: (1) Observation: the subject attempted to perform the tasks while the kinematics were controlled by the computer; (2) Constrained BCI: the subject's decoded neural activity (from either M1 or S1) controlled the computer cursor or robotic hand while the computer attenuated command signals orthogonal to the target direction. Neural decoding was performed using indirect optimal linear estimation based on an assumed linear encoding model where firing rates were considered to be a linear combination of the 2D endpoint velocities for each task. We examined the fit to the encoding model for each unit under multiple lag conditions. Examining the distribution of the encoding model fits for different lags neurons in M1 and S1 qualitatively appeared to be most strongly tuned to kinematics when no lag shift was implemented. However in the observed data for both the cursor and hand tasks no significant difference was found among the arrays for different shifts. For the constrained BCI dataset in the cursor and hand tasks both recording arrays were found to have fits for 0 and 50ms lag that were significantly different than the others tested and for both sensory arrays a zero lag yielded the best fit rejecting the null hypothesis. The sensory arrays were seen to have a slightly better fit than the recording arrays in the hand task; however the differences in their fits were not statistically significant. In an intact system M1 activity occurs prior to the executed movements while sensory activity lags behind resulting from inputs from peripheral afferents. Here we saw that M1 and S1 activity was predicted by movement; however this relationship was strongest with zero lag between neural activity and kinematics. Perhaps unexpected this result may be because the participant was attempting movement rather than overtly moving.

Afternoon Poster Session
Location: Row B
Poster #18

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Michelle Heusser	Graduate	Gandhi	Bioengineering

Single-trial classification of saccade metrics using superior colliculus population activity

Research in brain-computer interface (BCI) technology has gained popularity in recent years due to both its clinical applications (e.g. neuroprostheses) and scientific relevance. While the majority of current research involves skeletomotor (limb movement) BCI some groups are also venturing into the realm of oculomotor (eye movement) BCI. The superior colliculus (SC) is a deep brain structure crucial for converting sensory input into a motor command for generation of a fast eye movement. We have chosen the SC as a target structure for BCI because it is a hub of sensorimotor integration and is close to the end effectors (i.e. eye muscles) in the oculomotor pathway. The first step in the development of an oculomotor BCI is accurately predicting the intended eye movement and consequently eye end position after a saccade. Therefore we aimed to assess the feasibility of using SC neural activity for the classification of saccade metrics (direction and amplitude of eye movement). In this study we classified intended saccade endpoint during the motor epoch of a delayed saccade task using SC neural population activity. One rhesus monkey (macaca mulatta) was trained to perform a delayed saccade task to peripheral visual targets that varied in either amplitude or direction on a given recording session. A multicontact laminar electrode was used to record activity of many neurons within the SC. We trained a naïve Bayes classifier on population activity from a randomly selected subset of the trials and calculated the accuracy of classified target position for the remaining individual test trials. The mean classification accuracy was highest for targets within the population's response field and was above chance level for almost all targets and time bins of classification. Trends in classifier performance were consistent across recording sessions and did not largely vary with chosen classification bin width. Overall these results demonstrate that offline decoding of intended saccade metrics is feasible on a single-trial basis. In the future we plan to implement this technique online—decoding saccade metrics in real time and incorporating saccade dynamics into the decoding algorithm.

Morning Poster Session
Location: Row E
Poster #58

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Gil Hoftman	Postdoctoral	Lewis	Psychiatry

Altered Gradients of Glutamate and GABA Transcripts in a Distributed Cortical Circuit in Schizophrenia

Background: Visuospatial working memory (vsWM) which is impaired in schizophrenia requires information transfer from primary (V1) and association (V2) visual cortices in the occipital lobe to posterior parietal (PPC) and dorsolateral prefrontal (DLPFC) cortices via excitatory pyramidal neurons in layer 3. In primate cortex the layer 3 excitatory glutamate-containing neurons in V1 have a lower density of dendritic spines less complex dendritic arborization and smaller soma sizes compared with the homologous layer 3 pyramidal neurons in the DLPFC. The activity of layer 3 excitatory neurons is shaped by local inhibitory neurons. The relative number of these GABA-containing neurons and the expression of GABAA receptor α1 subunit mRNA are higher in V1 than DLPFC. These findings suggest that caudal and rostral cortical regions may differ in the relative amounts of glutamate and GABA inputs. Interestingly recent transcriptome studies reported the presence of rostro-caudal gradients of mRNA expression in the primate neocortex. Whether these gradients are present in cortical layer 3 for glutamate and GABA system transcripts in postmortem human tissue and if they are preserved in schizophrenia have not been studied. Therefore we sought to answer the following questions: 1) Are gradients in expression present across regions of the vsWM network? 2) Are these gradients altered in schizophrenia? 3) Is any disease effect conserved across regions? Methods: Using laser microdissection tissue samples of layer 3 were obtained from V1 V2 PPC and DLPFC from 20 matched pairs of schizophrenia and unaffected comparison subjects. Quantitative PCR was used to measure mRNA levels of functionally analogous transcripts of the following glutamate and GABA system: glutamate (GLS1) and GABA (GAD67) synthesizing enzymes; vesicular glutamate (vGLUT1) and GABA (vGAT) transporters; synaptic glutamate (EAAT2) and GABA (GAT1) transporters; NMDA receptor subunit (GRIN1); AMPA receptor subunit (GRIA2); and GABAA receptor subunit (GABRG2) in all samples. Results: To assess the presence of mRNA expression gradients we measured the levels of these glutamate and GABA transcripts in unaffected comparison subjects. Transcript levels for the glutamate markers EAAT2 (F3 56=19.2 p<0.001) vGLUT1 (F3 56=57.1 p<0.001) and GRIA2 (F3 56=59.3 p<0.001) showed a caudal-to-rostral gradient with lowest expression in visual cortices and highest in DLPFC. In contrast the GABA transcripts GAD67 (F3 56=4.5 p<0.007) vGAT (F3 56=11.8 p<0.001) and GABRG2 (F3 56=34.1 p<0.001) showed the opposite gradient with highest expression in visual cortices and lowest in DLPFC. To determine if these regional gradients were altered in schizophrenia we generated normalized composite measures for the five glutamate and four GABA transcripts studied. These measures confirmed the presence of opposite regional gradients for glutamate (F3 114=14.5 p<0.001) and GABA (F3 114=5.4 p=0.002) system transcripts in unaffected comparison subjects. In contrast in the subjects with schizophrenia the regional gradient for glutamate transcripts was diminished (F3 114=1.3 p=0.28) whereas the regional gradient for GABA transcripts was enhanced (F3 114=15.8 p<0.001). That is in the schizophrenia subjects both the glutamate and GABA system transcript levels were higher in V1 and lower in the DLPFC relative to the unaffected comparison subjects. Since the regional gradients of glutamate and GABA system transcripts were differentially altered in schizophrenia we examined whether there was a disease effect on transcript levels that was conserved across regions. Levels of vGLUT1 mRNA were significantly lower in schizophrenia in all

regions studied (V1: -18% p<0.01; V2: -14% p<0.05; PPC: -14% p<0.05; DLPFC: -22% p<0.01). Levels of EAAT2 mRNA were significantly higher in visual cortices (V1: +286% p<0.001; V2: +258% p<0.001) but not in DLPFC or PPC. All other glutamate and GABA system transcripts studied did not show an effect of illness that was conserved across regions. We also examined whether the difference between glutamate and GABA composite measures within a region was significantly different in schizophrenia subjects and found no significant effect of diagnosis on transcript expression (F1 114=0.3 p=0.56). Conclusions: In layer 3 glutamate and GABA system transcripts exhibit opposite expression gradients across a vsWM cortical network suggesting that molecular regulation of excitatory-inhibitory balance differs across cortical regions. Altered expression of some of these transcripts in schizophrenia may disrupt normal regional patterns of excitatory-inhibitory balance (i.e. markers of excitatory-inhibitory balance are downregulated in the DLPFC and upregulated in V1) contributing to the neural substrate for vsWM deficits in the illness.

Afternoon Poster Session
Location: Row E
Poster #57

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Chengcheng Huang	Postdoctoral	Doiron	Mathematics

Modeling within and across area neuronal variability in the visual system

Neural variability has important consequences on neural coding. Shared variability among neurons (noise correlation) has been commonly observed in multiple cortical areas (Cohen and Kohn 2011). Moreover noise correlation can be modulated by cognitive factors such as attention (Cohen and Maunsell 2009). Recently new data suggests that attention not only decreases correlations within a cortical area but also increases correlations between cortical areas V1 and MT (Ruff and Cohen 2016). The observed opposite trends of change in correlations between-areas and within-area impose further constraints on circuit mechanisms for the generation and propagation of noise correlations. We developed a spiking neuron network with spatiotemporal dynamics which exhibits macroscopic chaos in population rates. Such chaotic dynamics result in positive and low-dimensional noise correlation in the network. Attentional effects can be modeled as depolarizing the inhibitory population which reduces the internally generated variability and allows the network to better track input signal.

Morning Poster Session
Location: Row A
Poster #1

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Yunhong Huang	Graduate	Thathiah	Department of Neurobiology

The phosphorylation barcode of GPR3 modulates Aβ generation

Alzheimer's disease (AD) is the most common type of dementia and is characterized by the insidious degeneration of brain networks involved in memory and cognition. Accumulation and aggregation of the amyloid β (Aβ) peptide in the brain are pathological hallmarks of AD. Sequential cleavage of the amyloid precursor protein (APP) by the β- and γ-secretases generates Aβ. Given that both secretases cleave numerous substrates selective modulation of APP cleavage is a major concern with targeting these two secretases for AD therapeutic development. The orphan G protein-coupled receptor 3 (GPR3) selectively regulates activity of the γ-secretase in the absence of an effect on Notch proteolysis one of the major γ-secretase substrates. Genetic deletion of Gpr3 reduces amyloid pathology and alleviates the cognitive deficits in various AD transgenic models suggesting that GPR3 is a relevant therapeutic target for AD. Mechanistic studies indicate that an interaction between GPR3 and the scaffolding protein β-arrestin 2 is involved in the modulation of Aβ generation. β-arrestin 2 belongs to a small family of multifunctional GPCR regulatory proteins which bind to activated GPCRs and play an almost universal role in facilitating traditional GPCR desensitization; however these proteins are also capable of initiating distinct signals in their own right conveying receptor subtype-specific signaling events. Here we demonstrate that the phosphorylation status of GPR3 regulates β-arrestin 2 recruitment and Aβ generation. Mutagenesis of specific serine residues in the C-terminus of GPR3 differentially regulate the interaction between GPR3 and β-arrestin 2 and subsequent Aβ generation. Genetic deletion of individual G protein–coupled receptor kinases (GRKs) which regulate GPCR phosphorylation leads to a reduction in Aβ generation suggesting that GRK-dependent phosphorylation of GPR3 is involved in the modulation of Aβ generation. Collectively these studies demonstrate that differential phosphorylation of specific serine residues in the C-terminus of GPR3 by GRKs are important for β-arrestin 2 recruitment and Aβ generation.

Morning Poster Session
Location: Row D
Poster #53

Presenting Author:	Author Type:	Mentor/Lab:	Department:
James Hyde	Postdoctoral	Ahmari	Psychiatry

In vivo calcium imaging of pharmacologically induced perseverative grooming in awake behaving mice

Title: In vivo calcium imaging of pharmacologically induced perseverative grooming in awake behaving mice Author(s): Dr. James Hyde Dr. Susanne Ahmari Obsessive compulsive disorder (OCD) is characterized by intrusive obsessive thoughts and abnormal repetitive behaviors. Studies of several independent mouse models of OCD-like behavior suggest that perseverative grooming in mice is related to the compulsive behaviors seen in OCD. Understanding the mechanisms leading to the development of abnormal grooming is therefore relevant to OCD pathophysiology. However the changes in cellular activity that are correlated with the development of perseverative grooming are unknown. Using miniaturized head-mounted microscopes and calcium imaging we therefore examined changes in cellular activity in the ventromedial striatum (VMS) during pharmacologically- induced perseverative grooming behavior. Drd1a-tdTomato mice were injected with the genetically encoded calcium indicator AAV9.hsyn.GCaMP6m and implanted with a microendoscope (6.1mm x 0.5mm GRIN lens) in VMS. 4 weeks after virus injection mice were fitted with a microscope baseplate. After recovery behavioral experiments were performed. Using a cross-over within subjects experimental design mice were treated with either the D1 agonist SKF38393 to induce perseverative grooming or vehicle. Both behavior and calcium signaling was monitored continuously for 10 minutes prior to injection and 30 minutes post injection. Calcium transient data was extracted from processed videos to analyze event frequency and time-locked activity. As expected grooming activity increased after SKF injection in VMS implanted mice. In vivo microendoscopy demonstrated that under SKF exposure the average calcium event rates decreased during grooming while event rates increased when the mouse was not grooming. Event rates during saline control experiments showed no differences between grooming and non-grooming time periods. These results suggest selective changes in firing patterns relating to perseverative grooming. Ongoing analysis is delineating the precise relationship between changes in network level activity and bouts of perseverative grooming.

Morning Poster Session
Location: Row B
Poster #16

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Vladimir Ilin	Postdoctoral	Burton	Neuroglogy

Evaluation of presynaptic dopaminergic function in the intact CNS of a genetic model vertebrate

Evaluation of presynaptic dopaminergic function in the intact CNS of a genetic model vertebrate Vladimir Ilin MD Edward A. Burton MD DPhil FRCP Pittsburgh Institute for Neurodegenerative Diseases and Deaprtment of Neurology University of Pittsburgh School of Medicine Parkinson's disease (PD) is characterized by loss of substantia nigra dopaminergic neurons and formation of Lewy bodies (cytoplasmic inclusions containing aggregates of α-synuclein) in surviving cells. To determine the role of α-synuclein in PD pathogenesis we have generated zebrafish over-expressing human α-synuclein in their dopaminergic neurons or lacking endogenous zebrafish synucleins. In order to understand how these experimental manipulations affect the synaptic physiology of dopaminergic neurons prior to degeneration of terminals or cells we have developed an experimental approach to record dopaminergic synaptic potentials in live intact zebrafish larvae. The zebrafish homologue of the mammalian substantia nigra is found in the ventral diencephalon; dopaminergic neurons in this location project both to the forebrain and to the spinal cord. There are direct synaptic connections between the dopaminergic diencephalospinal tract and spinal cord motor neurons which are relatively accessible for intracellular electrophysiological recordings from intact animals. We have obtained stable whole-cell patch recordings from zebrafish spinal cord motor neurons and identified glutamatergic GABAergic and dopaminergic synaptic inputs. By application of pharmacological agents we have isolated and recorded spontaneous dopaminergic postsynaptic potentials. This approach will allow us to analyze how the function of dopaminergic terminals is altered by accumulation or loss of synucleins or by other genetic or environmental factors relevant to PD. Importantly we predict that changes in synaptic physiology will be informative for understanding upstream events in pathogenesis and for testing therapeutic interventions designed to target proximate mechanisms.

Afternoon Poster Session
Location: Row A
Poster #12

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Yoh Inoue	Graduate	Schwartz	Department of Neurobiology

Effects of speed tuning on trajectory decoding

Movement speed acts as a gain factor on the cosine tuning of motor cortical firing rate to movement direction. Failure to account for this effect can lead to decoding problems when using firing rates from a population of cells to predict movement trajectory. This may be especially problematic when the sample of recorded cells has preferred directions that are not distributed uniformly. To better characterize this problem we used a set of coefficients to fit the following equation 1: FR=b0+bxVx+byVy+bsS; where Fr is firing rate Vx and Vy are the x and y components of arm velocity and S is the speed of the arm. Empirical data from a 2D center-out task were selected from a prototype neuron and used to fit the coefficients of the equation. A set of firing rates were then calculated for a population of simulated neurons by choosing bx and by to produce different preferred directions. The average speed profile from the empirical data was used in the simulations. \tDecoding was performed using the population vector algorithm. Each unit's contribution to the population vector was calculated using the simulated firing rates from Eq. 1 in the conventional cosine tuning model: FR=br0+brxDx+bryDy where Dx and Dy are the x and y components of target direction. br0 brx and bry were found through regression. Each unit's contribution was a vector in the direction brx bry with a magnitude M= (FR-br0)/mag where mag is the magnitude of the vector [brx bry]. \tTwo simulated populations were created. The first was constructed by choosing bx and by to be uniformly distributed. The second population was non-uniform bx and by were chosen only from one half of the unit circle. Population vectors were constructed from each population to each target using the empirical speed profiles and Eq. 1 for firing rates and the conventional cosine model for each contribution. We measured the angle error time length and trajectory length and population vector magnitude for the 2 populations. The trajectories for all targets were fairly straight in uniform condition. Across targets duration trajectory length and angle error were not significantly different. The population vector length was highly correlated to speed. In contrast for the non-uniform condition the initial portions of the trajectories of all targets were skewed by the over-represented preferred directions in the sample. Compared to the uniform condition population vector magnitudes were less related to speed. \tA failure to account for speed tuning can lead to significant decoding distortion of both speed and direction when the sampled population has a non-uniform directional distribution.

Morning Poster Session
Location: Row B
Poster #23

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Pablo Iturralde	Graduate	Torres-Oviedo	Bioengineering

Intertrial variability of EMG reveals lack of bilateral or inter-joint muscle synergies for walking in unimpaired and post-stroke patients

Activation of 'muscle synergies' has been proposed to underlie neural control of movement and cortical damage is thought to change the structure of these neural commands (Cheung et al. 2014). To test these hypotheses we identified muscle synergies in unimpaired and post-stroke subjects that were independent from task requirements. We specifically recorded 30 bilateral muscles in 16 chronic post-stroke subjects and 16 age and sex matched controls under two walking conditions imposing distinct movement demands: normal walking vs. split-belt walking in which legs move at different speeds. We identified muscle synergies by computing covariance matrices indicating correlated activity across muscles. Importantly we dissociated covariations in EMG signals due to task requirements and those due to common neural drive by analyzing 1) rectified and filtered EMG data ('full dataset') and 2) fluctuations in EMG recordings from the mean activity across strides ('intertrial dataset'). We found anatomical multijoint and bilateral muscle co-activation in the full dataset analysis but only anatomical in the intertrial dataset analysis. This was indicated by significant correlations across muscles within the same anatomical groups (22/22 signif. correlations median r2=.73) across multiple-joints (119/188 r2=.30) and legs (149/225 r2=.29) identified in the full dataset. However only anatomical correlations were observed in the intertrial dataset (22/22 r2=.36) while the others became much weaker (r2<=.08). We also found that muscle co-activation from the full dataset change across walking conditions to match changes in task constraints (interlimb median r2 change =.14) whereas the intertrial muscle synergies were maintained the same. Lastly anatomical muscle co-activations identified in the intertrial dataset of patients were the same (22/22 r2=.40) as controls and surprisingly symmetric across legs. Conversely full dataset analysis revealed that stroke patients have less multijoint (94/188 r2=.38) and bilateral (113/225 r2=.30) muscle co-activations than controls suggesting a deficit in patients task performance or reduced task demands (since all patients walked at slower than controls). Taken together these results suggest that only anatomical groups might receive unified neural drive but correlated activity in muscles across joints and legs (multijoint and bilateral muscle synergies) reflects task demands rather than shared neural control signals. As such differences in multijoint and bilateral muscle synergies between patients and controls may represent patients' deficits in task performance or reduced task demands and not clear differences in neural commands.

Morning Poster Session
Location: Row F
Poster #70

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Tija Jacob	Postdoctoral	Jacob	Pharmacology and Chemical Biology (& CNUP)

Balancing neurotransmission: rapid agonist induced GABAergic synaptic and functional plasticity

γ-aminobutyric acid (GABA) begins as the key excitatory neurotransmitter in newly forming circuits with chloride efflux from GABAA receptors (GABAARs) producing membrane depolarization which promotes calcium entry dendritic outgrowth and synaptogenesis. As development proceeds GABAergic signaling switches to inhibitory hyperpolarizing neurotransmission. Despite the evidence of impaired GABAergic neurotransmission in neurodevelopment disorders little is understood on how agonist dependent GABAAR activation controls the formation and plasticity of GABAergic synapses. We have identified a weakly depolarizing and inhibitory GABAAR response in cortical neurons with well-established GABAergic synapses that occurs during the transition period from GABAAR depolarizing excitation to hyperpolarizing inhibitory activity. We show here that GABAAR agonist treatment at this stage mediates structural changes that diminish GABAergic synapse strength through postsynaptic and presynaptic plasticity via intracellular Ca2+ stores ERK and BDNF/TrkB signaling. We show that GABAAR stimulation results in delayed activation of the ERK pathway a cellular response distinct from early excitatory depolarizing GABAAR activity. Application of the GABAAR agonist muscimol decreases synaptic localization of surface γ2 GABAARs and gephyrin postsynaptic scaffold while β2/3 non-γ2 GABAARs accumulate in the synapse. Concurrent with this structural plasticity muscimol treatment decreases synaptic currents while enhancing γ2 containing GABAAR tonic currents in an ERK dependent manner. We further demonstrate that GABAAR activation leads to a decrease in presynaptic GAD-65 levels via BDNF/TrkB signaling. Together these data reveal a novel mechanism for agonist induced GABAergic synapse plasticity that can occur on the timescale of minutes contributing to rapid modification of synaptic and circuit function.

Afternoon Poster Session
Location: Row C
Poster #29

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Uday Jagadisan	Postdoctoral	Gandhi	Bioengineering

Analysis of spiking activity and local field potentials reveals patterned information flow within the superior colliculus

The superior colliculus (SC) is a major hub of sensorimotor integration in the gaze control network and plays a pivotal role in the generation of saccadic eye movements. The sensory-to-motor transformation is enabled by the intermediate and deep (collectively deeper) layers of the SC. However it is unknown whether neurons in these layers constitute a homogeneous network performing similar computations or if there exists finer spatiotemporal patterning therein. To study this in greater detail we combined linear microelectrode array recordings with multi-channel signal analyses. Linear arrays are especially amenable to recording from a column of neurons to access computations evolving in parallel within the column. We recorded from the SC in two monkeys (Macaca mulatta) performing a delayed saccade task. The electrode contacts (n=16) spanned the dorso-ventral extent of the SC allowing for the simultaneous recording of spiking activity and local field potentials (LFPs) within the deeper layers. We performed coherence and Granger causality analyses to assess the flow of information within SC. We found the following: (1) Following target onset spike-spike coherence increased between most channel pairs but only the dorsally located channels exerted a Granger causal influence on the spiking of other channels suggesting a unidirectional flow of information during sensory processing. In contrast during the saccade the middle channels exerted a causal influence on channels located both dorsally and ventrally indicating bidirectional information flow during peri-saccadic processing. (2) Spike-LFP coherence revealed stronger coherence between spiking activity recorded from dorsal contacts and LFPs recorded more ventrally both following stimulus onset and following the saccade. Intriguingly there was no significant increase in coherence in the lead up to the saccade. (3) For both epochs the spike-LFP coherence profile was biphasic with an early narrow transient and a late broader peak. Granger analyses suggested that both early coherence peaks could be the result of causal dorsal-to-ventral influence of spikes on LFP whereas the late peaks could be the result of the causal influence of LFP on spikes. (4) In all cases coherence and causality decreased as a function of distance between the pair of contacts. Moreover the strongest influences in all cases were in the sub-beta band (<30 Hz) with a slightly weaker effect in the low-gamma range (30-50 Hz) between dorsal channels. These results point to distinct communication channels for spikes and LFPs in the SC and provide evidence for multi-phase processing during sensorimotor integration.

Afternoon Poster Session
Location: Row E
Poster #60

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Maria Jalbrzikowski	Postdoctoral	Luna	Psychiatry

The development of white matter microstructure and intrinsic functional connectivity between the amygdala and ventromedial prefrontal cortex

Study: Connectivity between the amygdala and ventromedial prefrontal cortex (vmPFC) is compromised in multiple psychiatric disorders many of which emerge during adolescence. To identify what extent deviation of amygdala-vmPFC maturation contributes to the onset of psychiatric disorders it is essential to characterize amygdala-vmPFC connectivity changes during typical development. We examined 1) age-associated changes in structural and functional connectivity of amygdala and vmPFC sub-regions 2) how development of amygdala-vmPFC functional connectivity is related to development of white matter microstructure between the amygdala and vmPFC and 3) how amygdala-vmPFC maturation is related to anxiety and depression. Methods: An accelerated cohort longitudinal design (1-3 time points) was used to characterize developmental changes of amygdala-vmPFC connectivity using resting state fMRI and diffusion-weighted imaging (N=246 10-25 years). Anxiety/depression scores were calculated from responses on the Youth and Adult Self-Reports. Results: Functional connectivity between the centromedial amygdala and rostral anterior cingulate anterior vmPFC and subgenual cingulate significantly decreased from late childhood to early adulthood in both males and females. Importantly this finding was replicated in an independent cohort (10-22 years N=327). Similarly structural connectivity as measured by quantitative anisotropy (QA) significantly decreased in the same regions. Functional connectivity between the centromedial amygdala and rostral anterior cingulate predicted structural connectivity in these same regions during early adulthood (ages 22-25). These results suggest that amygdala functional connectivity specific to vmPFC regions involved in the cognitive control of emotions show decreases that continue into adulthood when amygdala-vmPFC functional connectivity predicts structural connectivity. Finally a novel time-varying coefficient analysis showed that increased amygdala-vmPFC FC was associated with greater anxiety and depression symptoms during early adulthood while increased structural connectivity in amygdala-vmPFC white matter connectivity was associated with greater anxiety/depression during late childhood and early adolescence suggesting that we may be able to identify developmentally-sensitive biomarkers for those at risk for developing psychiatric disorders. Conclusion: Specific developmental periods of functional and structural connectivity of amygdala and prefrontal systems may contribute to the emergence of anxiety and depression symptoms and play a critical role in the emergence of psychiatric disorders in adolescence.

Morning Poster Session
Location: Row F
Poster #72

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Juliann Jaumotte	Faculty	Jaumotte	Neurology

Isolated housing decreases the immune response in sera and brain following exposure to a bacterial toxin in older rats.

As people age they often are more likely to become ill. Among the many factors that could explain their reduced health span is the increasing isolation commonly experienced by the elderly as well as other segments of our society. This in turn can be associated with an impaired immune system including a decline in B- and T-cell production which is reflected by changes in the expression of cytokines produced in response to exposure of viral or bacterial agents. In this experiment we examined the immune response elicited by exposure to lipopolysaccharide (LPS) an endotoxin produced by bacteria. We first examined a small dose-response curve for LPS (0-2 mg/kg i.p.) in 28-month-old male Fisher 344/Brown Norway hybrid rats (F344/BN) to determine the highest tolerable dose of a single intraperitoneal injection of LPS. We then used an intermediate dose from that analysis (empirically determined to be 1 mg/kg) and delivered it to male F344/BN rats housed housed in our facility for 8 months beginning at 19 months of age. The two groups studied were either singly housed in a standard shoebox cage (18 cm W x 38 cm D x 27 cm H; SE) or a relatively enriched environment consisting of a large cage (1 m W x 1m D x 0.6m H) containing 6 rats running wheels tunnels platforms and toys (EE). Seven days after the LPS injection all animals were euthanized and brain and serum collected. Using a Luminex multiplex assay kit we observed that several cytokines and chemokines were significantly altered in both sera and brain from isolated animals in comparison to those in enriched housing. The pattern of change indicated that in isolation led to a reduction in the immune response. Cytokines and chemokines that changed in response to isolation included G-CSF (sera) IL-1 alpha (sera and brain) IL-1-beta (sera and brain) IL-4 (sera and brain) IL-6 (sera) IL-10 (sera) IP-10 (sera) INF-gamma (sera and brain). These data suggest that older isolated animals have a less reactive immune response than their more enriched counterparts which could indicate a lowered ability to fight off infections or stave off neurological disease that have an immunological component including Alzheimer's and Parkinson's disease.

Morning Poster Session
Location: Row F
Poster #73

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Gabrielle Kaplan	Graduate	McClung	Psychiatry

CLOCK represses the expression of tyrosine hydroxylase via recruitment of the metabolic sensor SIRT1

Many studies strongly implicate alterations or disruptions to circadian rhythms as contributors to the pathophysiology of mood and addiction disorders. We have shown previously that Clock mutant mice (Clock□19) display a behavioral repertoire similar to human bipolar mania with a particular sensitivity to rewarding stimuli. Clock□19 displayed enhanced cocaine conditioned place preference (CPP) along with increased dopamine cell firing in the VTA. mRNA and protein levels of tyrosine hydroxylase (TH) the rate-limiting enzyme in dopamine synthesis was also increased in the VTA of Clock□19 mice suggesting TH is a direct target of CLOCK. We investigated how CLOCK represses TH expression in the VTA and whether these mechanisms are involved in the hyperhedonic phenotype. We focused on two particular proteins that dynamically interact with CLOCK across the light-dark cycle phosphoactive CRE-element binding protein (P-CREB) and the histone deacetylase sirtuin 1 (SIRT1) a sensor of intracellular changes in metabolism. CLOCK typically drives circadian rhythms in gene transcription. However we found that CLOCK is a transcriptional repressor of TH in the VTA through interactions with P-CREB and SIRT1 at particular diurnal phases. CLOCK and P-CREB bind the TH promoter in antiphase. SIRT1 interacts with CLOCK to inhibit CREB-mediated transcription of TH. P-CREB binding and TH expression were constitutively elevated in the VTA of Clock mutants while SIRT1 protein levels were significantly reduced. Both mCREB and SIRT1-OX in the VTA of Clock mutants reduced TH expression and attenuated cocaine CPP suggesting CREB-inactivation and restoring SIRT1 levels in mutant mice reversed the hyperhedonic phenotype. Excess NAD and NAM blocked the ability of CLOCK to suppress TH expression. These studies demonstrate a link between metabolic and circadian pathways and how disruption to these pathways are important for behavioral phenotypes relevant to addiction.

Afternoon Poster Session
Location: Row A
Poster #8

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Ahmed Kashkoush	Graduate	Fisher	Physical Medicine and Rehabilitation

A Prospective Study of Acute and Sub-Chronic Modulation of Phantom Limb Pain using Epidural Spinal Root Stimulation

Recent evidence suggests that phantom limb pain (PLP) is regulated by the lack of sensory feedback from the amputated limb and thus restoring non-painful phantom sensations may alleviate the condition. This study aims to use cervical spinal root stimulation to produce sensations localized to the amputated limb to modulate PLP and demonstrate a clinically significant reduction of PLP. Two subjects with transhumeral amputations were implanted with 3 spinal cord stimulator leads (Boston Scientific) in the epidural space targeting the C6-C8 spinal roots for a maximum length of 29 days. Stimulation amplitude (50-6000 μA) frequency (1-400 Hz) and pulse width (0.05-1 ms) were modulated across trials. Subjects reported the modality ('Mechanical' 'Tingle' 'Movement' 'Stimulation Pain' 'Naturalistic' 'Phantom Limb Pain') and magnitude (0-10 visual analog scale) of sensations after stimulation. Multivariate regression was used to assess the combined effects of stimulation parameters and sensation characteristics on PLP episode incidence (categorical 'yes' vs. 'no') and PLP episode intensity (continuous 0-10). Additionally the McGill Pain Questionnaire (MPQ) was administered at baseline on a weekly basis and one month following explantation to assess sub-chronic PLP modulation. A total of 1 276 trials were performed across both subjects of which 370 PLP episodes were reported (29.0%) at a mean intensity of 2.1 ± 0.2 (Table 1). Of 94 electrodes modulating stimulation was significantly associated with PLP frequency on 17 (18.1%) and PLP intensity on 6 (6.4%). Multivariate regression demonstrated stimulation amplitude to be an independent predictor of PLP intensity (p<0.01 regression coefficient [B]=0.19/mA) and pulse width of PLP frequency (p=0.03 B=0.93/ms). Both PLP frequency and intensity were positively associated with the intensity of non-PLP sensations (p<0.01) except for those of movement (p=0.162) and naturalistic (p=0.69) sensations. Both subjects experienced a clinically significant reduction (>5 points) in PLP from baseline throughout the study and at 1-month follow-up with 9 (26%) and 8-point (24%) reductions on the MPQ respectively (Figure 1). This study suggests that decreased stimulation amplitude and pulse width may reduce the intensity and likelihood of a PLP episode respectively given their positive associations with PLP. We further observed time-dependent PLP modulation such that restoring sensory feedback from the amputated limb is associated with increased PLP in the immediate post-stimulation phase but may also be coupled to a long-term reduction in PLP.

Morning Poster Session
Location: Row B
Poster #21

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Cynthia Kenmuir	Faculty	Kenmuir	Neurology

Acute Stroke Thrombectomy Outcomes for Patients Transferred Directly to the Angiosuite in an Effort to Reduce Delay to Reperfusion

Introduction: Time from symptom onset until reperfusion is correlated to outcome following acute stroke intervention. Ongoing efforts focus on streamlining the time needed to adequately assess a patient during an acute stroke in order to offer endovascular therapy as quickly as possible. Methods: A retrospective chart review was conducted to evaluate outcomes for acute stroke patients treated with endovascular therapy at the University of Pittsburgh Medical Center comparing patients who were taken directly from the helipad to the angiosuite versus those who received additional assessments in the emergency room prior to endovascular reperfusion. Results: Cases were reviewed from Jan 2013 to July 2015 in order to capture all cases who were brought directly to the angiosuite upon arrival. Of 379 endovascular stroke cases 32 (8.4%) were taken directly to the angiosuite – 30 (8%) had large vessel occlusions (LVO) – 19 MCA occlusions and 11 basilar occlusions. 8 patients received IV tPA. 9 patients had tandem cervical lesions that required intervention. Mean door to puncture time was 21.1 minutes. All 30 patients were successfully revascularized (TICI2b/3 reperfusion). There was a trend towards smaller final infarct volumes in patients taken directly to the angiosuite versus patients who underwent additional assessment prior to endovascular treatment (26.4 cc vs 34.0 cc). Mean length of stay was similar between the groups (5.4 days ICU 12.8 days total). MRS at discharge was improved in patients taken directly to the angiosuite (mean 2.9 versus 3.9) but MRS at 90 days was unchanged (3.4). At 90 days 12 patients (40%) had a good outcome (MRS0-2) though 8 patients were deceased (26.7%). Conclusion: Taking patients directly to the angiosuite for endovascular reperfusion during an acute stroke can reduce the delay from symptom onset to reperfusion. In 30 patients with LVO there was a trend towards smaller infarct volumes without significant change in 90-day MRS.

Afternoon Poster Session
Location: Row B
Poster #27

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Sanjeev Khanna	Graduate	Smith	Bioengineering

Spiking correlations in the frontal eye fields during eye movement planning

Pairs of nearby cortical neurons exhibit correlated spiking activity. There is a strong link between the correlation among neurons and the amount of information that can be represented in a neuronal population. That link is particularly important at the decoding stage when sensory signals are used to guide motor output such as eye movements. Very little is known however about the correlated activity in areas that bridge the sensory and motor divide. The frontal eye fields (FEF) are considered to be the primary locus of cortical signals controlling eye movements. Because of this and the presence of neurons with both visual and motor responses they are an ideal candidate for studying the role of correlated activity in planning and executing movements. Of particular interest is the connection between the populations of visual and motor neurons which might be important for eye movement planning. We used a linear electrode array to record from groups of FEF neurons in alert rhesus macaque monkeys performing a conventional memory guided saccade task. We measured neuronal correlation of spiking activity on both short and long time scales (spike count correlation and synchrony). We found that correlated spiking activity in FEF was similar in a number of ways such as dependence on distance and tuning similarity to previous measurements in early visual cortex. When we focused specifically on connections between visual and motor neurons we found a distinct pattern of results. The overall level of correlation between these groups was lower than visual-visual or motor-motor pairs but it showed the strongest dependence on the direction of the planned eye movement. These findings suggest that visual and motor populations of neurons in the FEF play a unique role in transforming visual information to motor output.

Morning Poster Session
Location: Row E
Poster #63

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Erin Kirschmann	Postdoctoral	Torregrossa	Psychiatry

Effects of age of initiation on cannabinoid self-administration and corresponding cognitive consequences in male Sprague-Dawley rats

Marijuana (Cannabis sativa) is the most commonly used illicit drug in the US. Retrospective clinical studies suggest that initiating cannabinoid use in adolescence increases risk for negative outcomes such as cognitive impairment and risk for addiction relative to initiation in adulthood; however potential pre-existing cognitive differences among individuals and poly-substance use makes attributing negative effects specifically to marijuana difficult. We examined self-administration (SA) of the selective potent cannabinoid receptor agonist WIN55 212-2 (WIN) in adolescent vs. adult male rats and compared abuse potential and long-term effects on cognitive performance. Adolescent (starting postnatal day 28; p28) and adult (>p70) male rats were trained to SA intravenous infusions of WIN (0.0125mg/kg/infusion) on an FR1 schedule in daily sessions. Following SA rats were tested for cue-induced reinstatement of WIN-seeking after increasing periods of abstinence. The adolescent SA group was trained and tested on a delayed-match-to-sample working memory (WM) task in drug-free conditions as adults; performance was compared to adults trained to SA sucrose during adolescence. The adult SA group was trained and tested on the WM task after a similar abstinence period. An additional group of adults were trained on WM prior to initiation of WIN SA to determine the acute effects of WIN SA on WM. Adolescent and adult rats acquired WIN SA and displayed stable levels of intake during the last days of training. However while all adolescent rats met acquisition criteria only a subset of adults acquired. Adolescents and adults had similar levels of cue-induced WIN-seeking early in abstinence; the adolescent SA group (tested as adults) exhibited a further significant increase in WIN-seeking in continued abstinence suggesting an “incubation of craving.” Adult rats did not increase WIN-seeking in continued abstinence suggesting that adult-onset SA does not result in an incubation effect. Finally we found that WIN SA during adolescence resulted in improved WM performance in adulthood relative to sucrose controls if rats were abstinent. WIN SA during adulthood yielded no such improvements after abstinence. Additionally acute effects of adult WIN SA impaired WM performance relative to baseline performance. Interestingly rats with better baseline performance went on to take very low amounts of WIN; however the detrimental effects of WIN SA were magnified in this group and did not recover with abstinence. Our findings suggest that adolescent-onset cannabinoid use does produce indications of abuse liability while these indicators are blunted in adult-onset. Paradoxically adolescent WIN SA and abstinence resulted in better adult WM performance.

Afternoon Poster Session
Location: Row C
Poster #41

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Griffin Koch	Graduate	Coutanche	Psychology

The neural basis for trait memory differences

We draw on a variety of neural systems in the course of learning and then remembering the wide range of information that we encounter every day. Although all healthy humans have access to the same brain systems people differ in the extent to which they draw on one type of memory versus another. Some people tend to emphasize the factual components of a past event (semantic) while others are biased to forming memories that are rich in spatiotemporal and contextual features (episodic). The current study investigates the neural basis for trait differences in the use of semantic episodic and spatial memory systems across individuals. We scanned the brains of 20 individuals using magnetic resonance imaging (MRI) and related the volumes of key brain regions to scores in the Survey of Autobiographical Memory (SAM) which quantifies a person's self-reported episodic semantic and spatial memory traits in addition to future prospection. We find that the brain regions associated with memory systems differ in relative volume across the population in a way that systematically tracks trait memory differences. Our findings include the result that individuals with stronger semantic memory characteristics have a larger percentage of brain volume occupied by the right and left temporal poles. These anatomical findings contribute additional evidence towards identifying the anterior temporal lobes as a type of "semantic hub". More generally this study provides evidence that anatomical data can reflect an individual's memory characteristics.

Afternoon Poster Session
Location: Row B
Poster #17

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Takashi Kozai	Faculty	Kozai	Bioengineering

Decoding the Brain Tissue-Microelectrode Interface

Intracortical electrode arrays that can record extracellular action potentials from small targeted groups of neurons are critical for basic neuroscience research and emerging clinical applications. In general these electrode devices suffer from reliability and variability issues that impact their performance on the order of months to years. The failure mechanisms of these electrodes are understood to be a complex combination of the biological reactive tissue response and material failure of the device over time. The breaching of the blood–brain barrier (BBB) to insert devices triggers a cascade of biochemical pathways resulting in complex molecular and cellular responses to implanted devices. Molecular and cellular changes in the microenvironment surrounding an implant include the introduction of mechanical strain BBB leakage activation of glial cells loss of perfusion secondary metabolic injury and neuronal degeneration. The resulting inflammation is a key hypothesized cause of neural recording failure and at times mirror other brain injury and neurodegenerative diseases even if the scope and timescale differ. Our findings from electrophysiology impedance spectroscopy and post-mortem histology demonstrate a very poor relationship between histology and impedance to electrophysiology. For example tissue with low-levels of glial encapsulation healthy neuronal proximity and low impedance can still have poor recording performance even with neural activity is behaviorally driven. Previously we demonstrated that mechanical mismatch between iridium and silicon led to material failure in chronically implanted planar silicon electrodes. These findings were confirmed with chronic in vivo data (133–189 days) in mice V1m cortex by correlating a combination of single-unit electrophysiology evoked multi-unit recordings electrochemical impedance spectroscopy and scanning electron microscopy from traces and electrode sites with our modeling data. Several modes of mechanical failure of chronically implanted planar silicon electrodes were found that result in degradation and/or loss of recording. This can confound correlation analysis between recording performance and histological outcomes. Here we compare the results from histology and mechanical failure to recording performance and identify loss of neural recording signal despite intact electrode material and good histological outcomes. Early in vivo multiphoton data suggest dramatic axonal degradation around implanted electrodes. These results emphasize the complexity of the biological pathways that govern the reactive tissue response and longitudinal electrophysiological recordings from penetrating electrode arrays. BBB injury is not limited to chronic BBB leakage but can include vascular occlusion edema and ischemia/hypoxia which may not necessarily cause gliosis and neuronal death but can heavily modulate nearby neural activity.

Morning Poster Session
Location: Row F
Poster #76

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Rebecca Krall	Graduate	Tzounopoulos	Neurobiology

Endogenous extracellular zinc is neuroprotective against glutamate excitotoxicity mediated via NMDA receptors

Zinc is an endogenous modulator of neurotransmission, notably through its inhibition of NMDA and AMPA receptors (NMDARs and AMPARs), and potentiation of glycine receptors (GlyRs).The majority of free zinc in the brain is loaded into vesicles by the zinc transporter Znt3, and co-released with glutamate. However there is an additional, Znt3 independent extracellular tonic pool of zinc that inhibits extrasynaptic NMDARs and potentiates GlyRs (Anderson et al., PNAS 112:E2705; 2015; Rosello et al., Neurobiol Dis 81:14; 2015). Because extrasynaptic NMDARs receptors are implicated in excitotoxicity (Parsons & Raymond, Neuron 82:279; 2014),we investigated whether the tonic zinc pool limits excitotoxic injury via its inhibition of NMDARs. To quantify tonic zinc levels, we used the extracellular ratiometric zinc probe LZ9. We measured nanomolar levels of extracellular zinc in rat mixed cortical cultures, similar to those measured in fresh brain slices of the dorsal cochlear nucleus. DL-threo-β-benzyloxyaspartate (TBOA; 75 µM), a glutamate transporter inhibitor, induced glutamate toxicity and caused a ~30% decrease in cell viability as measured by LDH cytotoxicity assays ($p < 0.05$). Chelation of endogenous extracellular Zn^{2+} with ZX1 (3 µM), a high-affinity extracellular zinc chelator, increased the toxicity of TBOA treatment, reducing viability to ~50% of control ($p < 0.05$). In both cases, the NMDAR antagonist memantine (30 µM) blocked cell death. These results indicate that extracellular tonic zinc is neuroprotective via its inhibition of NMDA receptors.

Morning Poster Session
Location: Row D
Poster #43

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Lindsay Kutash	Undergraduate	Bondi	Physical Medicine and Rehabilitation

Effects of chronic unpredictable stress on cognitive and depressive-like behaviors following experimental brain trauma

Traumatic brain injury is highly prevalent affecting nearly 2 million Americans annually. Outcomes often involve frontal lobe dysfunction resulting in cognitive impairment and increased vulnerability to neuropsychiatric disorders. Similarly chronic unpredictable stress (CUS) has been found to elicit similar consequences. Currently we are assessing the clinically relevant cognitive behavior and anxiety-like dimensions of TBI in conjunction with CUS. After implementing a controlled cortical impact (CCI: 2.8 mm cortical depth at 4 m/s) or sham injury over the right parietal cortex rats were randomly assigned to receive 21 days of CUS. Upon cessation of stress rats were tested for perceived state of anxiety (open field test) and anhedonia (preference of 1% sucrose-water versus regular water overnight). At 4 weeks post-surgery rats were tested on the attentional set-shifting test a series of increasingly difficult discriminative tasks measuring various aspects of cognitive flexibility and were lastly sacrificed for serum analysis of corticosterone and inflammatory markers. Results demonstrate an expected decrease in cognitive and behavioral performance in the TBI-CTRL and CUS-SHAM groups. However TBI-CUS group showed paradoxically ameliorated behaviors and serum markers which may have many significant implications regarding the recovery process post-TBI especially in conjunction with environmental enrichment a rodent model of neurorehabilitation.

Afternoon Poster Session
Location: Row D
Poster #46

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Cecile Ladouceur	Faculty	Ladouceur	Psychiatry

Interfering with Interference: Positive Reinforcement Modulates Fronto-limbic Systems and Reduces Emotional Interference in Adolescents

The ability to resist interference from distracting emotional information while sustaining attention on goal-directed behavior is critical for adaptive behavior and depends on complex cognitive-affective processes. There is mounting evidence from developmental affective neuroscience research demonstrating greater neural activity in subcortical regions such as the amygdala to emotionally salient information in adolescents particularly those at risk for affective disorders. In parallel studies show that positive reinforcement can enhance attentional control by promoting the recruitment of prefrontal cortical regions and that this effect is greater in adolescents compared to adults. The aim of this study was to examine the functioning of fronto-limbic systems subserving emotional interference in adolescents and to test whether differential reinforcement of correct responding can enhance attentional control and modulate these neural systems in ways that promote insulation from emotional distraction. Forty healthy adolescents (ages 10-13; 19 girls) completed an emotional delayed working memory task during fMRI with emotional distracters (none neutral negative) while positive reinforcement (i.e. monetary reward) was provided for correct responses under some conditions. As in adults adolescents showed a decline in performance to negative and neutral compared to no distracters and greater activation in amygdala and dorsal and ventral prefrontal cortices. Positive reinforcement yielded an overall improvement in response accuracy and reaction times and counteracted the effects of negative distracters as evidenced by significant reductions in activation in the amygdala and prefrontal cortical regions. The present findings extend results on emotional interference from adults to adolescents and highlight positive reinforcement as a potential mechanism that can boost attentional control of emotion. These findings also suggest that it may be possible to harness adolescent neural response to the effects of positive reinforcement on prefrontal cortical function to counteract negative environmental influences and facilitate coping. Future work in a larger sample is needed to investigate underlying developmental mechanisms in healthy and at-risk youth. A challenge for the future will be to build upon these findings for constructing reinforcement-based attention training programs that could be used to reduce emotional attention biases in anxious youth.

Afternoon Poster Session
Location: Row D
Poster #49

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Adam Large	Graduate	Oswald	Neuroscience

Somatostatin interneurons mediate an activity gradient in piriform cortex

Odor information is processed and encoded by the neural circuitry of the piriform cortex. Compared to primary sensory cortices anterior piriform cortex (APC) lacks topographic representations of odor identity and appears to be a fairly homogenous structure in terms of connectivity and sensory processing. In order to observe the spatial structure of odor-evoked neuronal populations in APC we utilized Targeted Recombination of Active Populations (TRAP) to fluorescently label neurons expressing the immediate early gene c-fos during odor presentation. We find that this active population decreases in density along the rostrocaudal (RC) axis of the APC. To investigate potential underlying mechanisms for an activity gradient we optically stimulated interneurons in APC slices from vGAT-ChR2 mice while recording IPSCs in piriform pyramidal cells and demonstrate a clear caudal bias of inhibition onto pyramidal cells. Surprisingly we also find that a majority of inhibitory interneurons receive biased inhibition but with an opposing RC gradient. Since FS cells are a major source of inhibition onto pyramidal cells we believe that the activity gradient is due to modulation of inhibition onto FS cells. This suggests that the source of FS-cell inhibition needs to decrease along the RC axis. Using genetically targeted fluorescent labeling we find that somatostatin-expressing (SST) interneurons decrease in density along the RC axis. We also find that SST-cells can provide biased inhibition to inhibitory interneurons. Taken together these results suggest a disinhibitory circuit mechanism supports an increasing gradient of inhibition resulting in enhanced odor-evoked activity of rostral pyramidal neurons but a decreasedn recruitment of caudal neurons.

Afternoon Poster Session
Location: Row D
Poster #54

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Jongwon Lee	Graduate	Kandler	Department of Otolaryngology

Development of structural and functional connectivity of MNTB axon collaterals to the mouse superior paraolivary nucleus

The medial nucleus of trapezoid body (MNTB) is the major source of inhibition in the auditory brainstem providing inhibitory inputs to the lateral superior olivary (LSO) as well as the superior paraolivary nucleus (SPON). Projections from the MNTB to these nuclei are tonotopically organized. In the developing LSO the tonotopic precision substantially increases via synaptic silencing and axonal pruning. In this study we investigated whether the refinement of individual MNTB axon collaterals in the LSO and SPON is coordinated. Anatomical reconstructions of biocytin-filled MNTB axons show the presence of tonotopy in the MNTB-SPON pathways shortly after birth (P2-4). Over the next three weeks axons expand and add new boutons but this growth was proportional to the expansion of the SPON resulting in no change in the tonotopic precision. Ongoing studies to map functional connectivity using laser-scanning photostimulation further support the early tonotopic organization of the MNTB-SPON projection and the absence of tonotopic refinement during the first three postnatal weeks. Our results demonstrate that MNTB axon collaterals show a dramatically different degree of tonotopic refinement and axonal pruning depending on whether they innervate the LSO or MNTB indicating that axonal pruning of these inhibitory axons is determined by the postsynaptic target.

Afternoon Poster Session
Location: Row E
Poster #56

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Michael Leone	Graduate	Doiron	Mathematics/Center for the Neural Basis of Cognition

Improved Reliability of Synaptic Transmission Reduces Neuronal Correlations in Balanced Network Models

Neuroscientists have known for decades that synapses in the central nervous system are highly unreliable often failing to release neurotransmitter following an action potential. This stochasticity can change dynamically as a result of prior activity and behavioral state. However previous theoretical studies of recurrent networks exhibiting balanced excitation and inhibition have neglected this important feature of biology. By way of mathematical theory of a balanced network with correlated feedforward input and variable synapses we have found that unreliability of recurrent synapses robustly increases spike count correlations while the opposite is true of unreliability of synapses in the feedforward pathway. We replicated these findings via simulations of a conductance-based exponential integrate-and-fire model. Previous studies of rat barrel cortex indicate that pyramidal-cell synaptic reliability increases following stimulus onset and coincides with decreased spike count correlations. Our results are consistent with these observations and furthermore implicate improved synaptic reliability as a causal factor in the observed correlation reduction. In addition we found that unreliable transmission is a major source of intrinsically generated variability in balanced networks of arbitrary population size. This result strengthens previous claims that high spike count variability consistently observed in cortical data may arise due to synaptic unreliability. Together our results highlight the importance of modeling variable synapses in theoretical studies of cortical networks.

Morning Poster Session
Location: Row A
Poster #9

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Daniela Leronni	Postdoctoral	Friedlander	Neurological Surgery

Toward a Gene Therapy for Huntington Disease

Huntington Disease HD is an autosomal dominant neurodegenerative disease due to an extended CAG repeat in the gene encoding for the protein huntingtin (htt). Melatonin has been shown to be neuroprotective in cellular models of HD and to decrease mortality in mouse models of HD. Melatonin inhibits cytochrome c release activation of the caspase cascade and cell death. HD patients show a gradual decrease of melatonin blood level and a reduction of Arylalkylamine N-acetyltransferase (AANAT) the rate-limiting enzyme in the production of melatonin from serotonin. We want to investigate if restoring of the level of melatonin produced in HD cells could provide a potential treatment for HD. To overcome the problem of continuous drug administration and to restore the melatonin synthesis in HD cells one potential powerful approach is gene therapy. HSV-based vectors have provided one method of long-term delivery of transgenes. We aim to overexpress two enzymes involved in the synthesis of melatonin (AANAT) and its precursor serotonin (aromatic l-amino acid decarboxylase AADC) in HD cells. We have created three different HSV-based vectors: one for each enzyme independently and one overexpressing both. We will then deliver our transgene(s) in wt(htt) and mut(htt) mouse stratal neurons derived cell lines in order to compare the level of melatonin and consequently the release of cytochrome c in the two cell lines. The results of these experiments will indicate 1) which step of the melatonin synthesis pathway is impaired in HD cells and 2) if restoring or even increasing levels of melatonin produced in HD cell can have a neuroprotective effect. Future experiments will attempt to apply these vectors for infection of mouse brain by direct inoculation.

Morning Poster Session
Location: Row B
Poster #22

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Lingjue Li	Graduate	Poloyac	School of Pharmacy

No-reflow phenomenon Revisted: Alteration of Cerebral Microcirculation after Cardiac Arrest in Developing Rats

Introduction: As early as 1968 the no-reflow phenomenon was described by Ames in a global ischemia rabbit model however this phenomenon has never been observed in vivo. Our previous studies in a pediatric asphyxial cardiac arrest (CA) model observed decreased cortical blood flow from 15-180 min post-CA. In order to further elucidate the mechanism underlying the cortical hypoperfusion we propose to evaluate cortical microvascular dysfunction in our pediatric CA model with the goal of enhancing the understanding of vascular dysfunction post-CA and establishing a scaffold to evaluate potential vasoactive therapeutic agents. Hypothesis: Disturbances in cortical microcirculation are present post-CA consistent with the no-reflow phenomenon. Methods: Postnatal 17 day old rats underwent tracheal intubation arterial and venous cannulation and were equipped with a cranial window for in-vivo two photon laser scanning microscopy. Asphyxial CA of 9 min was induced by cessation of mechanical ventilation after neuromuscular blockade. Rats were resuscitated with chest compressions epinephrine and sodium bicarbonate. Using in-vivo multiphoton microscopy we serially assessed cortical microcirculatory blood flow pre- and post-CA. We measured the diameter of cortical microvessels red blood cell (RBC) velocity and density pre- and post-CA. We quantified the mean transit time using intensity tracking during bolus dye injection. Data were processed in MATLAB and SPSS. Results: We assessed 44 capillary branches from 12 rats. The RBC flow was continuous at baseline. At 30 min post-CA 14 (25.4%) capillaries had no-reflow at 30 min and 8 (18.1%) capillaries have no-reflow at 60 min post-CA. For capillaries with continuous RBC flow we collected 33 capillary branches from 4 sham rats and 39 capillary branches from 8 CA rats. No significant differences were identified in RBC velocity or density post-CA compared with baseline or sham animals. Microvessel diameters were found to have high variability post-CA. The mean transit time from cortical artery to veins was increased at 30 min post-CA compared with sham rats suggesting obstruction in cortical microcirculation. Conclusions: We are first to identify the no-reflow phenomenon in-vivo in a clinically relevant pediatric asphyxial CA model. Additionally we observed important alterations of the cerebral microvascular circulation with highly variable vessel diameter and increased mean transit time. Significance: Approximately 16 000 pediatric patients suffer CA each year in the US with asphyxia as the major cause. Hypoxic ischemic encephalopathy is the limiting factor for recovery post-CA. We identified important alterations of the cortical microcirculation consisting of areas with no reflow areas of low flow and increased variability of capillary diameters. Understanding the cerebral microvascular dynamics post-CA is paramount to identifying therapeutic targets for mitigation of ischemic encephalopathy post-CA.

Research / Grant Support: NIH R01 HD075760 1S10RR028478-01 Brain 2015 Conference Young Investigator Travel Bursary

Afternoon Poster Session
Location: Row C
Poster #36

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Yuanning Li	Graduate		Neurological Surgery

Distributed Information Processing across OFA and FFA Represents Individual Face Identities

In contrast to traditional hierarchical models, most current models of visual perception suggest that distributed networks of regions across the visual processing stream underlie visual recognition. For example, multiple face patches, including the occipital face area (OFA) and the fusiform face area (FFA) likely work in concert to encode individual faces. However, direct evidence for distributed computation of individual faces does not exist because to date no methods exist to examine the information represented in neural interactions. Here we develop a novel pattern recognition method, called Multi-Connection Pattern Analysis (MCPA), to extract the discriminant information about cognitive conditions solely from the shared activity between two neural populations. In MCPA, functional connectivity models are built based on shared multivariate neural activity using canonical correlation analysis for each condition. Then using these models the activity in one area is predicted solely based on the activity in the other area for each condition. Classification is achieved by comparing the predicted activity with the true activity, revealing the representational structure of the shared neural activity (e.g. the information represented in the functional interaction). MCPA was applied to analyze intracranial EEG (iEEG) data recorded simultaneously from OFA and FFA in a human subject. Our results support the hypothesis that individual-level face information is not only encoded by the population activity within certain brain populations, but also represented through recurrent interactions between multiple distributed populations at the network level. In addition, the critical time window for face individuation based on MCPA was approximately 200 – 500 ms after stimulus onset, which is consistent with our previous study based on iEEG recording from FFA only. This suggests the involvement of FFA in the face individuation process is a result of temporally synchronized, recurrent interactions between FFA and other nodes in the face-processing network, including the OFA.

Morning Poster Session
Location: Row D
Poster #51

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Kimberly Lin	Graduate	Price	Department of Psychiatry

Changes in Visual Attention and Cognitive Function Following Attention Bias Modification for Treatment of Anxiety

Changes in Visual Attention and Cognitive Function Following Attention Bias Modification for Treatment of Anxiety Kimberly S. Lin and Rebecca B. Price University of Pittsburgh School of Medicine Background: Increased attention to threat-related stimuli in our environment serves an adaptive function in detecting and responding to danger. However in clinical anxiety this threshold for attention to threat is significantly lowered (1 3). The neural circuitry facilitating this heightened attention towards threat involves a balancing act between the amygdala and the ventral pre-frontal cortex (vPFC): early engagement of the amygdala mediates a bottom-up subcortical pathway that initially orients attention toward threat followed by the vPFC mediating a top-down cortical pathway to regulate amygdalar activity. Studies have shown anxious individuals exhibit a hypersensitive amygdala when compared to healthy individuals as well as weaker negative correlations with the vPFC in amygdala regulation. While cognitive-behavioral therapy the gold standard treatment for anxiety targets the top-down cortical component it is thought that targeting the sub-cortical component may be more effective not only because it is earlier in the cascade but because attentional perturbation may be more easily shaped here than in cortical areas (2 3). Attention Bias Modification (ABM) is a translational neurocognitive treatment that targets this implicit pathway using repetitive computer-based training methods in which anxious individuals practice an automated task that conditions their attention away from threat stimuli. Because attention is involved in cognitive processes it is relevant to consider how cognitive changes play a role in ABM outcomes (4). We examined whether changes in a) visual attention to threat and b) general cognition tracked with reduction in clinical symptoms of anxiety and depression following ABM. Methods: 62 adults with elevated clinically impairing anxiety were randomized to receive 8 sessions of ABM treatment (n=42) via a word-based 'dot-probe' task or a sham control version (n=20) over a period of one month. Self-reported questionnaires including the Mood and Anxiety Symptoms Questionnaire (MASQ) Beck Depression and Anxiety Inventories (BDI BAI) and Response Style Questionnaire (RSQ) were administered pre- and post-treatment to mark changes in clinical symptoms of anxiety and depression. Change in attentional patterns were assessed via eye-tracking during the dot-probe task. The Stroop color-word task was used to measure executive cognitive function pre- and post-treatment. Results: All symptom measures decreased from pre- to post-ABM. Following treatment eye-tracking data showed slower disengagement from threat words (relative to neutral words) in the ABM group (p=0.026 d=0.436) while there was no significant change in disengagement in the control group (p=0.539 d=0.169). In the ABM group changes in disengagement were positively correlated with reduction in self-reported clinical depressive and anxiety symptoms (p=0.001 – 0.027). The ABM group also showed significant improvement in measures of cognitive performance (p<0.001 d=0.766) while the effect was smaller and non-significant in the control group (p=0.087 d=0.404). In the ABM group Stroop improvement was negatively correlated with reduction in self-reported depressive and ruminative symptoms (p=0.014 – 0.031). Conclusions: As is consistent with existing literature reductions in clinical depression and anxiety symptoms were

observed following ABM a translational neurocognitive intervention (4). Interestingly the mechanisms of symptom decrease included slower disengagement from threat stimuli and altered executive function. One potential explanation is that ABM treatment allowed anxious individuals to overcome chronic and excessive avoidance of threat and engage a normative amygdalar-vPFC threat-detection system that has evolutionary relevance. The improvement observed in cognition following ABM suggests that ABM may have widespread effects on the frontoparietal neural circuitry underlying general executive and cognitive abilities. The paradoxical finding that lesser cognitive improvement tracked with greater reduction in depressive and ruminative symptoms may be consistent with previous findings linking perseverative thinking styles (e.g. rumination worry) to a performance benefit on certain cognitive tasks (i.e. those requiring inflexible goal maintenance such as the Stroop task). The exact neurocognitive mechanisms of ABM and its utility in treatment of psychiatric disorders remains a promising area to be explored. References: (1)\tBar-Haim Y Lamy D Pergamin L Bakermans-Kranenburg MJ and Van Ijzendoorn MH. Threat-Related Attentional Bias in Anxious and Nonanxious Individuals: A Meta-Analytic Study. Psychol Bull. 2007;133(1):1-24. (2)\tHakamata Y Lissek S Bar-Haim Y Britton JC Fox N Leibenluft E et al. Attention Bias Modification Treatment: A meta-analysis towards the establishment of novel treatment for anxiety. 2010;68(11):982-990. (3)\tPine DS Helfinstein SM Bar-Haim Y Nelson E Fox NA. Challenges in Developing Novel Treatments for Childhood Disorders: Lessons from Research on Anxiety. Neuropsychopharmacol. 2009;34:213-228. (4)\tRozenman M Weersing VR Amir N. A Case Series of Attention Modification in Clinically Anxious Youths. Behav Res Ther. 2011;49(5):324-330.

Morning Poster Session
Location: Row B
Poster #28

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Mark Linsenmeyer	Postdoctoral	Galang	UPMC Department of Physical Medicine and Rehabilitation

Disorders of consciousness due to anoxic brain injury: a case series of 8 patients

Authors: Mark Linsenmeyer Shanti Pinto Gary Galang OBJECTIVE: To characterize common medical complications treatments and recovery in patients with disorders of consciousness (DOC) due to anoxic brain injury. DESIGN: Retrospective case series at a single academic inpatient rehabilitation (IPR) center. Patients with current or recent DOC due to anoxic brain injury who were admitted to IPR from 2015-2016 were considered for inclusion. Patients were excluded if there was head trauma. History and clinical course were reviewed from electronic records. Uniform Data System (UDS) data was used to determine FIM scores. RESULTS: 8 patients were identified. On admission to IPR 4 were vegetative 1 was minimally conscious and 3 had recently emerged. While at IPR 1 vegetative and 1 minimally conscious patient emerged. 1 vegetative patient became minimally conscious. FIM scores on admission were 22 or below for all patients and improved in 4 patients by an average of 40.5 points. Scores did not improve for the remaining 4. All patients were given neuropharmacologic medications for arousal and attention. Paroxysmal sympathetic hyperactivity (PSH) affected 6/8 patients and clinically resolved for 2 of these patients prior to discharge. 6/8 patients had spasticity resolving in 3 by discharge. 5/8 patients exhibited movement disorders primarily myoclonus. No patients developed seizures during IPR admission but 2/8 patients experienced status epilepticus prior to IPR. 2/8 had MRI evidence of focal ischemic stroke in addition to hypoxia. 2/8 were briefly transferred from IPR to acute care for sepsis and 7/8 had urinary tract infections while on IPR. Overall 6/8 patients were discharged home. CONCLUSIONS: DOC due to anoxia is a unique clinical entity accompanied by specific clinical and social challenges. Common limitations to rehabilitation include the severity of deficits in arousal and cognition PSH spasticity movement disorders and a high rate of infection. Further investigation into predictors of outcome and optimal medical management for this population is warranted. Disclosures: None

Afternoon Poster Session
Location: Row D
Poster #47

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Witold Lipski	Postdoctoral	Richardson	Neurosurgery

Speech encoding in human subthalamic nucleus neurons and sensorimotor cortex

Speech production and control is disrupted in a number of neurological diseases that involve the basal ganglia. Notably hypophonia and hypokinetic dysarthria (characterized by decreased motor gain) are prevalent in patients with Parkinson's disease (PD). Deep brain stimulation (DBS) of the subthalamic nucleus (STN) produces predictable improvements in other motor symptoms of PD but does not result in consistent improvement in speech and can negatively impact language function. These observations and other accumulating evidence indicate an important role for the basal ganglia in speech. However a major impediment to developing treatments for speech deficits in movement disorders and reducing speech-related side effects of DBS is the absence of a neurophysiological model for basal ganglia participation in speech production. We recorded STN neuron activity STN local field potentials (LFP) electrocorticography (ECoG) over articulatory sensorimotor cortex and spoken acoustics while 9 PD subjects performed a speech task during DBS surgery in order to test how general tenets of basal ganglia organization and function apply to the speech motor system. We hypothesized that the STN contributes at multiple levels to the hierarchical control of speech production by encoding articulatory orofacial muscle movements as well as voice quality measures such as such as volume pitch and fluency. Indeed we found that of 44 isolated unit recordings in the STN 23 showed either increases or decreases in firing rate during speech production. Preliminary analysis also revealed differential STN activation during speech involving early- versus late-learned phonemes suggesting that the STN is involved in processing phonological information. Furthermore we found that speech robustly modulated beta (12-40 Hz) and gamma (75-250 Hz) STN and cortical oscillatory activity in all subjects with preliminary findings also indicating changes in cortico-subthalamic spike-phase synchronization during speech. Testing how general tenets of basal ganglia organization and function apply to the speech motor system presents both unique challenges for clinical neuroscientists and significant opportunities to advance the cognitive neuroscience of speech production. Our findings support the hypothesis that both motor and linguistic speech information is encoded at multiple levels of granularity within the STN-cortical network.

Afternoon Poster Session
Location: Row E
Poster #58

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Bing Liu	Faculty	Liu	Computational and Systems Biology

Computational Modeling of Amphetamine-stimulated Dopamine Dynamics

Dopamine (DA) plays key roles in the pathology of neurological disorders such as Parkinson's disease and drug abuse. DA transporter (DAT) provides a primary mechanism that maintains the DA homeostasis. Amphetamine (AMPH) exposure induces euphoria and hyperactivity by increasing extracellular DA through a variety of mechanisms: (i) competitively binding to DAT (ii) eliciting DA efflux (iii) and enhancing DAT internalization which are governed by a network of biochemical reactions. The network involves multiple feedforward and feedback mechanisms and thus analyzing its complex dynamics requires systems biology approaches. To identify potential intervention strategies for modulating extracellular DA level we construct a comprehensible model for the downstream interaction network that underlies the AMPH-induced DA efflux and DAT trafficking. Our mathematical model takes into account the activation of Rho PKA PKC CaMKII and and G-protein signaling pathways that regulate the AMPH-stimulated DA dynamics. The model was calibrated by an optimal fit of the time course of surface DAT and cAMP levels under two conditions and was further verified to reproduce the time course of Rho activation and AMPH-cAMP dose response. Sensitivity analysis and in silico knockdown experiments suggest that AMPH modulates extracellular DA level mainly through the DA efflux pathways than DAT internalization. Interestingly simultaneously inhibiting DA efflux and DAT internalization might lead to a synergistic enhancement of DA reuptake. Our results also identify a feedforward loop that governs the time window of Rho activation and fine-tunes AMPH induced DAT internalization. These systems-level insights we gained could contribute to the development of pharmacological strategies for disrupting AMPH action.

Afternoon Poster Session
Location: Row C
Poster #35

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Shi Tong Liu	Graduate	Sadagopan	Bioengineering

OPTIMAL FEATURES FOR ACOUSTIC CLASSIFICATION

The recognition and categorization of complex sounds is a central goal of auditory processing. In vocal animals conspecific vocalizations or 'calls' are an ethologically central set of complex sounds that these animals are able to perceptually recognize and categorize. Typically the vocal repertoire of a given species might consist of several categories with overlapping spectral profiles making them impossible to classify using low-level cues such as the long-term spectrum. In addition because different vocalization tokens within a class exhibit high variability both within and between animals any classifier should be able to generalize across this variability. Here we propose that combinations of acoustic features of intermediate complexity can be used to categorize vocalizations. We start by extracting a large number random acoustic features from one class of marmoset calls. We use an information maximization approach to score each feature on its ability to correctly classify this call type from all other types. We then use a greedy search algorithm to select a set of features that maximize classification accuracy while minimizing redundancy. We show that high classification accuracy can be achieved using a small set of such features. If cortical neurons were indeed encoding such features we demonstrate that they would exhibit highly nonlinear and selective tuning properties. Such neurons have been observed in single-unit recordings from marmoset auditory cortex supporting the feature-based classification model. Similar feature-based approaches might be used to implement more complex tasks such as speech recognition.

Morning Poster Session
Location: Row F
Poster #71

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Joshua Lorenz-Guertin	Graduate	Jacob	Pharmacology and Chemical Biology

Characterizing a Novel Tool to Monitor Pharmacologically-Induced Changes in GABA(A)R Trafficking

Surface regulation of the γ-aminobutyric acid type-A receptor (GABA(A)R) is a critical aspect of both baseline inhibitory neurotransmission and responsiveness to pharmacological treatments. We recently engineered a novel GABA(A)R γ2 subunit that is capable of tracking receptors through nearly all phases of trafficking. The fluorogen-activating peptide dual L5 (DL5) was inserted into a previously characterized γ2 subunit construct already encoding a pH-sensitive green fluorescent protein (pH-GFP) (γ2pH-DL5). DL5 is an antibody variable fragment which selectively binds and activates malachite green (MG) dyes that are otherwise non-fluorescent in solution. MG dyes have distinct characteristics including cell permeability pH-sensitivity and fluorescence properties. We find that γ2pH-DL5 is fully expressed at the cell surface in transfected cortical neurons and forms synaptic clusters. Additionally GABA(A)Rs incorporating γ2pH-DL5 respond to the endogenous ligand GABA and exhibit positive modulation via the γ2 subunit-requiring benzodiazepine type drug Diazepam in electrophysiological recordings. Imaging studies demonstrate that γ2pH-DL5 is able to bind and activate the fluorescence of the MG dyes MG-βT and the pH-sensitive dichromphore pH-se-Red. Neurons pulse-labeled with cell membrane impermeable MG-βT exhibit a time-dependent accumulation of fluorescent signal colocalized with the lysosomal marker LAMP-1 RFP indicating surface γ2pH-DL5 can be tracked to lysosomes. This work aims to use advanced live-imaging approaches to identify pharmacologically-induced changes in GABA(A)R regulation and ultimately provide critical information about the receptor as a clinical target.

Morning Poster Session
Location: Row D
Poster #47

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Anna Manelis	Faculty	Manelis	Psychiatry

Anticipatory brain activation and current depression and mania symptoms predict subsequent recognition of emotional faces in depressed individuals with bipolar disorder depressed individuals with major depressive disorder and healthy controls

Title: Anticipatory brain activation and current depression and mania symptoms predict subsequent recognition of emotional faces in depressed individuals with bipolar disorder depressed individuals with major depressive disorder and healthy controls Anna Manelis Ph.D.; Tina Liu BS; Holly Swartz MD; Mary L. Phillips MD MD (Cantab) Abstract Due to the higher prevalence of depressive over hypomanic symptoms reliably differentiating unipolar from bipolar depression remains challenging in clinical practice. Therefore understanding the range of functional psychopathology in these disorders is especially important. Neuroimaging studies using dimentional approach to examine depressed individuals with bipolar disorder (BDD) and depressed individuals with major depressive disorder (MDD) may help to understand neural mechanisms underpinning impairments in emotion and cognitive processing and to identify neurobiological diagnostic markers of these disorders. According to previous studies depressive episodes are characterized by altered anticipation of positive and negative events. In this study we have examined how current and life-time depression and mania symptoms together with anticipatory activation during preparation to processes emotional faces affect subsequent recognition of emotional faces in BDD MDD and healthy controls (HC). Participants were presented with fear happy and neutral faces and had to identify the gender of the person on the picture. Each face presentation was preceded with an anticipatory cue that indicated the emotional valence of the upcoming stimulus with a symbol. A surprise memory test was conducted outside the scanner to test subjects' memory for faces. We found that lower anticipatory activation preceding presentation of happy faces in the right middle frontal gyrus right intraparietal gyrus (RIPS) and left middle temporal gyrus was related to better subsequent recognition of happy faces. A follow-up step-wise regression analyses with anticipatory brain activation and current and life-time depression and mania symptoms showed that anticipatory activation in the right intraparietal sulcus (IPS) and current depression and mania severity explained 34% of variance in recognition of happy faces. The same analysis conducted across BDD and MDD confirmed that greater anticipatory RIPS activation and greater current mania severity reduced recognition of happy faces. The IPS is involved in preparatory control. Excessive preparatory control before processing of happy faces and the presence of mania symptoms (e.g. irritability impulsivity) could inhibit formation of memory representation for happy faces. These findings suggest that previously reported memory impairments in BDD and MDD may be related to aberrant anticipatory brain functioning and mania symptoms and highlight the importance of studying anticipatory processes to better understand emotion and cognitive impairments in mood disorders.
This research was supported by the NIMH K01 grant to AM (NIMH K01MH104348)

Morning Poster Session
Location: Row A
Poster #8

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Ashwinee Manivannan	Undergraduate	Modo	Department of Neuroscience

Evaluating tractography parameters to visualize connectivity at the mesoscale in an ex vivo human hippocampus from a patient with temporal lobe epilepsy

Understanding the biology of hippocampal atrophy due to mesial temporal lobe epilepsy is imperative to improving treatment for the condition. A key hypothesis states that an aberrant connection between the dentate gyrus and stratum moleculare is an underlying cause of the disorder. This cannot be investigated using macroscopic or microscopic techniques. Instead mesoscale diffusion tensor imaging (DTI) a type of magnetic resonance imaging that measures the direction of diffusion of water molecules may provide better insight. Using DTI diffusion tensor tractography (DTT) computes streamlines visualizations of neuronal connections. Although tractography calculation has many parameters that influence streamline connectivity parameters that afford a reliable and accurate representation of neuronal connections have not been previously investigated. Diffusion images of the left hippocampus sample of a 42-year-old man with intractable epilepsy were analyzed in DSI Studio a program used to analyze DTT. Our investigations found that a lower threshold for step size functional anisotropy and minimum length provided reliable results while a higher threshold was better for angle. Seed sample was inconclusive. Further investigation will allow for accurate and reliable visualization of extra- and intra-hippocampal connections as well as the ability to non-invasively investigate the human hippocampus for better understanding of tissue architecture.

Morning Poster Session
Location: Row C
Poster #34

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Jacob Mann	Graduate	Donnelly	Neurobiology

Optogenetic induction of neurodegenerative proteinopathy

Aberrant protein misfolding and aggregation has long been considered a common pathological hallmark of a number of different neurodegenerative diseases including Alzheimer's Disease (AD) Parkinson's Disease (PD) Huntington's Disease (HD) Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS) amongst others (1). Current cellular models of these neurodegenerative proteinopathies often rely on the overexpression of disease-linked mutant proteins to induce pathological protein aggregation. However the vast majority of patients suffer from sporadic forms of the disease with no familial mutations. In ALS for example ~97% of all patients show pathological cytoplasmic aggregation of the DNA/RNA-binding protein TDP-43 but mutations in the TARDBP gene only account for ~1% of sporadic (sALS) and 4% of familial ALS (fALS) cases (2 3). Similarly rodent models of ALS produced from the overexpression of these mutant proteins have been historically unreliable and often fail to generate TDP-43-positive inclusions (4). Here we present a novel optogenetic-based technique to induce pathological protein aggregation using the Arabidopsis thaliana photoreceptor cryptochrome 2 (Cry2). Using this approach we show the light-induced oligomerization and aggregation of TDP-43 and disease-related truncations of the protein occur. These Cry2-TDP-43 aggregates appear to share similar pathological characteristics with TDP-43 inclusions observed in ALS patient tissue. Furthermore light-induced aggregate formation also appears to result in endogenous TDP-43 loss-of-function mechanisms that have been previously implicated in disease progression. This technique can be applied to a number of different disorders will allow for more precise temporal and spatial control over protein aggregation than has been previously possible. Additionally the ability to reliably induce protein aggregation with light alone will allow for in-depth investigations into the effects of these pathological aggregates on various cellular pathways and downstream pathological processes.

Afternoon Poster Session
Location: Row A
Poster #10

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Hongwei Mao	Postdoctoral	Schwartz	Systems Neuroscience Institute

Neuronal responses in the primary somatosensory cortex during reach-to-grasp movements using native and robotic arm

Primary somatosensory cortex (SI) receives afferent input from the peripheral sensory apparatus and responds with high fidelity according to characteristics of the stimulus such as location and modality. In addition to this well-recognized afferent driving of SI we are interested in the possibility of non-peripheral activation of SI cells during movement. While operating a robot arm via a brain-computer interface (BCI) movement commands from motor cortex are used to control the device and interactions between the robot hand and environment are monitored via visual feedback which might have the potential to drive SI responses. Thus this paradigm provides a unique opportunity to study SI activity during motor control but without peripherally driven somatosensory feedback. \tTwo sets of microelectrode arrays were implanted in two hemispheres of a non-human primate. Each set had one array (88 electrodes) placed in the upper arm area of the primary motor cortex (MI) and one array (32 electrodes) in the hand and finger representation of SI . The subject was first trained to perform a reach-to-grasp task using his native arm. Action potentials from arrays contralateral to the performing arm were recorded for this hand-control (HC) experiment. In the BCI experiment neural activity from the MI array was used to control the robot arm to perform the same reach-to-grasp task. Simultaneously recorded SI activity (in the same hemisphere as the MI array) and kinematics of the robotic arm were saved for offline analysis. An accelerometer attached to the arm contralateral to the recorded units was used to determine whether movement of the arm might be generating peripheral sensation during the task. Trials contaminated by movements of the native hand were excluded from analysis for the BCI experiment. \t In the HC experiment the overall activity of SI neurons was depressed during reaching began to increase before object contact and sharply peaked shortly after contact. In the BCI experiment 9 out of 29 SI neurons showed modulation around object contact. These included 7 cutaneous and 2 proprioceptive units with receptive fields in the fingers. Most of these units had a peak in activity around object contact or during grasping shortly after initial contact. One a cutaneous unit was most active when the robot hand started to close around the object at the end of reaching. Object-related activity peaks during the BCI tasks were broader than those of the same neurons in the HC tasks. These results show that SI can be modulated during motor control by both peripheral and non-peripheral input.

Morning Poster Session
Location: Row C
Poster #38

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Ian Marshall	Undergraduate	Bondi	Neuroscience Physical Medicine and Rehabilitation

Frontal lobe traumatic brain injury induces executive function impairments in male rats

Introduction: More than 10 million people worldwide sustain a traumatic brain injury (TBI) each year. The majority of survivors suffer long-lasting cognitive impairments associated with frontal lobe disturbances as well as psychological consequences such as being vulnerable to developing a psychiatric disorder. Previously we demonstrated that a controlled cortical impact (CCI) injury over the parietal cortex produced significant deficits in executive function in the attentional set-shifting test (AST) in rats a complex cognitive paradigm analogous to the Wisconsin Card Sorting Test which is used to measure strategy-switching deficits in patients with frontal lobe damage TBI and psychiatric disorders. Hypotheses: This study aims to investigate complex cognitive deficits after experimental TBI in rats subjected to frontal lobe injury a clinically relevant location by testing the hypothesis that a frontal TBI will impair executive function and cognitive flexibility in a cortical deformation depth-dependent manner. Methods: Thirty-one isoflurane-anesthetized adult male rats were subjected to CCI injury (2.0 2.2 and 2.4 mm cortical tissue deformation depth at a speed of 4 m/sec) or sham injury over the prefrontal cortex region in the right hemisphere. Rats were tested on the AST at four weeks post-surgery. The AST consists of two superimposing perceptual dimensions that the rat must use to retrieve food: scent (aromatic odor on the pots) and digging medium (different materials inside the pots). The test involves a series of increasingly difficult discriminative stages to obtain food reward including simple and compound discriminations stimulus reversals and intra- and extradimensional (ED) shifts. Dependent measures include number of trials to reach criterion of six correct consecutive responses number or total errors and number of set loss errors (i.e. after 50% or more of the contingency has been achieved). Results: Frontal CCI produced significant deficits in attentional performance on the ED stage and stimulus reversals of AST at four weeks post-injury seen as increased total trials to reach criterion and significantly higher total errors compared to SHAM rats (p<0.05 for Injury n=7-8/group). These effects were particularly robust in the two more severe injury groups namely 2.2 and 2.4 mm cortical deformation depth (p<0.05). Conclusions: These results suggest that frontal lobe injury negatively impacts complex cognitive functioning. Ongoing and future studies will focus on further disentangling brain constructs and neurotransmitter alterations responsible for such attentional deficits following brain trauma. Significance: Considering that a large percentage of TBIs occur via direct impact to the frontal part of the skull (e.g. hitting the windshield during a car accident) this approach is clinically-relevant and may prove extremely valuable for successful translation from bench to bedside identifying necessary pharmacotherapies for cognitive performance and advance rehabilitation research.

Research/Grant Support: Supported in part by UPP/UPMC Academic Foundation (Corina O. Bondi Ph.D.) and NIH grants NS060005 HD069620 and NS084967 (Anthony E. Kline Ph.D.).

Afternoon Poster Session
Location: Row B
Poster #20

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Corentin Massot	Postdoctoral	Gandhi	Bioengineering

Insights into sensorimotor transformation in the superior colliculus through current-source density analysis

The superior colliculus (SC) is crucial for transforming sensory signals that register a target into motor commands that produce an orienting movement to the stimulus. The sensory response is represented as a burst of activity in visual and visuomotor neurons in the superficial and intermediate/deep (collectively deeper) layers. Saccadic eye movements are produced by yet another burst of activity in the visuomotor and motor neurons in the deeper layers. However the underlying input signals that produce this pattern of activity are not well understood. We address this gap in knowledge by recording spikes and local field potentials (LFPs) from a 16-channel laminar probe in the SC of a monkey performing randomly interleaved delayed visually-guided and memory-guided saccades. The electrode penetration was orthogonal to the SC hence the optimal target locations and/or saccade vectors were comparable across all recording contacts. The target was positioned either close to the center of the response field or at the diametrically opposite location. Here we quantify LFP information with current-source density (CSD) analysis to emphasize the location and timing of incoming (source) and outgoing (sink) electrical currents across layers. Preliminary analyses reveal the following observations: The sensory burst is coincident with a robust current source signal in the intermediate layers with bleeding into the superficial layers. The magnitude of this source decreases gradually during the delay period and then increases modestly at the time of saccade onset. In contrast a current sink was observed deeper in the SC at sites of visuomotor spiking activity. This CSD switched to a weak source signal during the delay period before re-transitioning to a sink at the time of saccade onset to reveal a transient source/sink reversal between intermediate and deep layers. Intriguingly the CSD trace in the deep layers revealed a potent source signal immediately following the saccade. This cannot be a visual signature since it was also observed for memory-guided saccades. Across all layers modulations in both LFP and CSD signals during the delay and presaccadic periods were weak compared to the fluctuations observed during sensory and post-saccadic epochs. Taken together these results show key differences between the target and the motoric burst and reveal that each SC layer is involved in different local and global network activity during sensorimotor transformation.

Morning Poster Session
Location: Row B
Poster #18

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Kevin Mastro	Graduate	Gittis	Neurobiology

Cell-specific pallidal intervention induces long-lasting motor recovery in dopamine depleted mice

In Parkinson's disease (PD) the external segment of the globus pallidus (GPe) is a key contributor to the induction propagation and maintenance of network dysfunction within the basal ganglia. In the classical rate model of basal ganglia dysfunction the loss of dopamine shifts the balance of the two functionally opposing pathways: motor-facilitating direct and motor-suppressing indirect. An overactive indirect pathway leads to the cardinal symptoms of PD: bradykinesia and immobility. To test the efficacy of pallidal stimulation to reduce indirect pathway activity and alleviate parkinsonian motor symptoms we used an optogenetic approach to modulate activity in the GPe in a global or cell-selective manner. Our results demonstrate that global increases or decreases in GPe activity are minimally effective at restoring movement in bilaterally dopamine-depleted mice but in contrast cell-specific stimulation strategies were highly effective. Specifically activation of Parvalbumin-positive (PV-GPe) neurons or inhibition of Lim homeobox 6-positive (Lhx6-GPe) neurons restored movement to near pre-lesion levels. Intriguingly this behavioral rescue did not cease at the end of stimulation but persisted for hours. At the end of the 4-hour experiment all mice still exhibited near pre-lesion levels of locomotion. For comparison we tested the ability of direct-pathway stimulation to rescue movement in bilaterally-depleted mice. Behavioral recovery as a result of direct pathway stimulation was neither as robust nor as persistent as cell-specific manipulations in the GPe. In future experiments we will use in vivo electrophysiology within the output nucleus of the BG to observe circuit-level alterations before during and after the optogenetic stimulation. In summary these results demonstrate that cell-specific activation of PV-GPe or inhibition of Lhx6-GPe neurons provide a long-lasting recovery in motor function and establish the existence of two functionally distinct cell populations in the GPe.

Afternoon Poster Session
Location: Row B
Poster #26

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Kevin Mohsenian	Graduate	Gandhi	Bioengineering

Interceptive saccades revisited: a comparison of saccades to stationary and moving targets

Natural environments are dynamic and filled with sensory information that could be used by an organism to guide behaviors necessary for survival. Animals are able to extract relevant information from their environment by aligning their specialized sensory apparatus (e.g. the retinal fovea) with stationary and moving objects. Rapid eye movements have been used to study sensory motor and cognitive processes in primates but most of this research has emphasized the use of stationary targets. Under these circumstances the metrics and kinematics of saccades have been well characterized (Leigh & Zee 2015); however there have been relatively few in-depth descriptions of horizontal vertical and oblique interceptive saccades using a large range of target speeds and directions. The current abstract reports data collected from two rhesus monkeys and five human subjects who performed a delayed saccade task in which the delay duration starting target location and target speed (range: 10¬60 deg/s) and direction (inward outward upward downward) were varied randomly to elicit saccades with different vectors (amplitude and directions). Delay trials using stationary targets placed along moving target paths were randomly interleaved with delay trials using moving targets. Eye position was recorded using magnetic search coils and an eye¬tracker system for non¬human primates and humans respectively. Preliminary data are similar for both species. Analyses indicate that saccade metrics between stationary and moving targets may be more similar than previously proposed (Guan et al. 2005 Keller et al. 1996). We observed no differences in the duration peak velocity average velocity latency and saccadic error between amplitude matched saccades used to foveate stationary and moving targets across directions and speeds. The discrepancies between our observations and those previously reported could be a function of task differences. For instance we used a delay saccade task and most previously reported data were collected using a step saccade task. We also interleaved many more target trajectories than previous studies. These results suggest that the interceptive saccade vector encoded in the programming pathway is transformed in a similar temporal pattern in the brain stem as traditional saccades.

Afternoon Poster Session
Location: Row E
Poster #65

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Shahir Mowlaei	Postdoctoral	Ghuman	Neurological Surgery

Intrinsic Brain Networks are Organized by Frequency Relationships

Studies have increasingly demonstrated the importance of oscillatory dynamics in neural coding and interregional communication. While it has become clear that frequency-specific activity is a critical feature of brain activity it remains unclear whether brain networks organize by “frequency band” or whether the spectrum does not enforce functional brain network organization. Specifically here we ask if there is a functional parcellation of the frequency spectrum or not in resting-state magnetoencephalography (MEG) data based on large-scale brain network connectivity patterns. To answer this question we used network analyses and unsupervised and supervised pattern recognition algorithms in conjunction with whole brain MEG resting-state connectivity measures. Specifically we recorded 5 minutes of eyes open fixated resting-state MEG data from 34 healthy subjects. After artifact removal in each subject for each frequency from 0.5-50 Hz with 0.5 Hz steps we calculated the source-localized all-to-all connectivity matrix based on phase locking values between each pair of points on the cortex (5124x5124 connectivity matrix). Using matrix and network similarity measures we then assessed the spatial similarity of these full connectivity matrices between each pair of frequencies. Unsupervised and supervised analyses were used to assess whether there was consistent groupings of frequencies across subjects. The results of this analysis show that there are between 7 to 9 data-driven frequency bands that organize intrinsic brain networks. These bands roughly correspond to classic frequency bands. The bands also show significant consistency across subjects allowing one to classify each frequency to the correct band at the single subject level with relatively high accuracy. The results also show that there is a substantial spatial overlap between the spatial topography of the theta and low beta bands. Furthermore the results show that the low and high beta bands are substantially distinct and therefore should not be grouped together. In addition we used network analyses to determine the characteristic brain networks that correspond to each frequency band. Taken together these results suggest that frequency bands are a strong and consistent organizing force of large-scale intrinsic brain networks.

Afternoon Poster Session
Location: Row F
Poster #69

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Matthew Murphy	Postdoctoral	Vazquez	Radiology

Comparison of Neuronal and Hemodynamic Dynamic Connectivity Calculated Using GCaMP Mice Data

Low-frequency, spatially coherent fluctuations present in functional magnetic resonance imaging (fMRI) time series have had a tremendous impact on brain connectomics. Their dynamic character has highlighted the complexity of brain rhythms [1-6]. Since hemodynamic signals (e.g. fMRI) are of vascular origin, the degree to which hemodynamic measurements can capture neuronal dynamics remains unclear. Hence, studies that investigate the relationship between dynamic connectivity metrics measured from neuronal and hemodynamic signals are needed. Our group previously used a transgenic animal model to simultaneously acquire bi-hemispheric images sensitive to neuronal and hemodynamic signals. We showed that hemodynamic connectivity is highly correlated with neuronal connectivity in scans >5 min [7]. This work used the same animal model and imaging method to evaluate the agreement between neuronal and hemodynamic signals using sliding window (SW) and dynamic conditional correlation (DCC) metrics [8]. Methods: Transgenic mice expressing GCaMP3, a fluorescent calcium indicator that reports changes in intracellular calcium concentration that accompany spiking activity [9], were used to simultaneously image ongoing changes in neuronal activity (GCAMP) as well as hemodynamic measurements of blood oxygenation (OIS-BOLD, analogous to fMRI) from the same animals (n=6). Bi-hemispheric GCAMP and OIS-BOLD images were acquired at 10 Hz from the exposed superior surface of the mouse brain under light ketamine anesthesia (30 mg/kg/hr) for 5 to 20 min periods. Pre-processing consisted of temporal band-pass filtering (0.02-0.20Hz). Then, k-means clustering was used on the GCAMP data to obtain 6 regions-of-interest (Figure 1) [6,7]. GCAMP and OIS-BOLD ROI time series were extracted for each mouse. We first examined the SW lengths for which the GCAMP and OIS-BOLD connectivity matrices were significantly correlated ($r>0.47$ corresponds to $p<0.05$). Over non-overlapping windows, the average SW correlation and fraction of windows with significant relationships are reported. We then examined the temporal sampling resolution for which comparisons between the GCAMP DCC and OIS-BOLD DCC connectivity matrices were significantly correlated. Results: GCAMP (neuronal) and OIS-BOLD (hemodynamic) time series were used to calculate SW and DCC connectivity matrices (Figure 2). In general, DCC captured more transient inter-node dynamics compared to SW, but these properties depended on the SW window length (Figure 2B and 2C). To examine this further, for each non-overlapping SW window, the inter-node connectivity of the GCAMP data was compared to that of the OIS-BOLD data and tested for significance using a correlation analysis. The average correlation shows significant relationships for window lengths over 20 sec, while the average fraction of significantly correlated windows was >80% for windows >40 sec (Figure 3). A similar analysis of the GCAMP and OIS-BOLD DCC connectivity shows that average significant relationships were observed for data with temporal resolution >1.4 sec, and >80% of the comparisons were significant for temporal resolutions >2.2 sec. Adjusting for temporal lags between the GCAMP and OIS-BOLD time series did not alter these results. Conclusions: The hemodynamic signals measured in this study were able to capture dynamic changes in neuronal connectivity over time scales >20 sec for sliding window correlation (SW) methods. In addition to capturing more transient changes in connectivity using the DCC algorithm, we also observed significant agreement between hemodynamic and neuronal connectivity measurements using DCC for data with temporal sampling >1-

2 sec (typical of many fMRI studies). The changes in neuronal and hemodynamic connectivity are likely bounded by the dynamics of the underlying physiology.

Afternoon Poster Session
Location: Row D
Poster #50

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Sarah Najjar	Graduate	Gold	Neurobiology

Optogenetic investigation of epithelial-neuronal communication in the colon

Functional gastrointestinal disorders such as irritable bowel syndrome (IBS) affect up to 25% of the U.S. population and their pathophysiology is largely unknown. These painful disorders are characterized by visceral hypersensitivity which originates in the primary afferent neurons innervating the colon. In addition to intrinsic changes in these afferents epithelial cells in the colon may also contribute to this hypersensitivity. It is known that these epithelial cells can release neurotransmitters such as ATP acetylcholine and serotonin but the nature of their communication with colonic afferents remains unclear. Using optogenetic techniques in which channelrhodopsin (ChR2) is targeted specifically to the colon epithelial cells we are able to activate these cells without the simultaneous activation of primary afferents that occurs with application of mechanical and chemical stimuli onto the colon. In an ex vivo preparation we isolated the distal colon and intact pelvic nerve and recorded the activity of single fibers. Our studies show that optogenetic activation of the epithelium can directly initiate robust action potential firing in colonic afferents of different functional classifications. We further showed through pharmacology that ATP is an important chemical messenger in this epithelial-nerve communication. Application of ATP receptor antagonists decreased or abolished action potential in over half of the afferents that responded to epithelial cell activation. With additional studies targeting other receptors on primary colonic afferents we seek to further elucidate the mechanisms of epithelial cell-derived activation of colonic afferents and its relation to pain. Furthermore we will investigate how this communication changes during a state of chronic inflammation as seen in inflammatory bowel disease. Thus better understanding of the epithelial-neuronal interaction will reveal potential targets for treatment of intestinal pain.

Afternoon Poster Session
Location: Row B
Poster #19

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Ameya Nanivadekar	Graduate	Gaunt	Bioengineering

Selectivity of afferent microstimulation at the DRG using epineural and penetrating electrode arrays

Introduction: We have previously shown that microstimulation of the dorsal root ganglia (DRG) using penetrating electrodes can selectively recruit distal branches of the sciatic and femoral nerves in an acute preparation. In chronic implants however the immune response to penetrating electrodes can diminishes the long-term viability of such an approach. Epineural electrodes such as nerve cuffs which do not penetrate the nerve can achieve a stable interface with peripheral nerves albeit with lower selectivity. The goal of this study was to evaluate the recruitment properties of epineural electrodes placed on the surface of the DRG and compare their performance with that of penetrating electrodes. Here we compare the number of selectively recruited distal nerve branches and the threshold stimulus intensities between penetrating and epineural electrode arrays. Methods: To quantify the selectivity of DRG stimulation we recorded antidromic propagation of evoked action potentials along many distal branches of the femoral and sciatic nerves in 3 cats. Antidromic activity was recorded via several nerve cuff electrodes implanted around up to 9 distal branches of the femoral and sciatic nerve trunks. In each cat five-contact nerve cuff electrodes were implanted around the sciatic and femoral trunks. Distal branches were instrumented with two-contact nerve cuffs made from split silicone tubing and stainless steel wire. A custom book electrode was implanted on the tibial nerve and its branches. A laminectomy was performed to isolate the L5-S1 DRGs and epineural electrodes (silicone and platinum 750 µm diameter; Ripple LLC) were placed on the epineural surface. A binary search was carried out to identify the minimum stimulus intensity that evoked a response at any of the distal cuffs as well as whether the threshold response selectively occurred in only a single distal nerve branch. Results: Epineural stimulation was selective for 71% of all electrodes (33/46) as compared to 85% for penetrating microelectrodes across six ganglia in 3 cats. The recruitment threshold (median = 5.81 nC/phase) and dynamic range of epineural stimulation (median = 0.89 nC/phase) was significantly higher than penetrating stimulation (0.68 nC/phase and 0.36 nC/phase respectively). The patterns of nerve recruitment for each DRG were similar for stimulation through epineural and penetrating electrodes. Conclusion: Despite higher recruitment thresholds epineural stimulation provides nearly comparable selectivity and superior dynamic range to penetrating electrodes. These results suggest that it may be possible to achieve a highly selective neural interface with the DRG without penetrating the epineurium.

Morning Poster Session
Location: Row C
Poster #42

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Kileigh Nassau	Undergraduate	Kline	Physical Medicine and Rehabilitation

Aripiprazole benefits functional outcome after experimental brain trauma and does not attenuate the benefits of environmental enrichment

Introduction: The typical antipsychotic drug (APD) haloperidol (HAL) a D2 receptor antagonist has been shown to impede functional outcome after experimental traumatic brain injury (TBI). Furthermore the deleterious effects persist for up to 3 months after drug withdrawal. Moreover a recent study showed that HAL reduced the effectiveness of environmental enrichment (EE) a preclinical model of neurorehabilitation. Because agitation is common after TBI patients are provided APDs so that they can be safely managed. However many patients in rehabilitation will only experience agitation occasionally and thus will receive APDs intermittently. Hypotheses: Aripiprazole (ARIP) a partial D2 and 5-HT1A receptor agonist will not impair recovery or reduce the effectiveness of EE regardless of whether administered once every day (i.e. chronic agitation) or once every other day (occasional agitation). Methods: Anesthetized adult male rats received a cortical impact of moderate severity or sham injury and were then randomly assigned to EE or standard (STD) housing. Treatments with ARIP (0.1 mg/kg; i.p.) or vehicle (VEH; 1.0 mL/kg; i.p.) began 24 hr after injury and continued once daily for 19 days or once every other day for the same period. Motor (beam-balance/walk) and cognitive (spatial learning) outcome were assessed on post-operative days 1-5 and 14-19 respectively. Results: Motor and cognitive function was significantly improved in the TBI+EE+VEH vs. TBI+STD+VEH group (p<0.05). Moreover the TBI+EE+ARIP groups regardless of dosing regimen performed significantly better on all endpoints relative to the TBI+STD+VEH controls (p<0.05) but did not differ from one another or from TBI+EE+VEH (p>0.05). Conclusions: The data replicate previous work from our laboratory showing the EE improves functional outcome after TBI. Furthermore ARIP unlike HAL did not impair recovery or reduce the efficacy of EE which supports the hypothesis. Significance: ARIP is beneficial on its own and does not negate the benefits of rehabilitation (i.e. EE) and thus may be used to control TBI-induced agitation and aggression without compromising recovery.

Afternoon Poster Session
Location: Row E
Poster #62

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Felix Nguyen	Graduate	Jankowitz	School of Medicine

Evaluation of Brain Injury and Cognitive Outcome Following Treatment of Unruptured Intracranial Aneurysms

Background: Unruptured intracranial aneurysms (UIAs) are treated through endovascular embolization or open surgical clipping to prevent the catastrophic outcomes that follow aneurysmal subarachnoid hemorrhage (aSAH). However treatment of UIAs is associated with a >10% risk of neurologic morbidity with nearly 6% of patients suffering persistent cognitive impairment 1-year after treatment. The structural etiology of impaired cognition following treatment of UIAs has not been delineated. One hypothesis is that cognitive impairment results from disruption of white matter fiber tracts caused by intra-procedural tissue retraction and/or ischemic mechanisms. The primary objective of this study was to characterize and quantify damage to white matter fiber tracts following surgical or endovascular repair of UIAs utilizing a diffusion spectrum imaging (DSI) technique called High Definition Fiber Tractography (HDFT). Methods: We performed a prospective observational study of patients undergoing treatment of UIA through either surgical clip occlusion or endovascular coil embolization. White matter fiber tract imaging and neuropsychological tests were administered both prior to and following treatment of UIAs. Imaging acquisition was performed on the 3T TrioTim MRI scanner (Siemens; Erlangen Germany). White matter fiber tracts analyzed included the arcuate fasciculus (AF) corpus callosum (CC) inferior occipitofrontal fasciculus (IOF) and uncinate fasciculus (UF). All fiber tractography was performed with DSI-Studio software using quantitative anisotropy (QA)-based generalized deterministic tracking; fiber tracts were reconstructed using regions of interest drawn on patients' diffusion maps. The presence of white matter tract damage was defined as a significant decrease post-treatment in mean QA percentage and volume when compared to pre-treatment values as determined through two-tailed unpaired t-test (a priori statistical significance p < 0.05). Results: Complete data were available for 3 patients undergoing treatment of UIA; 2 patients underwent surgical clipping and 1 had endovascular coiling for UIA repair. Patient 1 (right and left internal carotid artery aneurysms coil embolization) had reduced volume in the left AF (% change = -3.09) left IOF (% change = -6.75) and right IOF (% change = -3.49). No significant changes in QA for any track was observed in Patient 1. Patient 2 (right posterior communicating artery aneurysm clip repair) had decreased QA in the right AF (% change = -3.09) but this was not statistically significant (p = 0.129). The left UF of Patient 2 had significantly decreased QA (% change = -6.67; p < 0.01) and volume (% change = -18.1%). Patient 3 (right middle cerebral artery aneurysm clip repair) experienced volume decreases in the right IOF (% change = -23.4%) and right UF (% change = -19.3%). Reduced mean QA percentage was found in the right IOF (% change = -18.9 p < 0.01). No patient demonstrated decreased QA or volume in the CC tract. Conclusions: Surgical clip occlusion and endovascular coil embolization for repair of UIAs were both found to be associated with damage in white matter fiber tracts demonstrated by statistically significant decreases in AF IOF and UF mean QA percentage and volume. Forthcoming analyses will assess whether these findings correlate with cognitive outcomes measured by neuropsychological testing.

Afternoon Poster Session
Location: Row D
Poster #51

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Robert Nicholls	Faculty	Nicholls	Pediatrics

Porcine model of phenylketonuria generated by CRISPR/Cas9 genome editing will enable brain studies and discovery of novel neurotherapeutics

Phenylalanine hydroxylase (PAH) deficiency traditionally termed phenylketonuria (PKU) results in accumulation of phenylalanine (PHE) leading to neurotoxicity and severe developmental disabilities. For over 50 years dietary PHE restriction has been the standard intervention; however after adolescence therapy non-compliance is high. Indeed most adolescents and adults exceed the recommended therapeutic range for blood PHE (≤ 360 µMol/L) leading to late onset neurodevelopmental cognitive ADHD and psychiatric symptoms. Thus there is an urgent need for more effective therapeutic modalities for PKU and even a modest improvement in metabolic capacity that increases PHE tolerance would reduce reliance of dietary PHE restriction to ease the burden of therapeutic compliance which would lead to improved neurologic function. While rodent models biochemically model classical PKU they do not display the neurological manifestations of the human disease. Since pigs more closely resemble humans in brain size development and anatomy as well as physiology and genome we propose that a PAH-null pig will provide a superior animal model for characterizing PKU neuropathophysiology and exploring novel therapies. Using bioinformatics analyses of DNA sequence fragments we assembled the 13 exon pig PAH gene encoding a 452 amino acid enzyme and characterized expression of PAH in minipig tissues. The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 system utilizes a guide RNA (gRNA) to target the Cas9 endonuclease to a specific DNA sequence to generate a double-strand break (DSB). Repair of two DSBs often deletes the region between them. By expressing Cas9 in an in vitro cell model with pairs of CRISPR gRNAs targeting non-polymorphic sites in PAH introns 5 and 6 we identified optimal reagents that generate deletions or inversions of exon 6 that inactivate the gene. DNA sequence analysis confirmed the recombinant breakpoints and that DNA repair of the DSBs involved non-homologous end-joining. Using zygote injections of RNA encoding a pair of gRNAs and Cas9 and culture in vitro for 1 week ~ 48% of pig pre-implantation embryos had deletions of PAH-exon 6. Subsequently the procedures were repeated but with embryo transfer (ET) to surrogates with one of five ETs giving rise to a pregnancy from which two female piglets were delivered. Biochemical analyses at 5 days of age showed normal blood PHE levels in one (141 µM) with the other having hyperphenylalaninemia (2063 µM) consistent with classical PKU. Molecular analyses including deletion-PCR and DNA sequencing demonstrated that the former was heterozygous for a deleted allele and an intact allele having mutations at each gRNA target site while the PKU piglet has deletions involving each allele. Presently clinical neurological and behavioral phenotypes of the first PKU pig are under assessment. In conclusion we propose that our development of a porcine model of PKU will provide an optimal pre-clinical model for brain-related studies as well as for development of new therapeutic approaches such as new medical food formulations drugs or experimental gene and cellular (e.g. hepatocyte transplantation) therapy.

Afternoon Poster Session
Location: Row D
Poster #44

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Peter Niesman	Undergraduate	Kline	Physical Medicine and Rehabilitation

Motor and Cognitive Function of Day-tested Groups Compared to Night-tested Groups

The majority of behavioral assessment studies are conducted during the day which is not when rats are most active. This discrepancy may preclude optimal performance. Hence the goal of this study was to determine if differences in neurobehavior exist in traumatic brain injured (TBI) rats when assessed during the day vs. night. The hypothesis was that the night group would perform better than the day group in all behavioral tasks. Isoflurane-anesthetized adult male rats received a controlled cortical impact (2.8 mm depth at 4 m/sec) or sham injury and were randomly assigned to either day (1:00 - 3:00 p.m.) or night (07:30 - 09:30 p.m.) testing. Motor function (beam-balance and beam-walk) was conducted on post-operative days 1-5 and cognitive performance (acquisition of spatial learning) was assessed on days 14-18. No significant differences were revealed between the TBI rats tested during the day vs. night for beam-balance beam-walk or water maze (p's < 0.05). These data suggest that the time rats are tested has no impact on their performance which does not support the hypothesis. The finding is important because it validates the interpretations from numerous studies conducted when rats were tested during the day vs. their natural active period.

Afternoon Poster Session
Location: Row A
Poster #1

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Emily Oby	Postdoctoral	Batista	SNI

Learning to generate new patterns of neural activity

Learning requires networks of neurons to generate new patterns of activity. Brain-computer interface (BCI) users can learn to modulate neural activity to control a computer cursor via a relationship specified by the experimenter and this allows us to study the changes in neural population activity that accompany learning. We used a closed-loop BCI paradigm to study learning-related changes among a population of neurons recorded in the primary motor cortex (M1) of a Rhesus monkey. Here we examine the population neural changes that accompany learning by considering first behavioral changes and then examining neural activity changes directly. We use dimensionality-reduction techniques to observe neural changes. The activity of a neural population can be represented as a point in a high-dimensional neural space wherein each dimension corresponds to the activity of one neuron. Characteristic patterns of co-modulation among the neurons comprise a low dimensional subspace within the neural space. We refer to this space of naturally-occurring neural activity patterns as the intrinsic manifold (IM). We can create new BCI mappings for the monkey to learn that require the monkey to generate patterns within the IM or outside the IM. In our previous work we found that the existing patterns of neural co-modulation shape learning: monkeys could learn perturbations of a BCI that lie within the IM and thus conform to existing patterns of neural co-modulation on the timescale of hours but usually could not learn to generate neural co-modulation patterns outside of the IM at least not within a single day (Sadtler et al. 2014). In recent experiments we have seen that monkeys can learn to control a BCI that requires patterns outside of the IM given several days of practice. Thus outside-manifold perturbations are not fundamentally unlearnable and the constraints imposed by the IM are not absolute. Instead the constraints and presumably the IM itself are plastic. The improvements in BCI behavior during multi-day learning of outside-manifold perturbations imply that the co-modulation patterns of the neural population have changed. In particular as the performance with the outside-manifold perturbation improves over days the patterns of neural activity are correspondingly further from the natural patterns of neural activity described by the IM. We interpret this to mean that the monkeys have learned to produce novel neural activity patterns i.e. patterns of activity that lie outside the intrinsic manifold.

Sadtler PT Quick KM Golub MD Chase SM Ryu SI Tyler-Kabara EC Yu BM Batista AP. Neural constraints on learning. Nature. 2014 Aug 28; 512(7515):423-6.

Morning Poster Session
Location: Row C
Poster #37

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Darik O'Neil	Undergraduate	Bondi	Department of Physical Medicine & Rehabilitation

ENVIRONMENTAL ENRICHMENT ATTENUATES TRAUMATIC BRAIN INJURY-INDUCED INFLAMMATION AND OXIDATIVE STRESS

Environmental enrichment (EE) has been shown to facilitate motor re-cov-ery and hasten spatial learning and memory when pro-vided after traumatic brain injury (TBI). These effects are ob-served in both male and female rats as well as adult and pediatric populations. Typical explanations for the EE-mediated benefits are re-ductions in hippo-campal cell loss and in-creased neuro-genesis. The goal of this study was to assess other patho-logical mecha-nisms that are pre-valent after TBI. Anesthetized male rats received a controlled cortical impact or sham injury then were housed in EE or standard (STD) conditions and subsequently evalu-ated for motor (beam-walk/balance) and cognitive (Morris water maze) per-form-ance as well as in-flam-mation via micro-glial activation (Iba1) and oxi-dative stress (3-NT). EE impro-ved both motor and cognitive per-form-ance relative to STD (p < 0.05). More-over EE down-regu-lated TBI-induced Iba1 ex-pression levels in both hemispheres (p < 0.05) and also re-duced 3-NT immuno-staining in the ipsilateral hemisphere (p < 0.05). These data sug-gest that in ad-di-tion to neuro-genesis EE may mediate benefits after TBI by attenuating in-flam-mation and oxi-dative stress.

Morning Poster Session
Location: Row D
Poster #48

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Puja Parekh	Graduate	McClung	Neurobiology

Reduced excitatory synaptic plasticity of nucleus accumbens medium spiny neurons in a genetic mouse model of mania

It is well established that the circadian molecular clock regulates monoaminergic systems controlling mood anxiety and reward behavior. While disruptions in the circadian gene Clock are associated with increased risk for bipolar disorder (BD) the underlying molecular and synaptic mechanisms remain poorly understood. Using ex vivo whole cell patch clamp electrophysiology in ClockΔ19 mutant and wildtype (WT) mice we characterized alterations in excitatory synaptic transmission strength and intrinsic excitability of NAc neurons. We performed protein crosslinking and Western blot analysis to examine surface and intracellular levels and rhythm of the glutamate receptor subunit GLUA1 in the NAc. Viral-mediated overexpression of GluA1 in the NAc and behavioral analysis were used to determine whether the manic-like phenotype could be rescued. ClockΔ19 mice display reduced AMPAR-mediated excitatory synaptic responses (mEPSCs and EPSCs) at NAc medium spiny neurons (MSNs) across the light/dark cycle compared with WT littermates. We find that these alterations are likely postsynaptic as presynaptic release of glutamate onto MSNs is not disrupted in mutant mice. Additionally NAc surface protein levels and the rhythm of GLUA1 are decreased in Clock mice diurnally consistent with reduced functional synaptic response. Furthermore we observed a significantly hyperpolarized resting membrane potential of ClockΔ19 MSNs suggesting lowered excitability. Lastly overexpression of functional GluA1 in the NAc of mutant mice is able to normalize aspects of their manic-like phenotype. Together our novel findings demonstrate that NAc excitatory signaling is integral to the effects of Clock gene disruption on mania-related behaviors.

Afternoon Poster Session
Location: Row C
Poster #32

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Emily Parker	Graduate	Fisher	Department of Psychiatry

Pyramidal Cell morphology in mouse Primary Auditory Cortex

Schizophrenia (Sz) is a debilitating disease that besets approximately 1% of the global population. Dendritic spine deficits in primary auditory cortex (A1) likely contribute to auditory impairment in Sz GWAS and rare variant studies have identified risk genes associated with Sz including CACNB4, which encodes the beta4 subunit of voltage-gated calcium channels. Previously, we demonstrated that CACNB4 levels are inversely correlated with density of small dendritic spines in A1 in a postmortem study of Sz patients. Similarly, overexpression of CACNB4 in primary neuronal culture resulted in reduced density of small spines. Now we are interested in whether overexpression of CACNB4 in vivo confers morphological alterations of pyramidal cells (PCs) in A1. We performed a proof of concept study using an Adeno-associated vector expressing GFP (AAV2-CaMKIIα-EGFP) to visualize and characterize PC morphology in A1 in adult wild type mice. Determining normative morphology in A1 will enable us, and others, to better identify and characterize PC abnormalities in mouse models of auditory impairment and disease.

Morning Poster Session
Location: Row F
Poster #75

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Jenna Parrish	Graduate	Sibille	Psychiatry

Estradiol modulation of the renin angiotensin system and the regulation of fear extinction

Low estradiol levels during fear extinction impair extinction consolidation resulting in increased fear expression during extinction recall in women and female rats. However the mechanism by which this occurs is unknown. Estrogen modulates the renin angiotensin system (RAS) by downregulating the hypertensive axis (including angiotensin II type I receptors; AT1R) of the RAS. Our lab has found that systemic administration of the AT1R antagonist losartan prior to fear extinction enhances extinction consolidation and reduces fear during extinction recall in female rats with low estradiol levels. Next we investigated potential mechanisms by which estradiol interacts with the RAS to enhance extinction consolidation. Adult female Sprague Dawley rats received injections of levonorgestrel (0.5mg/kg/day) a hormonal contraceptive (HC) that lowers circulating estradiol levels or vehicle for 5 days. Blood and brains were collected for further analysis. Estradiol and angiotensin II levels were measured in serum. Brain sections were mounted on slides and AT1R autoradiography was performed to compare AT1R binding between groups. In a separate cohort brains were collected from rats treated with HC or vehicle. Tissue punches were taken from brain regions associated with fear and qPCR was performed to compare AT1R mRNA expression between groups. Finally another cohort of rats was run through a cued fear conditioning paradigm and angiotensin II or vehicle was administered systemically before or immediately after the extinction session in female rats with high estradiol levels. Extinction recall was tested 24 hours later. The HC treated group had significantly decreased levels of estradiol and significantly increased levels of angiotensin II compared to the vehicle treated group. No significant differences in AT1R expression or binding were found between HC and vehicle groups. Systemic angiotensin II had no effect on extinction acquisition. However pre-extinction session treatment with angiotensin II produced a non-significant increase in freezing during extinction recall. In conclusion angiotensin II which is part of the hypertensive axis of the RAS and an agonist of the AT1R was increased in rats with low estradiol levels but no differences were found at the receptor level. This suggests that extinction consolidation deficits in rats with low estradiol may be due to increased angiotensin II but additional behavioral studies are needed to clarify this relationship. Understanding the mechanism by which circulating hormones affect extinction learning could aid in the development of better treatments for people who suffer from anxiety disorders.

Morning Poster Session
Location: Row A
Poster #2

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Matthew Phillips	Graduate	Wills	Neuroscience

Enhancement of NMDA Receptor Desensitization by the Alzheimer's Disease Drug Memantine

NMDA receptors (NMDAR) play an essential role in synaptic development plasticity and neuronal survival principally through their collective effect upon magnitude and timing of Ca2+ influx. However pathological conditions can lead to overactivation of NMDARs resulting in excitotoxicity and cell death due to excess Ca2+ influx. Calcium-dependent desensitization (CDD) of NMDARs is a crucial process that under normal conditions works to prevent excess Ca2+ influx via a negative feedback mechanism initiated by increased intracellular levels of Ca2+. Although the structure of the NMDAR Ca2+-dependent desensitized state is unknown interactions of the carboxy-terminal domain (CTD) of the GluN1 subunit with allosteric regulators and CTDs of other NMDAR subunits are vital to CDD. Additionally recent work in our lab has found that the NMDAR channel blocker memantine (Mem) slows NMDAR recovery from calcium-dependent desensitized states. Here we further examine the relation between the GluN1 subunit CTD the Ca2+-dependent desensitized state and Mem using whole-cell recordings from HEK cells expressing wild-type NMDARs composed of the GluN1 and GluN2A subunits (GluN1/N2A receptors) or mutant receptors with truncated CTDs (ΔCTD). As expected GluN1ΔCTD/N2A receptors were found to exhibit reduced desensitization. Interestingly GluN1ΔCTD/N2A receptors displayed a decreased sensitivity to Mem and Mem had no effect on the time course of recovery from desensitization of GluN1ΔCTD/N2A receptors. These results support the hypothesis that Mem enhances desensitization of NMDARs through stabilization of a Ca2+-dependent desensitized state giving new insight into Mem’s mechanism of action.

Morning Poster Session
Location: Row E
Poster #55

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Sean Piantadosi	Graduate	Sibille	Psychiatry

Identifying cellular mechanisms underlying the anti-compulsive properties of fluoxetine

BACKGROUND: Serotonin reuptake inhibitors (SRIs) are the first-line and most efficacious pharmacotherapeutic treatment for obsessive compulsive disorder (OCD). However complete remission following SRI treatment is rare (< 20%) and only 40-60% of patients report improvement in symptoms following monotherapy. It is therefore important to determine the neural changes that underlie responsiveness vs resistance to treatment. Aberrant striatal activity may underlie OCD symptoms evidenced by functional imaging studies in OCD patients that demonstrate hyperactivity within the striatum. Notably successful treatment of OCD symptoms with SRIs reduces hyperactivity in the striatum of treatment-responsive patients suggesting a potential mechanism for treatment response. In addition a recent meta-analysis suggests that the therapeutic effects of SRIs in treatment-responsive OCD patients may occur much sooner than previously believed suggesting that short term changes in neural activity may be important. METHODS: Sapap3 knockout (KO) mice which have both a hyperactive striatum and compulsive OCD-like grooming phenotype were injected with AAV-GCaMP6m and implanted with a GRIN lens in the centromedial striatum (CMS) to visualize striatal calcium activity during spontaneous grooming behavior. All mice received 7 days of treatment with the SRI fluoxetine and underwent imaging and grooming assessments on days 3 5 and 7 of treatment. RESULTS: Sapap3-KO mice displayed elevated grooming behavior at baseline and treatment with fluoxetine decreased grooming. Interestingly in contrast to published studies this reduction in compulsive grooming occurred more rapidly than expected after just 3 days of treatment. At baseline Sapap3-KO mice also had elevated striatal activity as measured by calcium events relative to WT animals. This increase in calcium activity during grooming behavior was reduced by successful fluoxetine treatment. Preliminary studies selectively examining D1-medium spiny neurons (MSN) in Sapap3-KO mice also suggest increased baseline activity which may be decreased following treatment. Ex vivo data suggest that fluoxetine may be modulating the activity of striatal fast spiking interneurons (FSIs) in order to normalize striatal activity. CONCLUSION: Hyperactivity of the striatum and compulsive grooming behavior can be reversed with successful SRI treatment in a valid mouse model of OCD-like behaviors. SIGNIFICANCE: Understanding cell-type specific effects of successful and unsuccessful SRI treatment may help us develop treatments for patients that have better efficacy and fewer side effects.

Afternoon Poster Session
Location: Row B
Poster #22

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Joseph E. R. Pichamuthu	Postdoctoral	Vorp	BIOENGINEERING

WALL STRESS OF CEREBRAL ANEURYSMS DEPENDS ON RESIDUAL VOLUME AFTER COILLING NOT COIL PACKING DENSITIES

INTRODUCTION Endovascular coil embolization is commonly used for treating cerebral aneurysms (CAs) by placing metallic coils in the aneurysmal dome to induce a coil thrombus mass (CTM)[1]. Successful endosaccular packing mainly depends on the morphological features and size of the aneurysm and the relationship of the aneurysm to the cerebral arteries. However a significant number of CAs are incompletely coiled and recurrences are expected in the range of 11-36% after coil embolization depending on the degree of filling achieved [2]. The coil packing density (CPD) after coiling is therefore a major concern. Computational models of CA coiling have determined alterations on wall shear stress in the presence of the CTM [3] but the effect on wall stress has not yet been reported except in a recent study by our group on a single CA model [4]. Wall stress assessment may help clinicians determine the level of coil embolization that is necessary to prevent recanalization and help guide the need for subsequent re-intervention. Therefore the purpose of this work was to estimate wall stress in patient-specific CAs prior to coiling as well as after coiling with different degrees of CPD or different residual volume (RV) after coiling. METHODS Virtual 3D geometries of CAs were constructed from Digital Subtraction Angiography scans of patients (n=7) under observation using an approved IRB (#PRO13080334). First scans were imported into Mimics (Materialise Plymouth MI) where lumen boundaries of CAs and their parent vessels were profiled using a pixel thresholding algorithm. After isolation the boundaries were rendered into coarse 3D volumes modeling the CAs. The models were further smoothed corrected for rendering flaws and patched in Geomagic (3D Systems Rock Hill SC). Surface geometries of CA walls were then exported and a CTM was created for each CAs in SolidWorks (Dassault Systéms Waltham MA). CTMs were modeled as solids filling the dome region of the aneurysms. CA surface models and CTM solid models were then meshed into quadrilateral shell elements and tetrahedral solid elements respectively in the commercial finite element analysis software Abaqus (Dassault Systéms Waltham MA). Each CA wall was treated as a homogenous nonlinear isotropic hyper-elastic and incompressible material with a uniform thickness of 0.36mm and modeled as reported in the literature with the strain energy function Wwall [5]: W_wall=C_1 (I_1-3)+C_2 (I_2-3)+C_3 (I_1-3)(I_2-3) \t(1) where C_1 C_2 and C_3 are material parameters [59.8 16.8 5710] characteristic of CA wall properties in (kPa). I_1 and I_2 and are strain invariants. CTMs were modeled into distinct homogeneous nonlinear isotropic hyper-elastic and compressible materials. Five different mechanical properties of CTM were used in this analysis: four derived from in-vitro uniaxial compression test data of clotted blood with 0 10 20 or 30% CPD and one from literature measurement of the intraluminal thrombus from abdominal aortic aneurysm [6]. The strain energy function used for in-vitro data was derived using equation fitting built into Abaqus. A reduced fourth order polynomial strain energy function WCTM was created: W_CTM=∑_(i=1)^4▒〖C_i (I_1-3)〗^i (2) where C_i (defined in Table 1) is a set of parameters characteristic of CTM material properties. I_1 is a strain invariant. Table 1: Filling Material Parameters Filling\tCoefficient (kPa) \tC1\tC2 (x103)\tC3 (x104) ¬\tC4 (x106) Blood Clot\t92.14\t23.88 \t-80.41 \t11.03 CPD10\t405.97\t12.32 \t-35.26 \t4.41 CPD20\t336.03\t83.85 \t-281.30 \t38.53

CPD30\t702.10\t100.50\t-320.40 \t42.74 For RV simulation the distance between the parallel planes separating the sac base and dome was measured as aneurysm length and the solid sac was segmented into 25% 50% and 75% of this length which were used to quantify the RV after coiling. RESULTS Peak wall stress (PWS) was defined as the maximum wall stress noticed in the model and mean wall stress (MWS) was defined as the average von Mises stress acting on the aneu-rysm wall. Prior to coiling PWS (red color) was noticed at either dome or neck of aneurysm as seen in Fig. 1. Fig. 1: von Mises wall stress (Ncm-2) in representative side-wall (left) and branched (right) aneurysms using the mechanical properties of the AAA thrombus. PWS was maximum prior to coiling (top). When completely filled coiling effectively reduces PWS in the side-wall aneurysm but no beneficial effect on PWS was seen in branched aneurysm as there remained a stress concentration at the neck. Complete CTM filling eliminates PWS from dome and neck regions for all five CPD materials in simple aneurysms but not in branched aneurysms. There is no significant difference in the spatial distribution and magnitude of stress when the mechanical properties of clot versus intraluminal thrombus are used. In completely filled CAs the MWS was significantly lower than that of unfilled models (p < 0.05) for all CPDs and also between different CPDs (p < 0.05) as shown in Fig. 2. Fig. 2: Plot of dome mean wall stresses in log-scale for unfilled and different CPDs with no residual volume using the mechanical properties of clotted blood. MWS reductions in simple CAAs were significantly higher than that of branched models (p < 0.05). However within each model the MWS estimated for the aneurysmal dome region for each degree of RV (0 25 50 75 & 100) and for the parent vessels (P) were compared using the mechanical properties of the AAA thrombus for filling. Fig. 3 reflects the trend across our patient pool with wall stress averaged across all seven cases. Fig. 3: Comparison of AWS estimated for the aneurysmal dome region for different degrees of RV and for the parent vessel (P) in each patient model using the mechanical properties of AAA thrombus. Notice that the AWS of the unfilled aneurysmal dome region was twice that of the parent vessel in most of the models. The AWS of dome decreased to the level of the parent vessel in all cases for RV≤25% suggesting threshold filling. N=7 for each case. DISCUSSION Prior to coil embolization in both types of aneurysm the PWS was located in the aneurysmal region either at the neck or at the dome and the MWS of the dome region was at least twice that of the parent vessel. This is consistent with the greater propensity for rupture at the dome region seen clinically [7]. The CTM reduced the PWS in the dome region but the magnitude of PWS reduction depended on the type of CPD degree of RV and the aneurysm morphology. Our data suggests that for any useful outcome of coil embolization the CTM must cover the area of the wall where PWS occurs pre-treatment. Although statistically significant the reduction in resultant wall stress with increasing CPD is negligible in comparison to the difference observed after initial filling of CAs. The MWS of the dome was substantially reduced either to the level of MWS of parent vessel or less for RVs ≤ 25% suggesting the existence of a threshold level of RV for any beneficial wall stress shielding effect. These results support Sadato et al. which suggests that residual volume after embolization of CAs is the foremost consideration for preventing recanalization [8]. CTM filling did not show as much of a beneficial effect in branched aneurysm models as the PWS either remained nearly same at the neck or even elevated for different degrees of CTM filling. This may explain why certain patients are prone to recurrences and recanalization at the neck of the aneurysm after coil embolization. REFERENCES 1.\tRyttlefors M et al. Stroke 2008. 39(10): p. 2720-6. 2.\tPark JH. et al. Am J Neuroradiol 32 pp. 1756-1761. 3.\tKakalis NM. et al. IEEE tran med imag 2008. 27(6): p. 814-24. 4.\tPichamuthu J. et al. SBC 2012-80782 pp. 107-108 5.\tCostalat et al. J Biomech 44.15 2685-2691 2011 6.\tWang DH. et al. J Biomech Eng 123 pp. 536-539 7.\tCrompton M.R. Br Med J 1966. 1(5496): p. 1138-42 8.\tSadato et al. PLos One 11.5 2016.

Afternoon Poster Session
Location: Row E
Poster #68

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Alexander Poplawsky	Postdoctoral	Kim	Radiology

Vascular architecture with CLARITY suggests that contrast-enhanced high-resolution fMRI is dominated by microvessel dilation

Introduction: Functional magnetic resonance imaging (fMRI) measures the hemodynamic response to neuronal activity but more evidence is needed to understand how far the high-resolution fMRI response spreads relative to the evoked neuronal activity. The olfactory bulb is an ideal model system to study this issue because synapses localized to a single layer can be preferentially evoked by a selective stimulation. We previously showed that fMRI signal increases due to lateral olfactory tract (LOT) stimulation are highly localized to the evoked synapses in the external plexiform layer (EPL); but it is unknown whether dilation of local microvessels is the dominating source of our fMRI measurements. Methods: In α-chloralose anesthetized rats we stimulated LOT in a block design experiment (-200 μA 200 μs pulse duration 40 Hz ~1 min stimulus duration 4 min interstimulus interval); and acquired high-resolution (55 x 55 x 500 μm3) blood volume-weighted fMRI responses at 9.4 T. We then obtained line profiles from 330-μm thick slabs that orthogonally transected the bulb layers and measured the full width at half maximum (FWHM) of the evoked fMRI peaks due to LOT stimulation. In a different rat we rendered the right olfactory bulb transparent with CLARITY-based methods and stained the blood vessels with DyLight594 Tomato lectin (Vector Laboratories DL-1177) before imaging in 3D. We then compared the FWHM fMRI data to the vessel diameters lengths and volumes calculated by analysis of the CLARITY images. Results: The mean FWHM of the fMRI peaks was 347 ± 102 μm (mean ± SD n = 30 peaks from 5 rats 3 slices each rat 2 peaks each slice) where the mean anatomical thickness of EPL at these lines was 265 ± 65 μm. The fMRI spatial spread beyond the anatomical thickness of EPL was estimated by a least squares linear regression analysis. The regression intercept (± SE) which approximates this spread was 106 ± 65 μm (r2 = 0.34 p < 0.001 df = 28). With CLARITY microvessels that had diameters <12 μm accounted for the majority of the total vascular volume (65.8%) present in EPL and had an average length of 54.8 ± 41.2 μm (± SD n = 398 vessel segments). Conclusions: Our preliminary results indicate that the LOT-evoked fMRI signal spreads ~100 μm from the evoked layer EPL (~50 μm on each leg of the fMRI response peaks). This spread is consistent to the mean length of microvessels (~50 μm) the predominate vascular compartment in EPL.

Morning Poster Session
Location: Row B
Poster #27

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Arpan Prabhu	Graduate	Branstetter	Radiology

The CT Prevalence of Arrested Pneumatization of the Sphenoid Sinus in Patients with Sickle Cell Disease

Background: Arrested sphenoid pneumatization is an incidental radiologic finding on CT and MRI that may be confused with more aggressive pathologic conditions. No definite etiology for arrested sphenoid pneumatization has been established although changes in regional blood flow during childhood as is seen with sickle cell disease (SCD) have been proposed. The purpose of our study was to compare the prevalence of arrested pneumatization of the sphenoid sinus in patients with and without SCD. Methods: We retrospectively identified 146 patients with SCD who had undergone CT scans of the skull base between January 1990 and May 2015. We identified 292 control patients without SCD matched for age and sex in a 2-to-1 ratio. We tabulated the prevalence of arrested pneumatization along with the location and size of the lesions. We used Fisher's exact test to correlate SCD with arrested pneumatization of the sphenoid sinus and Student's t test to correlate SCD with lesion size. Results: Of the 146 patients with SCD 14 (9.6%) had arrested pneumatization of the sphenoid sinus. In the 292 control patients 6 (2.1%) had arrested pneumatization. Patients with SCD had a statistically significantly higher rate of arrested pneumatization compared to patients without SCD (p < 0.001). There was no statistically significant correlation between lesion size and diagnosis of SCD. Conclusions: Patients with SCD have a greater prevalence of arrested pneumatization of the sphenoid sinus than patients without SCD. This supports the theory that either regional blood flow anomalies or increased serum erythropoietin cause arrested sinus pneumatization.

Afternoon Poster Session
Location: Row E
Poster #61

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Eric Reseland	Graduate	Fernandez-Miranda	School of Medicine

HDFT segmentation and connectivity of the Human Uncinate Fasciculus

We show that even after chronic tetraplegia, both M1 and S1 units respond to attempted movements, both covert and overt. In general, units were broadly responsive to multiple movements. Further investigation is needed to examine specific movement parameters (speed, position, etc.) to determine if additional insight regarding unit behavior can be gained. Additionally, future work should examine the activation of S1 during sensory imagery as well as motor imagery.

Morning Poster Session
Location: Row A
Poster #6

Presenting Author:	Author Type:	Mentor/Lab:	Department:
William Reynolds	Undergrad	Wu	Developmental Biology

MRI Investigation of Hydrocephalus in Mutant Mouse Models with Congenital Heart Disease: Insights into the Pathogenesis of Congenital Hydrocephalus

INTRODUCTION: Neurodevelopmental disabilities are the most common and potentially most disabling long-term complication of congenital heart disease (CHD) and yet their etiology is not well understood. There are high incidents of hydrocephalus in particular external hydrocephalus with excess external cerebrospinal fluid (CSF) among CHD patients. The current therapeutic procedure for hydrocephalus the ventriculoperitoneal shunt to relieve the excessive CSF is invasive with high malfunction rate and revision surgery is often needed. Moreover despite the ventriculoperitoneal shunt many patients still suffer from life-long neurological disabilities. The causes of congenital hydrocephalus is not well understood and its pathophysiologoy is thought to entail ventricle enlargement with mechanical injury and eventual destruction of the periventricular white matter. While the etiology of congenital hydrocephalus is largely unknown this can be seen in patients with primary ciliary dyskinesia (PCD) a sinopulmonary disease due to motile cilia dysfunction. The goal of this study is to elucidate the pathophysiology of hydrocephalus in a PCD mutant mouse model to better understand the underlying cause for the poor neurological outcomes associated with hydrocephaly. METHODS: Animal model: Studies were conducted using mutant mice harboring a mutation in Dnah5 a gene encoding the outer dynein arm of motile cilia and a gene commonly associated with PCD. Dnah5 (Dynein Axonemal Heavy Chain 5) encodes an axonemal heavy chain dynein that comprise a force-generating protein with ATPase activity whereby the release of ADP is thought to produce the force-producing power stroke. The wild-type (WT) littermates were used as age-matched controls. The homozygous mutant mice and WT controls were subject to MRI evaluation. Brain MRI Analysis:\tMulti-modal magnetic resonance imaging (MRI) was performed at 7-Tesla (Bruker Avance III). In vivo T2-weighted RARE and T1-weighted anatomical images are used to quantify ventricular and gray matter development. Different brain areas such as ventricles hippocampus olfactory bulbs cerebral cortex thalamus hypothalamus caudate mid-brain cerebellum and brain stem are segmented computationally for volumetric and morphometric evaluation. Diffusion MRI followed by graphic analysis is used to evaluate brain injury white matter development and neuronal network. Motile cilia function assessment: Cilia in the tracheal respiratory epithelia as proxy for the ependymal cilia were analyzed for ciliary motion using vidoemicroscopy. Ciliary wave form and beat frequency were analyzed using the digital videos. RESULTS: In vivo MRI of the Dnah5 mutant mouse brains showed severe ventriculomegaly excessive CSF and extra-axial fluid in regions dorsal to the brain parenchyma. In several cases there were intraventricular and subdural hemorrhages and subdural collections. There was also significant cortical necrosis and overall abnormal gray matter dysplasia. It is generally believed that hydrocephalus in mutant mice in BL6 background was caused by aqueductal stenosis because BL6 mice have narrower cerebral aqueducts than other mouse strains. However despite significantly increased CSF and ventricular volume no aqueductal stenosis was observed in any of the hydrocephalus mice (n>100). Our data suggests the hydrocephalus in Dnah5 mutants may arise from motile cilia dysfunction rather then aqueductal stenosis. Our volumetric and morphometric analysis showed the hydrocephalus mutant mice displayed brain dysplasia especially in the olfactory bulb hippocampus cerebellum and

supratentorial regions. This observation is consistent with clinical presentation of hydrocephalus patients. In addition to gray matter and ventricular abnormality neural network analysis with diffusion MRI followed by graph analysis of fiber tracks showed aberrant neural networking with substantial disruptions in fiber tracks between various brain regions. Together these findings support the notion that cilia may play an important role in regulating neurogenesis and brain development. CONCLUSION: Our results suggest motile cilia plays an essential role in normal brain development with motile cilia defects causing not only ventriculomegaly but also brain dysplasia and aberrant neural network formation. These findings suggest the poor neurological outcomes associated with hydrocephalus despite intervention with ventriculoperitoneal shunt may arise from neurogenesis defects caused by the ciliary dysfunction and not simply mechanical injury from the ventriculomegaly.
ACKNOWLEDGEMENT: \tWe thank Michael Wang and Nikolai Klena for genotyping; Jennifer Hess Caleb Radomile and Jacob McLeary for animal breeding and care and Dr. Fang-Cheng Yeh for diffusion MRI analysis.

Morning Poster Session
Location: Row E
Poster #61

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Matthew Rich	Graduate	Torregrossa	Psychiatry

Cocaine-cue memory extinction is associated with depotentiation at amygdala synapses.

Extinction of memories associated with cocaine use may help reduce relapse. The basolateral amygdala (BLA) has been identified as a locus for cocaine-cue memory extinction and we have previously shown that manipulations of kinase/phosphatase activity within the BLA can enhance the efficacy of extinction. Depotentiation of excitatory synapses in the BLA has been proposed as a cellular mechanism for fear extinction but it is unclear if this mechanism explains the extinction of drug-associated memories. We tested if cocaine self-administration potentiates excitatory synapses in the BLA and if cocaine-cue extinction causes depotentiation. Rats self-administered cocaine or saline paired with an audiovisual cue (CS) for ≥10 days. 24 hours after the last training day were returned to operant chambers and received either 0 60 or 120 noncontingent presentations of the CS in the absence of reinforcer. The next day rats were euthanized and brains processed for whole-cell recordings of BLA principal neurons. Neurons were voltage-clamped at -70 mV. Thalamic afferents were stimulated with a concentric bipolar stimulating electrode and excitatory postsynaptic currents (EPSCs) were recorded. Cocaine training potentiated BLA synapses as shown by an increased EPSC amplitude relative to saline-trained controls. Cocaine-cue extinction depotentiated the synapse dose-dependently as 120 CS presentations fully reversed the potentiation caused by cocaine self-administration. Furthermore AMPA:NMDA ratio was increased in cocaine-trained animals relative to saline-trained and memory-extinguished animals. Cocaine-trained animals had a larger AMPA current suggesting that upregulation of AMPA receptors plays a role in the encoding of cocaine-associated memories. Internalization of the receptors during cue extinction may explain the resulting depotentiation and is likely an important factor for relapse prevention.

Morning Poster Session
Location: Row E
Poster #66

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Gregory Rompala	Graduate	Homanics	Neuroscience

Paternal preconception chronic stress exposure reduces ethanol drinking behavior in male mice

We have previously shown that paternal vapor ethanol (EtOH) exposure decreases EtOH drinking behavior increases sensitivity to an anxiolytic injection of EtOH and blunts HPA axis responsivity selectively in male offspring. Interestingly paternal chronic variable stress (CVS) has also been shown to similarly blunt HPA axis responsivity in the next generation. Since EtOH is a physiologic stressor paternal EtOH exposure and paternal CVS may have similar effects on behavior in offspring. Here we tested the hypothesis that paternal CVS impacts EtOH-related behaviors in the next generation. To test this hypothesis we exposed adult male mice to six weeks of CVS. This entailed random daily exposure to one of seven stressors (i.e. restraint novel object predator odor wet cage constant light white noise and multiple cage changes). CVS- and control (C)- males were bred with stress naïve females to produce male and female offspring to be tested for EtOH-related behaviors. For EtOH drinking tasks adult offspring were tested for two bottle choice EtOH drinking at concentrations of 3 6 9 12 and 15% (w/vol) and for binge-like EtOH consumption (20% w/vol) in a limited access paradigm. Sensitivity to an anxiolytic injection of EtOH (1.0 g/kg) was tested in the elevated plus maze. HPA axis responsivity was tested by collecting tail blood at time points 0 15 30 and 90 min from the onset of a 15 min restraint stress and measuring plasma corticosterone levels using an ELISA assay. In the two bottle choice EtOH drinking task CVS-sired male offspring exhibited reduced EtOH preference at concentrations of 3 6 and 9% and reduced EtOH consumption at concentrations of 9 and 12% vs C-sired males. Moreover when CVS-sired male offspring were tested for binge-like EtOH consumption in the limited access assay there was similarly a significant reduction in EtOH consumption vs C-sired male offspring. In contrast CVS-sired female offspring showed no difference in EtOH drinking behaviors vs C-sired females in either EtOH drinking paradigm. We did not find a difference in EtOH sensitivity or HPA axis responsivity to acute stress for CVS-sired males or females vs C-sired groups. These results show that paternal CVS attenuates intergenerational EtOH drinking behavior in mice. This suggests that paternal environmental exposures such as to alcohol or stress can lead to heritable changes in alcohol drinking behavior. Ongoing studies are exploring possible epigenetic mechanisms in sperm.

Afternoon Poster Session
Location: Row A
Poster #9

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Dylan Royston	Graduate	Collinger	Bioengineering

Native upper limb movement encoding by intracortical recordings in human sensorimotor cortex

After paralysis, attempted movement is known to activate primary motor (M1) and somatosensory (S1) cortex, although the latter is less well studied. Most previous work has been conducted with functional magnetic resonance imaging (FMRI) or magnetoencephalography (MEG). However, recent clinical brain-computer interface (BCI) trials, which have shown promise for improving function for people with paralysis, offer an opportunity to study human motor control at a single unit level. Here we investigated M1 and S1 activity using intracortical recordings while a person with tetraplegia attempted to perform movements of his arm and hand.

Afternoon Poster Session
Location: Row C
Poster #30

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Maria Rubio	Faculty	Rubio	Otolaryngology

The number and distribution of AMPA receptor channels containing fast kinetic GluA3 and GluA4 subunits are target-cell-dependent at auditory nerve synapses

Neurotransmitter receptor subtype and the number the density and their distribution relative to the location of transmitter release are likely to be the key determining factors of the properties of signal transmission. AMPA glutamate receptors containing fast kinetic GluA3 and GluA4 subunits are prominently present in subsets of neurons that are capable of firing action potentials at high frequencies such as the auditory relay neurons on bushy cells and fusiform cells of the cochlear nucleus. We examined the number density and organization of GluA3 and GluA4 at the synapse of the auditory nerve on bushy and fusiform cells. Using freeze-fracture immunolabeling (FRIL) we show a positive correlation between numbers of gold particles and the size of synapses for all pan AMPA GluA3 and GluA4 subunits in the auditory nerve synapses both on bushy and on fusiform cells. These synapse types have the same number of AMPA receptors but at auditory nerve synapses on bushy cells the gold density is higher than that on fusiform cells due to smaller postsynaptic densities. GluA3 gold labeling number and density are higher at auditory nerve synapses on bushy cells whereas GluA4 gold labeling number and density are higher at those on fusiform cells. The intrasynaptic distribution of gold labeling revealed that in auditory nerve synapses on bushy cells AMPA receptors -in particular GluA3 are concentrated at the center of synapse. The center concentration of AMPA receptors is absent in GluA3-knockout mice and gold particles are found evenly distributed along the auditory nerve synapse on bushy cells. GluA4 gold labeling was found homogenously distributed along both synapse types. Our findings show that GluA3 and GluA4 subunits are target-cell-dependent at auditory nerve synapses.

Morning Poster Session
Location: Row A
Poster #5

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Paige Rudich	Graduate	Lamitina	Pediatrics/Cell Biology

A C. elegans model for C9orf72-associated dipeptide toxicity

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing age-related neurodegenerative disease that affects ~30 000 Americans. ALS causes degeneration of the upper and lower motor neurons leading to paralysis. Currently there are no effective treatments for ALS and only ~50% of patients survive beyond three years after diagnosis. A recently discovered expanded hexanucleotide repeat in the first intron of the C9orf72 gene is the most common known genetic cause of familial and sporadic ALS. The repeat expansion is not thought to cause disease through alteration of C9orf72 function. Rather the expanded repeat is transcribed in both sense and antisense directions to produce repeat-containing RNAs that are then translated in multiple reading frames to yield up to five distinct dipeptide repeat proteins. This unusual mode of translation is termed Repeat Associated-non-ATG (RAN) translation. It is controversial whether the expanded repeats cause ALS through RNA toxicity RAN translated dipeptide toxicity or both. Using codon-varied transgenes we created a 'dipeptide-only' model in the nematode C. elegans to better understand the mechanisms of dipeptide toxicity. The arginine rich dipeptides PR and GR were toxic in C. elegans when expressed in multiple cell types including motor neurons. This toxicity was dependent on both the length of the dipeptide as well as its subcellular localization. Genetic inhibition of the insulin pathway a conserved regulator of ageing delayed age-onset toxicity caused by PR dipeptides suggesting that physiological age rather than chronological age is a determinant of PR toxicity. Currently we are performing RNAseq and using unbiased forward and reverse genetic screens to identify modifiers or arginine-containing dipeptide toxicity. Defining these modifiers will allow us to determine potential mechanisms for dipeptide toxicity and may lead to new disease biomarkers and/or therapies.

Morning Poster Session
Location: Row E
Poster #67

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Anthony Rudine	Faculty	Rudine	Newborn Medicine/Pediatrics

Antenatal Dexamethasone Exposure Differentially Affects Distinct Cortical Neural Progenitor Cells and Triggers Long Term Changes in Murine Cerebral Architecture and Behavior

Antenatal administration of synthetic glucocorticoids (sGC) is the standard of care for women at risk for pre-term labor before 34 gestational weeks. Despite their widespread use the type of sGC used and their dose or the dosing regimens are not standardized in the US or worldwide. Several studies have identified neural deficits and increased risk for cognitive and psychiatric disease later in life for children administered sGC prenatally. However the precise molecular and cellular targets of GC action in the developing brain remain largely undefined. In this study we demonstrate that a single of glucocorticoid during mid-gestation in mice leads to enhanced proliferation in select cerebral cortical neural stem/progenitor cell populations yet thinning of the cerebral cortex at birth. These alterations are mediated by dose dependent decreases in expression of cell cycle inhibitors and increased expression in genes that promote cell cycle re-entry. This leads to changes in neuronal number and density in the cerebral cortex at birth coupled to long-term alterations in neurite complexity in the prefrontal cortex and hippocampus in adolescents and changes in anxiety and depressive like behaviors in adults. Our results recapitulate outcomes observed in steroid-exposed children and provide insights into how sGCs may act at the cellular level in the embryo adolescent and adult. More research is urgently needed to develop modifications to the antenatal dosing strategies in humans so that the fetal brain is protected during critical developmental periods when exposed to a drug that has proven life-saving benefits for preterm infants.

Afternoon Poster Session
Location: Row C
Poster #40

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Douglas Ruff	Postdoctoral	Cohen	Neuroscience

Correlative and causal evidence that attention improves communication between cortical areas

Several recent studies have shown that in addition to affecting the firing rates of sensory neurons attention decreases the extent to which fluctuations in response to repeated presentations of the same stimulus are shared between pairs of neurons in the same cortical area that have similar tuning. This decrease in so-called spike count correlations combined with attention-related improvements in the sensitivity of single neurons provides support for the hypothesis that attention improves perception by affecting the fidelity with which visual stimuli are encoded within a cortical area. However attention has also been hypothesized to improve the communication of visual information between cortical areas. We tested the hypothesis that attention increases communication between areas on the timescale of behavioral trials using two independent and complementary approaches. First we recorded simultaneously from populations of neurons in primary visual cortex (V1) and the middle temporal area (MT) using similar tasks and data analysis methods as those used to measure the effects of attention within an area. We found that in contrast to its effects on correlations within an area attention increases correlations between pairs of neurons in different areas. Second we made a causal manipulation to test the hypothesis that attention improves communication between areas by electrically stimulating V1 neurons during the attention task. We found that attention increases the extent to which manipulating V1 activity affects the activity of downstream neurons in MT. Together our results provide evidence that attention acts on visual cortex in at least two ways: by affecting both the way visual stimuli are encoded within a cortical area and the extent to which visual information is communicated to downstream areas.

Morning Poster Session
Location: Row C
Poster #40

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Natalie Sandel	Postdoctoral	Kontos	Orthopaedic Surgery

Discrimination of Concussed from Healthy Controls Using a Multimodal Diagnostic Approach

Objective: Evaluate the efficacy of using a multimodal approach to discriminate between acutely concussed individuals and healthy controls. Participants and Methods: Participants included 23 concussed athletes (56.5% males) and 25 healthy age and sex matched controls (68% males) aged 12 to 20 years old (M=15.21 SD=2.03). Participants completed a multimodal evaluation that included the Post-Concussion Symptom Scale (PCSS) computerized neurocognitive testing (Immediate Post-concussion Assessment and Cognitive Testing [ImPACT]) the Balance Error Scoring System (BESS) and the Vestibular/Ocular Motor Screening (VOMS) tool. A discriminant function analysis was conducted to evaluate how well the multimodal approach classified concussed participants from healthy controls. Univariate analyses identified measures in the multimodal approach that best differentiated concussed from healthy participants. Results: The discriminant function yielded a significant model that differentiated concussed from healthy groups (χ^2= 24.382 df=6 p<.001). The model accurately predicted correct outcomes for 81.3% of cases (73.9%- concussed; 88.0%- healthy controls). Univariate ANOVAs revealed that the concussed and healthy control participants differed significantly on all predictor variables in the multimodal assessment: PCSS (F=30.45 p<.001) ImPACT Memory (F=4.72 p=.04) ImPACT Speed (F=6.78 p=.01) vestibular screening (F=23.62 p<.001) and near point convergence (F=7.30 p<.01) with the exception of balance testing (F=0.91 p=.35). Conclusions: Utilization of a multimodal approach to concussion management during the acute phase of the injury correctly discriminated concussed athletes from healthy controls in 81.3% of cases. A multimodal approach should include measures of symptoms cognitive and vestibular/ocular motor function. Balance testing did not discriminate concussed from control participants.

Morning Poster Session
Location: Row D
Poster #46

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Castro Sandra	Faculty	Castro	Neurology

Environmental isolation impairs measures of brain health

Many individuals experience an impoverished lifestyle often associated with cognitive emotional and motor decline and can lead to a reduced life span. Such individuals include elderly living with little social contact the homeless and those living in jails and prisons particularly those in solitary confinement. We are assessing the impact of housing under isolation conditions using a behavioral test battery and biochemical molecular biological and anatomical methods. F344/BN male rats 18 month old at the outset of our study were housed either individually in a standard shoebox cage (18 cm W x 38 cm D x 27 cm H; SE) or in groups of 6 in a relatively enriched environment (1 m W x 1m D x 0.6m H; EE) containing running wheels tunnels platforms and toys. Body weights remained relatively stable in the SE rats but increased by an average of 10% for the EE rats over a 4-month period. The SE animals showed relatively little behavioral activity which was consistent with the small space in which they were housed. In contrast the EE rats showed a good deal of exploration climbing playing and social interaction. After 4 months all rats were euthanized brain peripheral tissues and blood collected and the brain dissected into several regions. Assays are being performed and and comparison made between SE and EE groups. Although not all the differences were statistically significant a number of promising trends have already been observed. For example we found that the SE rats housed in isolated impoverished conditions had a 72% decrease in BDNF. These rats also had a 37% decrease in the ratio of dopamine (DA) metabolites to DA and a 30% decrease in the level of phosphorylated tyrosine hydroxylase in the striatum; both of which suggested a decrease in DA synthesis and release in that structure. There was a five-fold increase in mitochondrial DNA damage levels in hippocampus in the SE rats. In addition substantia nigra from rats in the SE showed a number of significant differences in mRNA expression including changes in Azin1 Tssc4 Ddit4 Nfkb1a Pdk4 and Sgk1 (downregulated) and Cxcl13 and slc47a1 (upregulated). Additional assays are ongoing. Thus far our results indicate that isolated housing produces significant changes consistent with decreased neuroplasticity. These results suggest that isolated impoverished living conditions can produce profound changes in the brain that may be at least partially responsible for the behavioral impairments observed in people experiencing such conditions.

Morning Poster Session
Location: Row A
Poster #10

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Mark Schurdak	Faculty	Schurdak	University of Pittsburgh Drug Discovery Institute

Application of Quantitative Systems Pharmacology to identify mechanistic probes and combinations of neuroprotective agents for Huntington's Disease

Huntington's disease (HD) is a devastating chronic neurodegenerative disorder currently afflicting 30 000 Americans with 150 000 more at risk of inheriting the disease from a parent. HD is caused by a highly penetrant autosomal dominant mutation in the HTT gene. Expansion of a series of CAG triplets at the 5'-end of this gene increases the number of tandem glutamine residues in the encoded protein (HTT) and is associated with neuronal death. Although the number of glutamine repeats negatively correlates with age of onset the mechanistic basis between glutamine expansion in HTT and neuronal death is not completely understood. Despite more than two decades of research since the discovery of the causative mutation and the development of more than 20 transgenic mouse models that recapitulate many aspects of the clinical phenotypes no effective treatment for HD neurodegeneration is available and the disease is universally fatal. It has been hypothesized that the pleiotropic effects of mutant HTT represent a major barrier to understanding mechanisms of HD progression and designing therapeutic strategies. To meet this challenge we have implemented a Quantitative Systems Pharmacology (QSP) platform. QSP is an approach to drug discovery and development that melds the fundamental principles of pharmacology and systems biology into a modular multidisciplinary broadly applicable platform enabling a quantitative network-centric understanding of the biology underlying disease progression (Stern et al. 2016). A hallmark of QSP is its iterative use of experimental and computational models that when integrated with comprehensive and unbiased multiplexed system-wide measurements and existing knowledge can identify emergent properties of diseases and corresponding drug-target interactions at multiple levels of biological complexity. Data-driven iteration through a QSP cycle is expected to improve the clinical relevant design of its component models with the prospect of increasing the robustness of target and companion biomarker selection. Accordingly it is anticipated that implementation of QSP will enable optimization of therapeutic strategies for HD and serve as a paradigm for studying other neurodegenerative diseases. Here we present the chemogenomic component of QSP to understand pathways involved in neuroprotection in HD. Chemogenomics is the systematic screening of small molecule probes with known targeted interactions to help elucidate the molecular modes of action of compounds giving rise to a specific phenotype. Using computational and experimental methods we identified a number of drugs/probes with different canonical mechanisms of action that exhibited neuroprotection as measured by a cytotoxicity experimental model. Further combinations of these drugs/probes showed enhanced protective effects relative to single probes suggesting distinct mechanisms may be involved. These data will help guide the elucidation of pathways/networks involved in HD neuroprotection.

Morning Poster Session
Location: Row C
Poster #32

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Enhua Shao	Graduate	Burton	Pittsburgh Institude for Neurodegenerative Diesase

The role of oligodendrocytes in axonal regeneration following spinal cord injury: live imaging in a novel zebrafish model

Axons in the human central nervous system (CNS) have limited capacity to regenerate after injury; consequently neurological deficits caused by axonal damage in spinal cord compression, subcortical stroke and traumatic brain injury are associated with a poor prognosis for recovery. This is thought to result from (i) a low intrinsic ability for CNS neurons to regenerate severed axons, and (ii) a CNS microenvironment that is inhibitory to axonal growth. In contrast, CNS axons in lower vertebrates such as zebrafish, robustly regenerate after injury, resulting in functional recovery. Our goal is to understand the mechanisms underlying axonal regeneration in zebrafish, since knowledge of the cellular and molecular mechanisms may be informative for development of therapies for human neurological disease. Recently we found that zebrafish mpz promoter was strongly upregulated in oligodendroglial lineage cells of the entire optic pathway following optic nerve crush injury in adult zebrafish. To elucidate the role of oligodendrocytes in the repair response, we have developed a novel spinal cord injury model in larval zebrafish. We have generated double transgenic zebrafish in which the neurons and their axons are labeled with mCherry and the oligodendrocytes are labeled with GFP. By taking advantage of the unique ability to image fluorescent proteins in the spinal cord of live zebrafish, we have been able to demonstrate: imaging of spinal cord neurons, axons and oligodendrocytes in a living animal; loss of cells at the site of the spinal cord transection; the oligodendroglial response to injury; and axonal regrowth. Importantly, imaging can be carried out in the same zebrafish on successive days, at subcellular resolution, allowing direct observation of the entire repair response. Coupled with functional analysis of recovery of swimming movements, our new model will allow us to test the role of oligodendrocytes in CNS axonal regrowth in the zebrafish and to elucidate the underlying molecular events.

Morning Poster Session
Location: Row C
Poster #30

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Yejie Shi	Postdoctoral	Chen	Neurology

Endothelial-Targeted Overexpression of Heat Shock Protein 27 Ameliorates Rapid Blood Brain Barrier Impairment and Improves Long Term Outcomes after Ischemia and Reperfusion

Introduction: The damage borne by the blood brain barrier (BBB) during ischemic stroke disrupts the neurovascular unit and leads to poor patient outcomes. We recently discovered that Caveolin-1-independent subtle structural aberrations of brain microvascular endothelial cells (BMECs), such as abnormal actin polymerization, stress fiber formation and subsequent junctional protein (JP) disassembly, are a novel mechanism for rapid BBB breach after ischemia/reperfusion (I/R) injury. Hypothesis: Heat shock protein 27 (HSP27) attenuates BBB breakdown and neurovascular injury after I/R by inhibiting actin polymerization and JP disassembly in BMECs. Methods: We created neuron- and EC-specific HSP27-overexpressing mice, which were subjected to 1h MCAO and reperfusion. Assessments for BBB damage were performed 1-24h after I/R; infarct volume and neurobehavioral performance were assessed up to 35d after I/R. I/R-induced BBB damage was also simulated in BMEC cultures, where gene manipulations were achieved using lentiviral vectors. Recombinant HSP27 containing a cell-penetrating domain (TAT-HSP27) was i.v. injected into mice after I/R to rapidly elevate HSP27 in BMECs. Results: Targeted overexpression of HSP27 within ECs—but not neurons—was sufficient to reduce early (1-3h) and late (24h) BBB damage after I/R ($p<0.01$). Mechanistically, HSP27 suppressed I/R-induced actin polymerization, stress fibers, and JP disassembly in BMECs, but independent of its anti-cell death properties. Intracerebral infiltration of neutrophils and macrophages was attenuated in EC-HSP27 mice by 35.3% and 59.6%, respectively ($n=6$, $p<0.05$) at 48h after I/R, thereby alleviating secondary injuries. Infarct was reduced by 35% at 72h, and sensorimotor functions ($p<0.01$, cylinder and corner tests) were improved in EC-HSP27 overexpressors up to 21d. Injection of TAT-HSP27 after I/R markedly reduced BBB damage 1-24h after I/R and elicited sustained (up to 35d) protection against neurological deficits. Conclusions: HSP27 protects against BBB disruption after I/R by inhibiting actin polymerization and JP disassembly in BMECs. HSP27 has translational potential as a therapy for ischemic stroke in conjunction with reperfusion.

Afternoon Poster Session
Location: Row C
Poster #38

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Lindsay Snyder	Graduate	Ross	Neurobiology

Modulation of multiple modalities of somatosensory information by peripheral kappa opioid receptors

Peripherally selective kappa opioids are emerging as a novel treatment for pain and itch that have shown efficacy in several recent clinical trials. Yet, the subtypes of somatosensory neurons that express KOR remain unclear. Using a newly developed KOR-cre knockin allele, viral tracing, and single-cell PCR we reveal that that KOR is expressed in a specific subset of peptidergic afferents that are tuned for inflammatory pain and itch, but not heat or mechanical force. Consistent with this, peripherally restricted KOR agonists inhibit behavioral responses to chemical pain and itch, but not acute heat responses nor punctuate mechanical sensitivity. Unexpectedly, we also find that KOR is expressed in subsets of primary afferents that form lanceolate or circumferential endings around hair follicles, suggesting an unappreciated role for KOR signaling in the modulation of low-threshold mechanosensation. At a functional level, optogenetic experiments reveal that dynorphin inhibits glutamate release from the central terminals of KOR-expressing afferents, and genetically-labeled afferents show inhibited calcium influx in response to kappa agonists. These experiments provide key insight for the rationale use of peripherally selective KOR agonists for the modulation of inflammatory pain, itch, and potentially mechanical allodynia.

Morning Poster Session
Location: Row D
Poster #50

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Adriane Soehner	Postdoctoral	Phillips	Psychiatry

Sleep Duration Variability Predicts Altered Dorsal Anterior Cingulate Activity During A Stressful Cognitive Control Task In Adolescents With Bipolar Disorder

Introduction: Altered function within fronto-limbic circuitry is observed during cognitive task performance in adults and adolescents with bipolar disorder (BD). However modifiable factors that may be impairing brain function in BD remain under-characterized. Sleep patterns are highly variable in BD but may be ameliorated with behavioral interventions. While links between disturbed sleep and altered brain function during cognitive tasks are well-established in healthy samples such relationships remain under-characterized in BD. Thus our aim was to test sleep duration variability as a predictor of neural response to a cognitive control fMRI task in adolescents with BD. Methods: Two groups of adolescents (13-22 years old) participated: 15 with BD type I II or NOS (BD; age=18.1±2.7 years; 11 female) and 25 healthy controls (CTL; age=19.4±2.7 years; 17 female). Sleep was monitored with actigraphy for 7-14 days prior to completing an adaptive version of the multi-source interference fMRI paradigm. Group status and sleep duration variability (intra-individual standard deviation) were examined as predictors of BOLD activity to a contrast of incongruent>congruent trials within a fronto-limbic region of interest. Results: A group-by-sleep duration variability interaction was observed for bilateral dorsal anterior cingulate cortex (dACC) activity to incongruent>congruent trials (p<.05 corrected): sleep duration variability and dACC activity were negatively associated in BD (r=-0.65 p<0.01) but not related in CTL (r=0.33 p=0.12). These patterns remained significant after controlling for age sex depressive symptoms and average sleep duration. Conclusion: In adolescents with BD sleep duration variability may modulate dACC engagement during cognitive control. Stabilizing sleep patterns may improve cognitive control neural circuitry function in BD which could in turn favorably improve emotional dysregulation.

Support: T32MH018269 (Soehner) The Pittsburgh Foundation (Franzen; Goldstein) UL1 RR024153 UL1TR000005

Morning Poster Session
Location: Row B
Poster #24

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Carly Sombric	Graduate	Torres-Oviedo	Bioengineering

Changes in perception of step length size after split-belt walking

Step asymmetry post-stroke significantly limits patients' mobility. It has been proposed that patients' reduced perception of their gait asymmetry contributes to their inability to recover symmetric walking (Wutzke et al. 2015). Thus there is an interest in understanding if the perception of step asymmetry can be altered. A recent study indicates that split-belt walking in which legs move at different speeds changes the perception of asymmetric walking speeds in unimpaired subjects (Vazquez et al. 2015). Here we hypothesize that the perception of asymmetric step lengths can also be altered after split-belt adaptation. To test this we investigated subjects' perception of step lengths for each leg before and after split-belt adaptation. Participants (n=7 25.9±6.1 yr.) first learned a spatial map of three distinct subject-specific step length sizes (short comfortable and long) by observing their step length and the targeted step size. All visual feedback was displayed with an Oculus Rift and Vizard software in order to remove the effect of peripheral vision on subjects' control of position. We assessed changes in step position for seven subjects during two pseudorandomly presented testing sessions: normal walking at 1m/s and split-belt walking at 1.5 m/s (fast leg) and 0.5 m/s (slow leg). Step length perception before and after walking was evaluated by recording step length accuracy while subjects walked at 1m/s with reduced visual feedback projecting only 35% of the actual step length error. Both testing sessions included 810 strides of walking before step length perception was assessed. A catch trial (both legs walk at 1m/s for 10 steps) was introduced during the walking period to identify motor after-effects induced by the split-belt walking condition. We found that subjects in the split-belt group had significantly more motor (slow leg catch: p<0.001; fast leg catch: p=0.007) and perception (short target slow leg: p<0.001; short target fast leg: p=0.019; long target slow leg: p=0.12; long target fast leg: p=0.001) after-effects compared to the control session. We also found that perception after-effects were distinct for each leg: the slow leg undershot the stepping target while the fast leg overshot it following split-belt walking. Interestingly a single rate can be used to fit the decay of perception across legs and targets (all fits R^2>0.72) even though the amplitudes of perceptual after-effects are different. Importantly split-belt walking did not disrupt subject's step size map even when no visual feedback was given (p>0.33). In sum we found that split-belt walking induces changes in the perception of step lengths. This is important since paradigms like split-belt walking could be used to alter patients' active perception of limb position and improve their awareness of asymmetric stepping.

Morning Poster Session
Location: Row E
Poster #59

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Susan Sonnenschein	Graduate	Grace	Neuroscience

Impact of withdrawal from prior D2 antagonist vs aripiprazole treatment on dopamine system activity in MAM model of schizophrenia

Novel target compounds for the treatment of schizophrenia have shown promise in preclinical research but failed to show efficacy in clinical trials. However preclinical research is typically performed on drug-naïve rats whereas clinical trials are performed on patients that have received only brief withdrawal from years of prior antipsychotic drug (APD) treatment despite potential pervasive changes to the DA system. We previously found that withdrawal from repeated haloperidol (HAL) treatment produces persistent changes interfering with the ability of a novel target compound to reverse the hyperresponsive state of the DA system in the methylazoxymethanol acetate (MAM) model of schizophrenia. In the current study we examined the effects of withdrawal from mechanistically distinct APDs with a focus on the D2 partial agonist aripiprazole (ARI). Saline (SAL) and MAM-treated offspring received repeated HAL (0.6 mg/kg) clozapine (CLO; 10 mg/kg or 20 mg/kg) ARI (10 mg/kg) or vehicle (0.23% glacial acetic acid) for 21 d p.o. followed by 7d withdrawal. The number of spontaneously active DA neurons in the VTA was measured using in vivo extracellular recordings from anesthetized rats. After electrophysiological sampling a subset of rats received a low dose of apomorphine (40 ug/kg i.v.) to test for removal of depolarization block followed by resampling the VTA in the opposite hemisphere. Recordings were also conducted in SAL and MAM rats 3 h following acute treatment with ARI (10 mg/kg p.o). Finally additional MAM and SAL rats withdrawn from repeated treatments were administered DA agonist quinpirole (8mg/kg i.p.) prior to measuring locomotion in an open field to test for DA supersensitivity. In contrast to D2 antagonists withdrawal from ARI treatment did not reduce the number of spontaneously active DA neurons in normal rats. Unlike the effect of ARI treatment in normal rats MAM rats withdrawn from repeated ARI demonstrated reduced DA neuron activity following both repeated and acute treatment which was maintained following administration of apomorphine suggesting that it is unlikely the result of depolarization block. Lack of evidence for depolarization block ARI-treated rats suggests that brief withdrawal from ARI treatment may not interfere with the antipsychotic efficacy of novel target compounds which remains to be tested.

Afternoon Poster Session
Location: Row B
Poster #23

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Patricia Stan	Graduate	Luna	Neurobiology

Differential Response Preference of Mouse V1 Excitatory Neurons to Cartesian and Non-Cartesian Stimuli

Patricia Stan Janne Kauttonen Brian Jeon Tai Sing Lee Sandra Kuhlman How neurons code different aspects of an image is central to our understanding of shape representation. Many studies have shown that neurons in the primary visual cortex (V1) have differential preference for elementary stimulus dimensions such as orientation and spatial frequency. However the majority of studies use conventional sinusoidal (Cartesian) gratings to probe the properties of these neurons and it is therefore unknown whether these neurons may have preferential responses to more complex stimuli. To further investigate this we developed a stimulus set composed of Cartesian gratings as well as polar and hyperbolic (non-Cartesian) gratings. We used in vivo two-photon Calcium imaging in awake mice to record responses of V1 excitatory neurons to Cartesian and non-Cartesian stimuli. We found that individual neurons in V1 showed variable preference to Cartesian and Non-Cartesian stimuli. Some neurons responded only to Cartesian gratings others were selective for non-Cartesian gratings and others responded to both Cartesian and non-Cartesian. Our results suggest that a subset of V1 excitatory neurons do not function as solely elementary stimulus dimension detectors but may be involved in the computation of complex shape representation. It is known that responses to Cartesian stimuli develop innately largely independent of experience. Future studies will include raising mice in the dark to determine if visual experience is required for the development of response selectivity to non-Cartesian stimuli.

Morning Poster Session
Location: Row C
Poster #29

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Yalikun Suofu	Postdoctoral	Friedlander	Neurological Surgery

The role of miR-155 in ischemic/reperfusion induced hemorrhagic transformation

miRNAs are non-coding small RNA molecules and recently emerged as key regulators of pathogenic response. However whether miRNAs play a role in neurovascular disorders after ischemic/reperfusion is unknown. One of extensively studied miRNAs is miR-155 which involves in inflammation auto-immunity and cell plasticity. Recently miR-155 was found to be a negative regulator of BBB function. In miR-155 knockout mice it was reported that central nervous system extravasation of systemic tracer was reduced both in an acute systemic inflammation model and experimental autoimmue encephalomyelitis in mice. It is not known however whether miR-155 plays a role in ischemic/reperfusion-induced hemorrhagic transformation. In this study we used mouse model of 1 hour reversible MCAO and 71 hours reperfusion. The brain slices were then stained with TTC and hemorrhagic volumes were quantified by imageJ. We found that miR-155 is significantly upregulated at 72 hours after cerebral ischemic stroke in wild type mice. miR-155 knockout did protect from ischemic injury as compared to wild type at 72 hours after stroke and there is significant reduction in infarct size in mir-155 knockout mice (p<0.05). We found that miR-155 knockout mice had none or smaller hemorrhagic dots whereas WT showed larger petechial hemorrhage or hematoma at 72 hours after ischemia. The quantification of hemorrhagic volume showed that miR-155 knockout mice have significant smaller hemorrhagic volume (p<0.05) and rate of hemorrhage is lower in miR-155 knockout mice as well (WT vs miR-155 is 100% vs 62.5%). In conclusion miR-155 knockout protects from ischemic/reperfusion induced hemorrhagic transformation and inhibition of miR-155 may benefit long-term stroke recovery.

Afternoon Poster Session
Location: Row A
Poster #13

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Steven Suway	Graduate	Schwartz	Neurobiology

Dynamic representation of reach speed in the motor cortex

In primate motor cortex (M1) single neurons are broadly tuned to reach direction with each cell discharging maximally for a particular direction. The speed of the reach also affects neural activity contributing both a multiplicative and additive influence on firing rates. Early studies reported a "representation" of reach speed in single units and in population analyses. However such studies commonly restricted analysis to the trial period in which the arm was moving. It was subsequently suggested that representation of speed is less robust in the firing rate fluctuations that continue after movement ceases. Recently our group identified distinct epochs in the activity of M1 neurons spanning the reaction time through the target-hold period of a reaching trial. Directional tuning of single neurons is robust and stable within an epoch but preferred direction may change from one epoch to the next. We wondered if speed encoding might also vary between epochs. We recorded spiking of M1 neurons from three monkeys during a center-out reaching task. Firing rates of each neuron were analyzed using two models: a direction-only tuning model and a velocity-speed tuning model. Both models were fitted during each epoch and the goodness-of-fit of each model was assessed. We found clear evidence of dynamic coding with the velocity-speed model fitting rates of many neurons markedly better during the early epochs. Using the population vector algorithm (PVA) we reconstructed reach trajectories using firing rates from only the speed-related epochs. We found the decoded trajectories were highly accurate and the time course of their magnitude was strikingly similar to the recorded reach speeds. Given that velocity can be extracted from the population with high fidelity by selectively utilizing segments of firing we wondered if a simpler computation using all the data could yield similar results. This would be useful for example in neural prosthetics because it would allow us to estimate arm velocity despite the ongoing changes in single unit tuning during a reach. We developed a simple regression method to find a linear combination of single unit firing rates that closely matches the measured arm velocity. The method identifies an axis in the n-dimensional population firing rate space. When the population activity is projected onto this axis we find robust and accurate velocity tuning while the hand is moving. When the arm comes to a stop and despite continued fluctuations in firing of most neurons activation along this axis drops nearly to zero. This method may be advantageous in neural prosthetics which often fail to afford subjects control of output speed.

Morning Poster Session
Location: Row F
Poster #74

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Chenxiao Tang	Graduate	Chenxiao	Pharmaceutical sciences

SCREENING 20-HETE INHIBITORS IN MICROSOMAL INCUBATES USING UPLC-MS/MS

Introduction: 20-hydroxyeicosatetraenoic acid (20-HETE) is a metabolite of arachidonic acid (AA) by cytochrome P450 (CYP) 4A11 and CYP4F2 in human with potent microvascular constriction activity. Inhibition of 20-HETE formation is neuroprotective in subarachnoid hemorrhage cardiac arrest and thromboembolic stroke preclinical models. This suggests that inhibition of 20-HETE formation is a potential therapeutic strategy for neuroprotection after brain injury. At this time a clinically relevant 20-HETE inhibitor is not available to evaluate as a therapeutic intervention. Our goal is to identify a selective metabolic stable and potent 20-HETE inhibitor. Hypothesis: Novel selective and specific 20-HETE formation inhibitors can be identified and confirmed by scaffold-hopping and human CYP4F2 homology model. Methods: Test compounds were obtained either via virtual screening against a CYP4F2 homology model or from a proprietary library available to our laboratory. 1.AA microsomal incubation assay: four different microsomal systems including human liver microsome (HLM) recombinant CYP4F2 (rCYP4F2) rat liver microsome (RLM) and rat kidney microsome (RKM) were used. AA was incubated with microsomes with/without compound for 20 min. 20-HETE formation rate was quantified using a validated UPLC-MS/MS assay and normalized by vehicle control group. Other eicosanoids including 15- 12-HETEs epoxyeicosatrienoic acids (EETs) and dihydroxyeicosatrienoic acids (DHETs) were monitored simultaneously. 2. Metabolic stability assay: selected compounds were incubated with HLM during a 60-minute incubation time. Remaining amount of compounds was quantified using UPLC-MS/MS and normalized to corresponding 0 min values. Results: Among 26 compounds that we screened comp 10 and 26 both inhibited 20-HETE formation in a dose-dependent manner. At 2500nM comp 10 reduced 20-HETE formation to 19.9±1.8% 24.0±5.5% in rCYP4F2 and HLM compared with control; comp 26 decreased 20-HETE formation to 32.4±6.5% 34.8±5.1% in rCYP4F2 and HLM respectively. After structure modification comp 19 and its hydrochloride salt comp 18 were the most potent and possessed dose-dependent inhibition against 20-HETE formation. At 2500nM comp19/18 brought down 20-HETE formation to 4.4±0.4%/6.0±0.3% 8.6±1.3%/9.8±1.6% in rCYP4F2 and HLM respectively without inhibitory effect on 15- 12-HETE EETs or DHETS formation. Comp 10 19 had 91.4±11.0% 100.4±1.7% remaining compound at 30min in HLM compared to 35.1±5.7% of 3-(4-n-butoxyphenyl)pyrazole. Comp 10 19 were more stable than 3-(4-n-butoxyphenyl)pyrazole which already had better stability than HET0016. Conclusions: These results suggested that compound 10 18/19 26 are potent 20-HETE formation inhibitors with better solubility microsomal stability and can serve as leads for further structure modifications that may lead to novel 20-HETE formation inhibitors. Significance: We have a rationally designed novel compound library and a CYP4F2 homology model for identification and lead compound optimization against 20-HETE formation. Selected lead compound with better solubility metabolic stability and potency could be used in preclinical animal model to evaluate its PK/PD and neuroprotective effect and could potentially serve as a clinically relevant drug for critically ill patients.

Morning Poster Session
Location: Row E
Poster #65

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Ian Mitch Taylor	Postdoctoral	Cui	Bioengineering

Development of novel electrochemical sensors for the real-time in vivo detection of cocaine and dopamine

The real-time in vivo detection of neurochemicals is highly intriguing due to their widespread implication in healthy and diseased brain function. Successful neurochemical sensors must be selective and sensitive for the neurochemical of interest exhibit high spatial and temporal resolution and maintain small physical dimensions to prevent insertion related tissue damage. We have developed three novel highly successful electrochemical sensors that provide clear and robust real-time detection of dopamine and cocaine. Our in vivo cocaine sensor incorporates a cocaine-selective electrochemically active DNA aptamer onto a single shank silicon neural recording probe. The sensor exhibits selective robust cocaine detection in the rat dorsal striatum in response to both local cocaine infusion and intravenous cocaine injection and clear measurement of spontaneous and evoked electrophysiological activity in the barrel cortex. We have also developed two dopamine sensors that incorporate PEDOT coatings onto carbon fiber microelectrodes (CFE). PEDOT/graphene oxide coated CFEs exhibit an 880% increase in dopamine sensitivity and a 50% decrease in LOD compared to bare CFEs whereas PEDOT/carbon nanotube coated CFEs exhibit a 4800% sensitivity increase and a potential for signal amplification by preconcentration. These sensors are a marked improvement over existing technology and will allow for greater understanding of brain function.

Afternoon Poster Session
Location: Row A
Poster #14

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Rex Tien	Graduate	Schwartz	Bioengineering

Object-dependent tuning of M1 neurons during grasping

Neurons in primate primary motor cortex (M1) display patterns of activity related to arm and hand kinematics and muscle activity (movement features or MFs) during the execution of grasping movements. Previous studies have characterized the neural encoding of MFs with the concept of a "tuning function" – a linear function relating a neuron's firing rate (FR) to a combination of MFs. A central assumption of many neural prosthetic algorithms is that each neuron has a single fixed tuning function across time and behavioral contexts. Here we present evidence that neurons' tuning functions may change depending on the identity of the object being grasped. Two monkeys each grasped six different objects while we recorded neural activity wrist hand and finger joint angles and arm muscle activity. We found that assuming a single constant tuning function for each neuron (modeled using multiple linear regression) could account for about half of FR variance. The residuals from these regressions contained object-related structure as evidenced by ANOVA and classification analyses suggesting that M1 neurons also encode object identity in some way. We hypothesized that M1 neurons could encode object identity directly in their FRs or that object identity could have a more complex effect on M1 tuning functions. Using dummy variable regression we determined that for the majority of neurons the best models were those that allowed tuning parameters to change depending on the identity of the grasped object. Comparing these parameters revealed that most neurons displayed large tuning changes between object conditions; statistically significant parameter changes were just as likely when comparing between two object-specific tuning models within a single neuron as between two randomly selected neurons. The finding that tuning functions change under different behavioral contexts contributes to our understanding of the natural cortical control of goal-oriented hand movements as well as to the design of effective future upper limb neural prostheses.

Afternoon Poster Session
Location: Row E
Poster #67

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Anne Van Cott	Faculty	Hetherington	Neurology

Magnetic Resonance Spectroscopic Imaging at 7T (7T MRSI) abnormalities in PTSD and mild TBI

The goal of this project was to examine the ability of magnetic resonance spectroscopic imaging at 7T (7T MRSI) to determine if the location of brain metabolite changes were capable of differentiating veterans with a chronic history of mTBI(s) and PTSD from those with PTSD alone. A distinct pattern of imaging abnormalities has emerged that has the potential to differentiate these two populations and serve as a metabolic imaging biomarker that may assist in the diagnosis prognosis and impact of targeted intervention of mTBI and PTSD.

Afternoon Poster Session
Location: Row B
Poster #24

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Yolandi van der Merwe	Graduate	Chan	Bioengineering

Citicoline preserves optic nerve integrity and visuomotor function following chronic intraocular pressure elevation

Purpose: Although lowering of intraocular pressure (IOP) is the only clinically proven glaucoma intervention in afflicted individuals glaucomatous neurodegeneration and visual impairment may continue to progress in some patients following this treatment. Recent studies suggest the potential of citicoline an intermediate in the generation of phosphatidylcholine from choline to improve visual outcome in glaucoma patients but its neuroprotective roles remain unclear. Here we examined the effects of oral citicoline treatment on white matter integrity and visuomotor response in a chronic IOP elevation animal model. Methods: Twenty-five Long Evans rats were intracamerally injected in the right eye with an optically clear cross-linking hydrogel consisting of 6% vinysulfonated hyaluronic acid (HA) and 6% thiolated HA that obstructed aqueous outflow. Eleven of the rats received daily citicoline treatment (500mg/kg) via oral gavaging for 7 days prior to and every 48 hours for 14 days after hydrogel injection. IOP and visual acuity (VA) were measured with a TonoLab tonometer and OptoMotry virtual reality system respectively before and for 5 weeks after hydrogel injection. Diffusion tensor imaging was performed using a 9.4 Tesla MRI scanner to measure white matter integrity indicated by fractional anisotropy (FA) in the prechiasmatic optic nerve (ON) at 5 weeks following hydrogel injection. Results: Hydrogel injection significantly elevated IOP in the right eye for 5 weeks with no pressure difference between citicoline treated and untreated animals (Fig. 1a). VA of left eye remained unchanged over time whereas VA of right eye deteriorated starting at day 7 and was significantly worse in untreated animals compared to citicoline treated animals. The decrease in FA in the ON was significantly smaller for citicoline treated animals compared to untreated animals (Fig. 1a & 1b). In addition FA in right ON was positively correlated with VA in right eye for all animals (Fig. 1c). Conclusions: Chronic IOP elevation for up to 5 weeks caused significant changes in visuomotor behavior and white matter integrity in the prechiasmatic optic nerve whereas citicoline treatment ameliorated the effects. Our results appeared consistent with recent literature that suggests citicoline can act upon impaired white matter and improve functional outcomes in neurodegenerative diseases.

Morning Poster Session
Location: Row B
Poster #19

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Amber Van Laar	Faculty	Van Laar	Neurology

A novel progressive endogenous synucleinopathy model of Parkinson disease in rats

One of the greatest obstacles in developing effective neuroprotective therapeutics for Parkinson disease (PD) is lack of a predictive preclinical research model that replicates the human disease with fidelity. We now report a new rat model in which brief pesticide exposure causes progressive accumulation and aggregation of endogenous α-synuclein culminating in a delayed and progressive behavioral and pathological parkinsonian phenotype over a period of months. Lewis rats (6-9 months old) received baseline behavioral testing and then were treated with rotenone (i.p.) once daily for 5 days only. During treatment rats became mildly parkinsonian but there was no morbidity or mortality. All rats recovered to their behavioral baseline over the succeeding week. They remained behaviorally normal until about 3 months at which point all rats began to show mild progressive parkinsonian symptoms including postural instability and bradykinesia. From onset symptoms progressed over 3-4 months and stabilized thereafter. Pathological studies indicate that during the quiescent latent period before symptom onset nigrostriatal neurons accumulate α-synuclein which becomes progressively consolidated into inclusions by 3 months. The accumulation of α-synuclein is accompanied by progressive microglial activation - and many microglia also contain intracellular α-synuclein apparently derived from nigral neurons. By the time of symptom onset there is loss of nigrostriatal dopamine neurons which continues to progress over a period of months. By 9 months there is α-synuclein accumulation in other brain regions including in the cortex and there are legitimate Lewy bodies in some remaining nigral neurons. These results indicate that a remote environmental exposure has the potential to set in motion a pathological cascade that results after a long latent period in parkinsonism. The model has many advantages over conventional models including the fact that (i) it is a spontaneously progressive endogenous synucleinopathy and (ii) potential disease-modifying treatments can be started at symptom onset which is analogous to current clinical practice.

Morning Poster Session
Location: Row A
Poster #12

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Victor Van Laar	Postdoctoral	Berman	Neurology

Evaluating mitochondrial biogenesis in a cell model of Parkinson disease via mitochondrial DNA replication in neuron cell bodies axons and dendrites

Evidence implicates dysregulation of mitochondrial homeostasis and quality control in neurodegenerative diseases such as Parkinson's disease (PD). We had previously found that exposure of primary neurons to chronic sublethal doses of rotenone a Complex I inhibitor linked to PD was associated first with increased mitochondrial density in distal neurites followed by later increases in mitochondrial density in cell bodies. The increased mitochondrial density in neurites prior to cell bodies was not accounted for by changes in mitochondrial transport or localized changes in mitochondrial degradation. This suggested the possibility that localized changes in mitochondrial biogenesis could be occurring in axons/dendrites but methodology for direct studies targeting neuroanatomical localization of mitochondrial biogenesis was lacking. We have optimized methodology to directly image localize and quantify replicating mitochondrial DNA (mtDNA) in neurons using BrdU incorporation and immunocytochemistry. We are able to visualize newly synthesized mtDNA replication within minutes in neurons in vitro. The BrdU incorporation is inhibited as expected by the addition of 2' 3'-dideoxycytidine (ddC) inhibitor of mitochondrial DNA polymerase gamma. Interestingly as neurons 'age' in culture from 7 to 21 days rates of mtDNA synthesis increase. This increase is also associated with increased expression of PGC1alpha suggesting increased mitochondrial biogenesis with senescence. To address the effects seen in our previous studies we are also evaluating the effects of chronic sublethal rotenone on localized mtDNA replication. These studies give us the ability to better elucidate mtDNA replication/mitochondrial biogenesis in neurons and under PD-relevant conditions.

Afternoon Poster Session
Location: Row D
Poster #48

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Alberto Vazquez	Faculty	Vazquez	Radiology

Inhibitory neuron activity contributions to hemodynamic responses: Optogenetic vs. sensory stimulation

Introduction The role of inhibitory neuron activity on hemodynamic responses have been difficult to determine because it is difficult to stimulate and isolate inhibitory neuron activity in vivo particularly in cortex [1]. Recent advances in optogenetics allow for the selective stimulation of cortical inhibitory neurons [2 3]. The goal of this work is to use this optogenetic model to investigate the contributions of inhibitory neuron activity including γ-aminobutyric acid (GABA) neurotransmission on vascular responses and hemodynamic signals. Forelimb sensory stimulation was used as reference. Methods Transgenic mice expressing Channelrhodopsin-2 (ChR2) under the control of the vesicular GABA transporter (VGAT) promoter were obtained from the Jackson Laboratory (Bar Harbour ME; n=17) for experimentation. Mice were induced using ketamine and xylazine and placed in a stereo-taxic frame. An acrylic well was placed over the somato-sensory cortex and a craniotomy was performed. The location of the forelimb area was mapped using optical imaging of intrinsic signals (OIS) at a wavelength of 570nm and sensitive to changes in cerebral blood volume (CBV). A fiber optic (125µm in diameter) electrode (to measure local field potential (LFP) and multi-unit activity (MUA)) and laser Doppler flowmetry (LDF) probe were placed in the forelimb area. Hemodynamic responses were measured using LDF (CBF) and OIS (CBV). Different light stimulation (or photo-stimulation) parameters were tested and delivered for 4-sec periods (every 60-sec) using a 473nm laser light source. Forelimb stimulation experiments were performed for comparison (1mA 0.5ms pulses). Experiments were performed under four pharmacological conditions: control (n=17) glutamate receptor blockade (GRB; n=8) GABA-and-glutamate receptor blockade (GGRB; n=6) and nitric oxide synthase (NOS)-and-glutamate receptor blockade (NOSGRB; n=3). The GRB condition was established by intra-cortical administration of ionotropic glutamate receptor antagonists APV (50mM) and NBQX (5mM) to block excitatory input to excitatory and inhibitory neurons while sparing GABA neurotransmission. Recent studies have found that inhibitory neuron activity can not only dampen excitatory activity but also increase excitatory activity via inhibitory-to-inhibitory connections that disinhibit excitatory neurons. The GGRB condition was established by the administration of APV+NBQX (as before) and BMI (0.5mM; a GABAA receptor antagonist) to further isolate inhibitory activity. Lastly the NOSGRB condition was established by administering APV+NBQX and the NOS blocker L-NNA (0.5mM) in a separate cohort of animals to investigate the role of nitric oxide on the inhibitory activity-driven hemodynamic response. Results and Discussion Photo-stimulation (PS) of inhibitory neurons under control conditions generated LFP and MUA responses that were effectively modulated by the photo-stimulus duration (Figure 1). More importantly the evoked hemodynamic responses were much larger than those evoked by forelimb stimulation (FL) and were also slower (longer time-to-peak; Figure 2). Inspection of the evoked LFP activity shows features similar to that of excitatory activity akin to that of forelimb stimulation. Experiments were performed under GRB conditions to isolate inhibitory activity and robust but slightly reduced LFP and hemodynamic responses were observed (Figure 3). Experiments were also performed under the GGRB condition to also block post-synaptic inhibitory neurotransmission. Electrophysiology experiments showed temporal narrowing of the LFP and significantly reduced

hemodynamic responses (Figure 3). Lastly NOSGRB experiments were performed and although the neural activity was maintained the hemodynamic response was significantly suppressed. Additional experiments under this condition are currently under way. Conclusions In summary increasing inhibitory activity has a profound impact on vascular regulation the hemodynamic response and its dynamic features.

Morning Poster Session
Location: Row B
Poster #17

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Manish Verma	Postdoctoral	Chu	Pathology

Role of Mitochondrial Calcium Uniporter SIRTUIN-3 and Calcium in LRRK2 mediated neurodegeneration.

Background: Leucine-rich repeat kinase 2 (LRRK2) is a large (~280 kDa) multi-domain protein containing GTPase and kinase domains that is predominantly localized to the cytoplasm. Mutations in various domains of LRRK2 have been associated with familial Parkinsonian neurodegeneration. Impaired oxidative phosphorylation perturbations of mitochondrial dynamics and increased sensitivity to mtDNA damage have been observed in cells expressing LRRK2. LRRK2 has been implicated in the regulation of various cellular pathways including regulation of calcium (Ca2+) homeostasis. Furthermore dysregulation of Ca2+ homeostasis has been shown to induce mitophagy leading to loss of dendritic mitochondria in LRRK2 mutant expressing primary cortical neurons. These studies indicate that dysregulation of Ca2+ handling may play a central role in neurodegeneration; however the mechanism through which LRRK2 acts to modulate mitochondrial Ca2+ homeostasis remains unclear. In the current study we delineate the possible molecular pathway through which mutant LRRK2 induces mitochondrial damage. Results: Mouse primary cortical neurons expressing PD-associated LRRK2 mutants showed simultaneous increase in cytosolic and mitochondrial Ca2+ upon KCl stimulation compared to those expressing either pcDNA or LRRK2-wild type. This increase in mitochondrial Ca2+ uptake in LRRK2 mutants was due to transcriptional upregulation of one of the mitochondrial calcium uptake transporter called mitochondrial calcium uniporter (MCU). Moreover pharmacological or siRNA mediated inhibition of MCU in neurons protected against LRRK2 mutations induced dendrite retraction. Interestingly inhibition of ERK signaling pathway prevented increased expression of MCU and in turn partially rescued mutant LRRK2 mediated neurite retraction suggesting that LRRK2 may function through ERK pathway. Additionally restoration of mitochondrial Ca2+ handling by overexpression of mitochondrial sodium/Ca2+ exchanger (NCLX) or SIRTUIN-3 (SIRT3) also protected against LRRK2 mediated neurite retraction. Conclusion: Mitochondrial calcium overload has been implicated in various diseases. Mutations in LRRK2 have been shown to dysregulate Ca2+ homeostasis leading to loss of functioning mitochondria. In the present study we show that LRRK2 causes increased mitochondrial Ca2+ uptake by inducing the expression of MCU. This increase in MCU expression could potentially increase the susceptibility of neurons to mitochondrial calcium overload leading to LRRK2 associated neurotoxicity. Mutant LRRK2 (R1441C and G2019S) increased ERK1/2 phosphorylation and inhibition of ERK activity protected against LRRK2 mediated neurotoxicity by repressing MCU expression. On the other hand increasing mitochondrial Ca2+ efflux by overexpression of NCLX was also shown to be neuroprotective.

Afternoon Poster Session
Location: Row E
Poster #59

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Amelia Versace	Faculty	Versace	Psychiatry

Effect of Higher and Lower Diffusion Gradient Directions on Fiber Estimability and Diffusion Metrics in Young Adults

Purpose: The aim of the current study was to examine in comparable diffusion imaging (DI) sequences the effect of number of gradient directions on fiber estimability and DI metrics. Materials and Methods: Twenty-nine young adults (Mean age= 21.5 SD=2.1; 16 females) completed two DI sequences with higher (197 directions with b=700 s/mm2 1000 s/mm2 and 2500 s/mm2) and lower (61 directions with b=1000 s/mm2) number of gradient directions and comparable acquisition time and parameters. Importantly for comparison purpose with the DI sequences with lower number of gradient directions the DI sequences with higher number of gradient directions was analyzed using a Gaussian mode (i.e. model 1 as proposed in bedpostX). In addition as recommended for DI sequence with multiple diffusion weightings analyses modelling non-mono-exponential diffusion decay (model 2 as proposed in bedpostX) are also reported for the DI sequence with higher number of gradient directions. Results: Using a triple tensor model (Figure 1) fiber estimability measures derived from the DI sequence with higher number of gradient directions showed increased brain coverage of voxels supporting three fibers and an increased relative volume fraction (proportion of volume per voxel accounting for the diffusivity signal of each modelled direction) in voxels supporting three fibers (Figure 2 A-B). In addition tract-based spatial statistics (TBSS) using estimates of volume fractions paralleled these findings showing widespread increased volume fractions associated with the third (and second) tensor across the skeletonized brain for the DI sequence with higher number of gradient directions. Conclusion: Findings provide preliminary evidence for improved estimability of intra-voxel crossing fibers in brain regions characterized by high complexity of fibers in data acquired with higher number of gradient directions supporting its use in future studies.

Morning Poster Session
Location: Row C
Poster #33

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Jessica Wallisch	Postdoctoral	Kochanek	CCM

Aquaporin-4 inhibitor AER-271 blocks early cerebral edema in pediatric rat asphyxial cardiac arrest

INTRODUCTION: Cerebral edema is associated with poor outcome in cardiac arrest (CA) patients. Aquaporin-4 (AQP4) is a major regulator of water transport within the CNS and may play a detrimental role after CA by exacerbating tissue swelling and promoting intracranial hypertension. This is supported by evidence that (1) cortical AQP4 levels increase following asphyxial CA in rats and (2) transgenic AQP4 gene knockout mice have reduced ICP and decreased neuronal loss after global ischemia vs. wild-type littermates. We hypothesize that pharmacologic inhibition of AQP4 by AER-271 a novel selective AQP4 antagonist reduces cerebral edema and improve outcomes in a pediatric rat model of asphyxial CA. METHODS: Post-natal day 17 Sprague-Dawley rats were anesthetized intubated and mechanically ventilated. Femoral venous and arterial catheters were placed for drug delivery and monitoring. Additional measurements included EKG ETCO2 EEG and pulse oximetry. To induce a 9-min asphyxial CA rats (n=6 per group) were given neuromuscular blockade with vecuronium and disconnected from the ventilator. CPR was initiated by resuming mechanical ventilation administering bolus epinephrine and sodium bicarbonate and rapid manual chest compressions. Experimental therapy was administered immediately after return of spontaneous circulation (ROSC). Injured rats were randomized to AER-271 (5mg/kg IP at ROSC & 60 min post-ROSC) or vehicle (identical volume/time points). Control (naïve) mice were not given surgery or CA. Rats were sacrificed 3 6 and 24 h post-arrest for cerebral wet-dry-weight analysis (110o C for 72 h). Additional rats were evaluated for early outcome with Neurologic Deficit Score (NDS) at 3 24 48 and 72 h post-arrest. RESULTS: AER-271 was well tolerated and did not alter HR MAP time to ROSC pH or base deficit after CA. At this dosage therapeutic drug levels in plasma were attained quickly and maintained throughout the entire model (mean 15 min plasma level 515.25ng/mL ±118.26 SEM; 80 min 1690.75 ±313.96; 3 h 785.25 ±116.19 by LC-MS). Cerebral edema was ameliorated in AER-271 treated CA rats vs. vehicle controls and had brain water levels similar to naïve (82.95 ±0.17 naïve % brain water; 83.87 ±0.08 vehicle; 83.28 ±0.05 AER-271 p=0.0018 one-way ANOVA). However by 6 and 24 h post-CA the percent brain water had returned to naïve levels in all injury groups. NDS scoring showed a trend toward improved neurologic functioning at 3 h post-CA for animals treated with AER-271 (0.83 ±0.83 total NDS Naïve; 335.83 ±29.34 Vehicle; 261.67 ±20.56 AER-271 p<0.0001 one-way ANOVA). CONCLUSIONS: AQP-4 inhibition by AER-271 prevents early edema formation with a trend toward reduced neurologic deficit at 3 h post-arrest in a model of pediatric asphyxial CA. The anti-edema effect of AQP4 inhibition was not evident by 6 and 24 h post-arrest but this may relate to the time course of swelling in the model rather than lack of drug efficacy. Longer durations of injury may extend the swelling in this model and is an area for future study. Finally additional testing is underway to evaluate therapeutic effects on neuronal death.

Afternoon Poster Session
Location: Row D
Poster #45

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Yao Wang	Postdoctoral		Neuroscience and Psychiatry

Prefrontal Cortex to Accumbens Projections in Sleep Regulation of Reward

Sleep profoundly affects the emotional and motivational state. In humans and animals loss of sleep often results in enhanced motivation for reward which has direct implications for health risks as well as potential benefits. Current study aims at understanding the mechanisms underlying sleep deprivation (SD)-induced enhancement of reward seeking. Young adult mice (8 – 12 weeks old) were trained to self-administer sucrose pellet until a stable baseline was achieved. They then underwent acute SD for 6 hr during the first half of the light phase during which they had full access to food and water. When tested immediately after SD mice exhibited selective increase in sucrose self-administration but not food intake suggesting enhanced motivation for reward. In the nucleus accumbens (NAc) a key brain region regulating emotional and motivational responses we observed a decrease in the ratio of the overall excitatory over inhibitory synaptic inputs onto NAc principle neurons after SD. The shift was partly mediated by reduced glutamatergic transmission of presynaptic origin. Further analysis revealed that there was selective reduction of the glutamate release probability at the medial prefrontal cortex (mPFC)-to-NAc synapses but not those from the hippocampus thalamus or the basal lateral amygdala. To reverse this SD-induced synaptic alteration we expressed the stabilized step function opsin (SSFO) in the mPFC; optogenetic stimulation of SSFO at mPFC-to-NAc projection terminals persistently enhanced the action potential-dependent glutamate release. Finally intra-NAc optogenetic stimulation of SSFO selectively at mPFC-to-NAc terminals restored normal sucrose seeking in mice with SD without affecting food intake. Our results highlight the mPFC-to-NAc projection as a key circuit-based target for sleep to regulate reward-motivated behaviors.

Afternoon Poster Session
Location: Row D
Poster #52

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Meryl Warshafsky	Undergraduate	Nicholls	Pediatrics

Characterization of a ferret brain cell line expressing gene markers of epithelial-mesenchymal transition (EMT)

Mouse as a mammalian model of human disease has been a pillar of the research community largely due to the genetics and longstanding ability to modify the genome. Nevertheless mouse is often a poor model of clinical phenotypes and therapeutic treatments poorly translate from rodent to patients. As a consequence mammalian models with a physiology anatomy and genome closer to humans are needed. Indeed for brain disorders species with a gyrencephalic brain ideally of a size on the same order of magnitude to the human brain would be ideal. The domestic ferret Mustela putorius furo (Mpf) is genetically more similar to humans than mice and represents a suitable laboratory model to study human disease especially of the lung and for brain development. As an entry point we have characterized a cell line derived from a six week old ferret brain Mpf cells (Trowbridge et al. 1982 In Vitro 18 952-60). An initial point of focus was our bioinformatics analysis of the ferret genome sequence to identify the orthologous cluster of ~12 paternally-expressed imprinted genes involved in Prader-Willi syndrome a neurobehavioral disorder including those encoding proteins or snoRNAs and the cis-regulatory regions for transcriptional and imprinting regulation. Additionally the Snord116 snoRNA duplicated family was characterized in detail by genomic PCR cloning and DNA sequencing of paralogous Snord116 copies. Chromosomal analysis of Mpf cells by G-banding as well as fluorescence in situ hybridization with a Snord116 genomic probe identified mosaicism with 70% of cells being pseudodiploid and 30% of cells having aneuploidy; we are now isolating clonal pseudodiploid sublines. To assess the ability of Mpf cells to undergo genome editing vectors encoding two CRISPR guide RNAs (gRNAs) and Cas9 components as well as an EGFP marker were transfected into Mpf cells. The guide RNAs direct the Cas9 endonuclease protein to complementary target sequences to catalyze a double strand break (DSB) with DNA repair of two DSBs resulting in the intervening fragment being deleted. Deletion-PCR and DNA sequencing of the breakpoint fragments confirmed a capability for efficient genome editing in Mpf cells. Cell morphology differed when Mpf cells were cultured in different media and at different cell densities including the formation of long cell extensions with branches or beading and increased expression of some neural markers. As well as candidate gene expression assessed by RT-PCR RNA-sequencing was performed to assess genome-wide gene expression. Many of the highly expressed genes including those for transcriptional regulators and others govern the process of epithelial-mesenchymal transition (EMT). This suggests a hypothesis that Mpf cells may be representative of an early stage in the process by which neuroepithelial progenitor cells commit to a neural fate and migrate a process likened to EMT. The detailed characterization of Mpf cells provides a new in vitro brain-derived cellular model and has general utility for optimization of genome editing reagents in the development of ferret models of human disease.

Morning Poster Session
Location: Row E
Poster #62

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Jillian Weeks	Graduate	Torregrossa	Neuroscience

Casein-kinase 2 activity may mediate CamKiia-dependent effects on reconsolidation of a cocaine-associated cue memory

Drug addiction is a widespread public health issue the resolution of which depends on treatment strategies that can produce long-term abstinence from drug use. However the complex milieu of cues that come to be associated with the drug presents a persistent challenge as these stimuli gain powerful incentive salience and can lead to robust motivation to seek the drug (craving) and relapse. Understanding of the processes by which these maladaptive memories are consolidated retrieved and potentially manipulated may present a critical outlet in developing more effective and lasting treatment strategies for drug addiction. Previous research in our lab has implicated Ca2+/calmodulin-dependent protein kinase II (CaMKIIα) in the reconsolidation of a cocaine-associated memory including phosphorylation on three threonine residues that have not previously been studied in the context of memory regulation. Bioinformatic databases suggest that these threonine residues (T334 336 & 337) are substrates for casein kinase 2 (CK2). Therefore the present experiments aimed to determine if CK2 is involved in CaMKIIα-mediated effects on reconsolidation of a cocaine-associated memory. Male Sprague-Dawley rats were trained to self-administer cocaine paired with an audiovisual cue. After lever extinction rats had the cue memory reactivated by brief presentation in a novel context. After reactivation rats were given vehicle or an inhibitor of CK2 activity 4 5 6 7-Tetrabromobenzotriazole (TBB) into the basolateral amygdala (BLA). A control group was exposed to TBB in the absence of memory reactivation (i.e. no cue presentation). We found that when cue memories were reactivated treatment with TBB but not vehicle produced a significant reduction in reinstatement responding while TBB did not reduce reinstatement in the no reactivation condition. Further experiments will aim to determine whether or not CK2 inhibition can reduce CaMKIIα activity in vitro as hypothesized by expressing CaMKIIα in HEK293T cells treating cultured cells with varying doses of TBB then assessing resulting CaMKIIα activity. The behavioral results of this study suggest that CK2 through its effects on CaMKIIα function may play a critical role in drug-related memory processes and thus serve as a target for future research and ultimately therapeutic applications.

Morning Poster Session
Location: Row C
Poster #31

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Gregory Weiner	Graduate	Jankowitz	Neurosurgery

Is the 64-Channel Multidetector Computer Tomography Angiography Reliable for the Diagnosis of Blunt Cerebrovascular Injury - The Importance of Digital Subtraction Angiography

Blunt cerebrovascular injuries (BCVI) are potentially associated with high morbidity and mortality. Since patients with BCVI are often asymptomatic at presentation, with neurological sequelae most commonly occurring within 72 hours, timely diagnosis is essential. To date, the use of 64-slice, multi-detector computed tomography angiography (CTA) has proven itself to be a non-invasive, cost-effective, reliable means of screening; however, the false-positive rate of CTA in diagnosing patients with BCVI represents a key drawback. Our objective was to examine the reliability of CTA in accurately diagnosing patients with BCVI when performing follow-up confirmatory digital subtraction angiography (DSA). Methods: We performed a retrospective analysis of patients with BCVI from 2013-2015 at two Level I trauma centers. All patients included herein underwent initial clinical screening based on the updated Denver Screening Criteria and were subsequently evaluated for BCVI via CTA. Patients who were found to have BCVI based on CTA underwent DSA to confirm BCVI diagnosis. Patient demographics, screening indication, CTA and DSA injury subtype and laboratory values were collected. Comparison of false positive rates stratified by CTA injury subtype was performed using Chi-squared testing. Results: One hundred and forty patients, 64% males with a mean age of 50 years presented with 156 cerebrovascular blunt injuries to the internal carotid and/or vertebral arteries. After comparison with DSA, CTA was incorrect in 61.5% of vessels studied and the overall CTA false positive rate was 47%. The positive predictive value for CTA was higher amongst worse BCVI injury subtypes on initial imaging (PPV 76% to 97%, for BCVI grades 2 & 4, respectively) compared to grade 1 injuries (PPV 30%, $p<0.001$). Conclusions: The utility of 64-slice, multi-detector CTA as a screening test for BCVI is well-established; however, its high false positive rate, especially in patients with BCVI grade 1 injuries, supports the utilization of DSA following all positive CTA findings in patients with suspected BCVI. The use of DSA as an adjunctive test in patients with positive CTA findings allows for increased accuracy in correctly diagnosing BCVI, which is crucial when considering the potential implications of initiating antithrombotic therapy in the polytrauma patient.

Afternoon Poster Session
Location: Row B
Poster #16

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Jordan Williams	Postdoctoral	Schwartz	Systems Neuroscience Institute

Virus opsin and immunomodulation approaches for optogenetic control of peripheral motor function

The incorporation of light sensitive opsins into peripheral motor nerves offers a promising alternative to traditional functional electrical stimulation in restoring lost motor function. Gene therapy to express such optogenetic constructs for functional optical stimulation of muscles has been successfully demonstrated in non-transgenic rodents. However the procedure for transducing opsins into peripheral motor nerves is technically difficult and only a limited catalog of proven constructs in this context exist to date. To realize a robust clinical outcome for this approach it will be necessary to demonstrate expression in primate peripheral nerves which has not yet been achieved. In light of this need our present study examines the efficacy of several viral vectors and opsins in transducing nerves sensitive to functional optical stimulation. Here we discuss ongoing experiments and results with several AAV-based vectors and non-replicating rabies virus (NRRV) vectors as well as results from constructs utilizing one of two opsins: the traditional channel rhodopsin (ChR2) as well as the more recently described Chronos. In addition we examine the efficacy of several methods and routes for virus injection including muscle nerve and spinal cord. Finally we will describe our protocol and results for immunosuppression to facilitate virus transduction into motor nerve cells. Hopefully our findings will provide valuable insight into approaches that will translate well to primate peripheral motor gene therapy.

Morning Poster Session
Location: Row D
Poster #54

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Jesse Wood	Postdoctoral	Ahmari	Psychiatry

Hyper-synchrony in medial orbitofrontal-ventromedial striatal circuits accompanies development of compulsive-like grooming in mice

The World Health Organization has identified OCD as a top ten cause of illness-related disability underscoring the heavy burden this disorder places on patients and the steep cost to society at large. Increased medial orbitofrontal cortex (mOFC) and ventromedial striatal (VMS) activity is thought to drive OCD symptoms though it is unclear how this circuit gives rise to compulsivity. It is therefore necessary to uncover pathological patterns of mOFC-VMS communication associated with compulsive behaviors to understand this relationship and potentially develop novel therapeutic approaches. To elucidate the relationship between compulsive-like behaviors and mOFC-VMS hyperactivity we performed repeated optogenetic stimulation of mOFC-VMS projections of mice over 10 days using a paradigm that causes progressive development of a persistent compulsive-like grooming phenotype. To understand how the networks underlying this phenotype change over time we simultaneously recorded the electrophysiological activity of mOFC and VMS neurons as we stimulated mOFC-VMS circuits for 5 minutes/day using ChR2 (473nm 10Hz 10msec pulse width). Our data suggest that during optogenetic stimulation of mOFC terminals in the VMS many mOFC neurons are activated nearly synchronously as measured by the presence of complex waveform population spikes. Prior to the first laser stimulation there was no mOFC synchrony in ChR2 animals (0/66 pairs of simultaneously recorded mOFC neurons). At the conclusion of the first day of optogenetic stimulation 3% of mOFC neuron pairs were significantly synchronous as measured by cross-correlation analysis. Synchrony continued to emerge in mOFC networks in association with repeated optogenetic stimulation. Prior to the final day of optogenetic stimulation (pre-stimulation period in session ten) 6.6% of mOFC pairs fired in synchronous fashion. Optogenetic stimulation on that day induced even greater levels of synchrony such that 14.3% of mOFC pairs fired synchronously. Significant levels of synchrony were never detected in control mice. Collectively these data suggest that development of the compulsive-like phenotype is associated with increased synchronous activity in mOFC networks. Increased synchrony in mOFC-VMS circuits could contribute to compulsive-like behavior by disrupting processing in striatal networks that subserve behavioral selection.

Morning Poster Session
Location: Row C
Poster #35

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Jue Wu	Postdoctoral	Escolar	Pediatrics

Improvements in brain development following stem-cell transplantation in Krabbe disease

Background: Krabbe disease is a rare but severe neurodegenerative disorder mainly affecting infants. It is characterized by the lack of a myelin-related enzyme galactocerebrosidase and this causes abnormal myelination in the central and peripheral nervous systems. Children with this autosomal recessive disease are born normal but have disease onset in early or late infancy. The neurological symptoms progress quickly and often lead to death with 2 years if treatment is not administered early. Hematopoietic stem cell transplantation (HSCT) is the only treatment available that can halt disease progression. While the benefits of transplantation have been shown in behavioral exams we set out to directly investigate the change in cerebral myelination by MRI and propose a more sensitive and objective tool to access the effects of this transplant treatment and compare them with the natural history of the disease. Method: Diffusion tensor imaging (DTI) was obtained to assess white matter integrity of the brain. DTI measures the water diffusion property in the white matter and reflects the direction of axonal microstructure. We longitudinally scanned 55 Krabbe patients with early infantile onset of which 14 were treated with HSCT after their first MRI scan. Quality of DTI images was checked and corrupted ones were excluded in the analysis. Age-specific brain atlases (neonatal 1 to 2 year-old 3 to 6 year-old) were built based on normal controls. Alignment of patient image to the atlas was made such that specific white matter tracts could be delineated. Fractional anisotropy (FA) was derived from DTI as a measure of the organization of the corticospinal tracts which relay action potential from motor cortex to spinal cord. Lower than normal FA values indicate disorganization of myelination around the tracts. Results: Patients treated with HSCT mostly followed the normal developmental trajectory of the corticospinal tract albeit in the lower part of the normal range. Patients that were not treated with HSCT started with lower than normal FA and the measure decreased significantly within two years after an initial increase. The FA values are consistent with the motor function as measured in the behavioral test. Conclusion: Diffusion based brain MRI measure indicates the compromised white matter integrity of early infantile Krabbe patients who are not treated with hematopoietic transplantation. In contrast patients who are treated with this transplantation early in life preserved the quality in the corticospinal tract as compared to normal controls and they appear to follow a normal development over time.

Morning Poster Session
Location: Row E
Poster #68

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Man Wu	Graduate		Neuroscience

New calcium channel gating modifiers with therapeutic potential that prolong channel deactivation and alter transmitter release at neuromuscular synapses

Previously we have developed novel analogs (including GV-58) of (R)-roscovitine that have reduced cyclin-dependent kinase (Cdk) activity and enhanced calcium channel gating modifier activity. The goal of this work has been to develop (1) tool compounds for studies of calcium channels and transmitter release and (2) therapeutic leads for the treatment of neuromuscular diseases. In particular Lambert-Eaton Myasthenic Syndrome (LEMS) is an autoimmune disorder that attacks and removes presynaptic calcium channels from motor synapses. As a result LEMS patients show a reduction in transmitter release leading to neuromuscular weakness. Current treatment for LEMS includes the potassium channel blocker 3 4-diaminopyridine (DAP) which widens the presynaptic action potential increasing the amount of calcium influx and thus increasing transmitter release. However 3 4-DAP has dose-limiting side effects preventing full symptomatic relief for some of these patients. Our previously reported compound (GV-58) is a gating modifier that increases total calcium entry by stabilizing the open state of the channel but is dependent on voltage-dependent calcium channel opening such that very brief depolarizations modified fewer channels than longer depolarizations. Our goal here was to develop and test additional analogs based on the GV-58 structure that might be more potent and act faster. Here we report the testing of eight new analogs four of which show promise: MF-06 MF-17 KK-75 and KK76. These new compounds included modifications to the placement of nitrogens around the core of the molecule in combination with alterations to two side chains. We tested the effects of these compounds on Cav2.1 calcium channels expressed in TSA201 cells using perforated whole-cell patch clamp techniques and on transmitter release using intracellular recordings from weakened adult mouse neuromuscular junctions. One of these compounds (MF-06) slowed channel deactivation to an even greater extent than GV-58. Interestingly both MF compounds appear to be slower to act than the KK compounds. Further these four compounds had variable cdk activity as compared with (R)-roscovitine. Effects of these compounds on transmitter release at weakened neuromuscular synapses are predicted to be complicated by their varying magnitude of effects on channel gating combined with their speed of action. Taken together these data increase our understanding of the structure-activity relationship for these gating modifiers with therapeutic potential and provide new tools for the study of calcium channels and calcium-triggered transmitter release.

Morning Poster Session
Location: Row A
Poster #7

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Yijen Wu	Faculty	Wu	Developmental Biology and Neurology

MR SPECTROSCOPIC AND IMAGING STUDIES OF A VARIABLE RAT MODEL OF EPILEPSY

Rationale: The development of spontaneous recurrent seizures (epilepsy) is a complex process that commonly ensues after an initial cerebral insult. While it is well known that metabolic dysfunction is common during this process there is little experimental data on how variation in seizure duration in experimental status epilepticus (SE) influences metabolic injury. Using lengthy periods of status epilepticus that are highly likely to result in the development of epilepsy several groups (1 2) have reported on the metabolic injury seen during the epileptogenesis period in chemoconvulsant models of epilepsy. These changes have been characterized as neuronal and glial in nature with declines in N-acetyl aspartate (NAA) increases in myo-inositol (Ins) and glutamine. In this report we use a variant of the Hellier Dudek model with a much shorter period of status epilepticus to assess the metabolic changes. In a subset of these animals we obtain histology to assess for neuronal injury and gliosis. Method: A short variant of the Hellier Dudek (3) low dose kainate (KA) model of temporal lobe epilepsy was used. Briefly 180-200g male rats (Charles River) were injected ip with 5 mg/kg KA (n=21) until a stage 3/4/5 seizure (modified Racine scale) was elicited. Status epilepticus was defined as the time after the first motor seizure started until 45min later when 20mg/kg diazepam was administered to terminate behavioral seizures. Controls (n=10) were similarly treated with sterile saline. Rats were evaluated twice by MR after status (3days 3d) and during the latent period (3weeks 3w). Rats were video monitored 24-7 for the duration of the study. MRI: A Bruker Biospec 7T 40cm horizontal MR system was used throughout with a 72mm volume transmit coil and 2 element receive array. Rapid T2 weighted images were acquired for optimal positioning of the hippocampus. Single voxel MR spectroscopy (8ul) was acquired with TR/TE 1.7s/10ms (17min per acquisition) from the left right dentate gyrus and CA3 region. LCM analysis was performed for determination of the metabolite profiles and taken as a ratio to total creatine tCr accepting Cramer Rao bounds of <12%. A total of n=21 kainate treated rats were studied with n=7 controls. Results: A hierarchical cluster analysis performed on the 3day data from n=21 kainate treated animals (dentate gyrus voxel) segregated into two clusters denoted by KM (more injured n=6) and KL (less injured n=15). While there was no difference in kainate dosing or seizure count between them the metabolic pattern of injury was different. The KM group displayed the largest significant changes in neuronal and glial parameters; the KL group displayed milder but significant changes. At 3weeks the KL group returned to normal compared to controls while the KM group persisted with declines in NAA/tCr Glutamate/tCr increased Inositol/tCr and Glutamine/tCr. The classification was also consistent with subsequent patterns of histology at 3weeks. Table 1 shows the differences in these groups. Conclusions: While a short status period might be expected to generate a continuous distribution of metabolic injury these data show that the short Hellier Dudek model appears to generate two levels of injury. The changes seen in segregated groups persisted into 3weeks and can be interpreted based on neuronal and glial biomarkers consistent with histology results. This work is supported by NIH R21 NS83035 and R01NS090417

Morning Poster Session
Location: Row A
Poster #11

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Svitlana Yablonska	Postdoctoral		Neurological Surgery

Localization of Huntingtin in mammalian mitochondria

Mitochondrial dysfunction is believed to be a crucial driver of Huntington's disease (HD) pathophysiology. HD is a hereditary progressive neurodegenerative disorder characterized by selective neuronal loss in the striatum and cortex caused by mutated huntingtin protein (mHtt). Though many mitochondrial related effects of Htt have been described the precise location and translocation of Htt in mitochondria has not been shown. We utilized fresh brain tissue of wild-type (WT) and transgenic mice expressing both full length mHtt (140CAG) and N-terminal fragment (R6/2) to purify synaptosomal and non-synaptosomal mitochondria. Utilizing treatment with protease and permeabilizing agent we localized WT and mutant full length Htt as well as fragments of mHtt inside mitochondria. By conducting the same assay on mitochondria isolated from post-surgical frozen human cortex we confirmed localization of human WT and mHtt in isolated brain mitochondria. Immunogold electron microscopy (IEM) demonstrated co-localization of mHtt fragments with synaptosomal mitochondria of R6/2 mice. The N-terminal 17-amino acids sequence (N17) of Htt plays a role in its mitochondrial targeting. We conducted structured illumination microscopy (SIM) and confirmed mitochondrial translocation of Htt's N17 fused with fluorescent protein. Therefore results of our study clearly demonstrate localization of Htt in mammalian mitochondria pointing towards its role in mitochondrial functions and involvement of mHtt in development of mitochondrial pathology.

Morning Poster Session
Location: Row B
Poster #25

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Chung-Yang Yeh	Graduate		Neurobiologu

Kv2.1-derived peptide ameliorates apoptosis in vitro and in an in vivo model of ischemic stroke

Neurodegeneration in the ischemic stroke penumbra involves caspase activation and represents an important target for therapeutic interventions. The voltage-gated potassium channel Kv2.1 has been shown to play an important role in programmed neuronal apoptosis. Previously, we have identified that Kv2.1 promotes caspase activation by generating a pronounced K+ efflux through de novo channel insertion. This process is modulated by Zn2+-dependent pathways leading to the phosphorylation of Kv2.1 at residues Y124 and S800, allowing interactions between the proximal Kv2.1 C-terminus (C1a) and the SNARE protein syntaxin 1A. Overexpression of the C1a decreases pseudo-apoptotic Kv2.1-S800E currents in CHO cells and improves neuronal survival after oxidative stress. Thus, suppressing apoptosis-permitting Kv2.1 currents through the competitive binding of syntaxin 1A represents a promising neuroprotective approach and is explored here through the evaluation of a peptide aptamer. Far-Western blot analysis of overlapping 15 a.a. segments of the C1a region found a 9 a.a. sequence with high binding affinity to syntaxin 1A. Conjugating the cell-permeable HIV trans-activator of transcription domain (TAT) to the N-terminus of this sequence resulted in an administrable peptide construct (TAT-C1aB). In vivo two-photon imaging with FitC-tagged TAT-C1aB confirmed that i.p. administration of the peptide reaches brain vessels within minutes. Whole-cell patch clamp recordings demonstrated that incubation with 10 µM TAT-C1aB significantly reduces pseudo-apoptotic Kv2.1-S800E current density (vehicle vs TAT-C1aB: 267.2±22.03 vs 189.5±19.64, Mean±SEM pA/pF, n=11; p=0.0159) in CHO cells. Further, 1 µM TAT-C1aB treatment significantly decreased lactate dehydrogenase release in rat cortical neuron cultures after excitotoxic insult (2.45±0.24 vs 1.31±0.077, Mean±SEM normalized LDH readout, n=4 each group, p=0.0038). Proximity ligation assay revealed that post-injury TAT-C1aB incubation prevents the dramatic increase in Kv2.1/syntaxin interactions 3 hr after treatment with an apoptogen. Notably, in a mouse model of transient middle cerebral artery occlusion, injections of TAT-C1aB (i.p., 6nmol/g, at 1+6h reperfusion) significantly reduced infarct size (0.20±0.019 vs 0.12±0.016, Mean±SEM infarct ratio, n=10 and n=7 respectively, p=0.0053). In all above experiments, TAT-conjugated scramble control had no detectable effects. Together, these findings characterized a promising neuroprotectant prototype and established the Kv2.1/syntaxin interaction as a novel molecular target in ischemic stroke as well as other neurodegenerative diseases.

Morning Poster Session
Location: Row A
Poster #3

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Yanjun Zhao	Postdoctoral	Wills	Neurobiology

Amyloid Beta Peptides Block New Synapse Assembly by Nogo Receptor Mediated Inhibition of T-Type Calcium Channels

Compelling evidence links amyloid beta peptide (ABeta) accumulation in the brains of Alzheimer's disease (AD) patients with the emergence of learning and memory deficits; yet a clear understanding of the events that drive this synaptic pathology are lacking. We present evidence that neurons exposed to amyloid beta peptides are unable to form new synapses an unappreciated feature of AD pathology. Further we demonstrate the Nogo receptor family (NgR1-3) act as amyloid beta receptors mediating an inhibition of synapse assembly and synaptic plasticity. Dual fluorescent sensor live imaging studies reveal that amyloid beta peptides activate NgRs on the dendritic shaft of neurons triggering an inhibition of calcium signaling. Finally we define T-type calcium channels as the target of ABeta-NgR signaling mediating ABeta's inhibitory effects on calcium synapse assembly and plasticity. These studies highlight deficits in new synapse assembly as a potential initiator of cognitive pathology in AD and pinpoint calcium dysregulation mediated by NgRs and T-type channels as key components.

Afternoon Poster Session
Location: Row A
Poster #6

Presenting Author:	Author Type:	Mentor/Lab:	Department:
Xin 'Sally' Zheng	Graduate	Cui	Bioengineering

Functional Evaluation of a Superoxide Dismutase Mimic Coating for Chronically Implanted Neural Electrodes

Recent advancement in brain-machine interface (BMI) has shown promise in enabling functional restoration of individuals with limb loss. Often a metal electrode array is chronically implanted into the brain region of interest and neural signals can be recorded and decoded to control an external prosthesis. However due to the brain's foreign body response microglia near the electrode site become activated and secrete pro-inflammatory cytokines recruiting additional macrophages and produce cytotoxic factors such as reactive oxygen species (ROS). The presence of ROS around the implant promotes neuronal death thereby degrading neural signal quality overtime. Superoxide dismutase (SOD) can remove superoxide (a form of ROS) through dismutation by converting superoxide to molecular oxygen and hydrogen peroxide. However due to its low stability and poor bioavailability SOD has been unsuccessful in treating neurological diseases induced by oxidative stress. SOD mimics (SODm) have shown to be neuroprotective in in vitro and in vivo models of disease influenced by oxidative stress such as Alzheimer's disease and stroke. When immobilized onto the surface of neural electrodes SODm may reduce neuronal death around the implant. Here we evaluate the acute and chronic performance of electrodes coated with immobilizable SODm (iSODm) in adult rats. 16-channel linear silicon probes with or without iSODm coating were implanted in the motor cortex of adult male rats for up to 3 months. In acute evaluations animals were sacrificed 1 week after electrode implantation and immunohistochemistry was performed to compare neuronal survival around the implant. In chronic evaluations weekly impedance measurements and neurophysiological recordings of spontaneous motor activity were acquired while the animals were freely moving. At endpoint all animals were sacrificed and immunohistochemistry was performed. Significantly greater neuron density in every 50 µm zone between (0 µm — 250 µm) around the coated implants were observed after 1 week of electrode implantation. Chronically the iSODm coating showed great promise in allowing electrodes to record high quality single units throughout the 3-month period with endpoint signal to noise ratio up to 7.91 and up to 50% in single unit yield. These results indicate the iSODm coating's efficacy in promoting neuronal health around neural electrodes and have the potential to benefit chronic neural recording for BMI or basic neuroscience research.