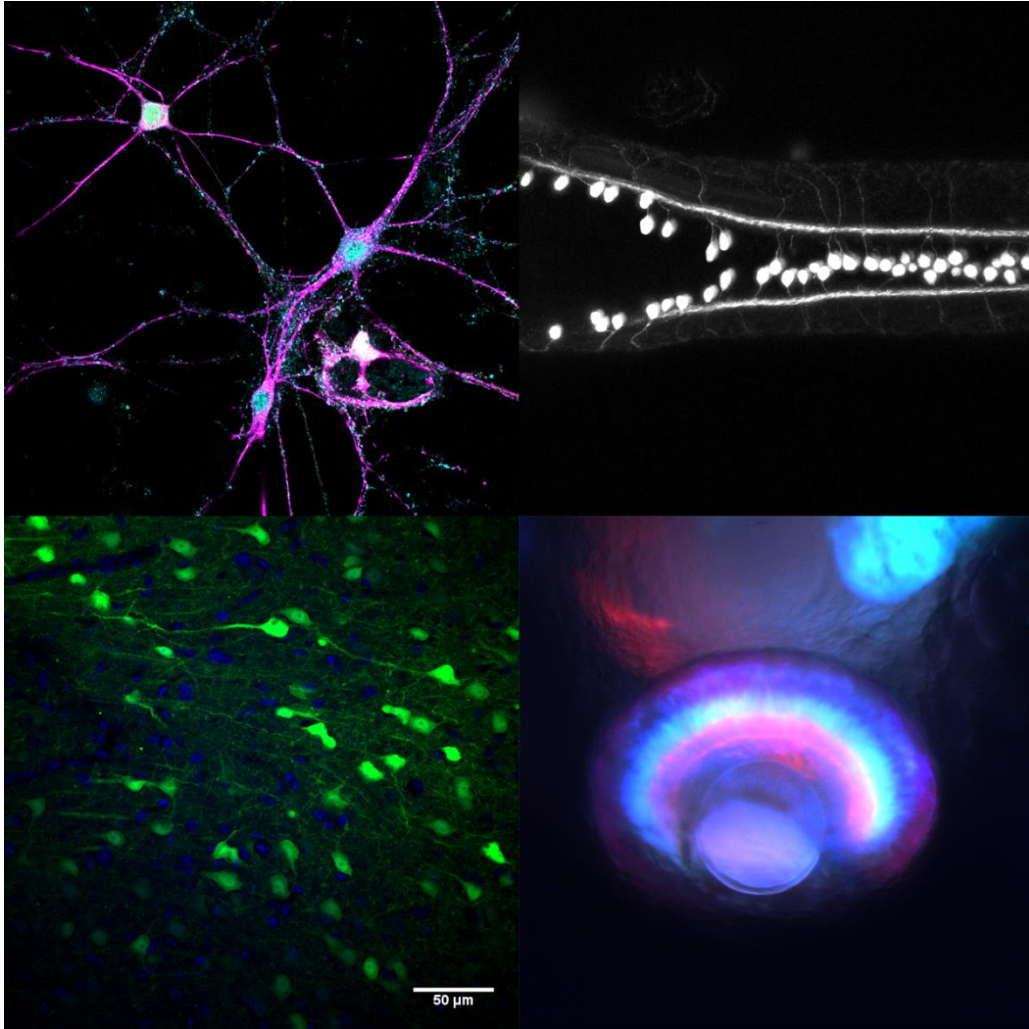# NINTH ANNUAL NEUROSCIENCE, BEHAVIOR AND HEALTH RESEARCH FORUM

The University of Vermont
Dudley H. Davis Center, Grand Maple Ballroom
February 8-9, 2019

Sponsored by:
University of Vermont Neuroscience, Behavior and Health Initiative
Vermont Chapter of the Society for Neuroscience Vermont Chapter
Images: Top left: Matt McCabe, top right: Ashely Waldron, bottom right: Theresa Legan, bottom left: Megan Shipman

February 1, 2019

Dear Colleagues:

Welcome to the Ninth Annual Neuroscience, Behavior and Health Forum, presented by the Vermont Chapter of the Society for Neuroscience in cooperation with the University of Vermont Neuroscience Behavior and Health Initiative. Neuroscience Forums have been held at the University of Vermont since 2005, and the partnership with the Neuroscience Behavior and Health Initiative began in 2011. Some of the original goals of this partnership included:

- To provide a forum to allow researchers from the diverse areas encompassed by the Neuroscience, Behavior and Health Initiative to learn about each other's work. A particular focus has been on facilitating communication between graduate students and faculty as well as other graduate students they would otherwise be unlikely to meet.

- To foster new and creative collaborations between scientists that may lead to stronger applications for extramural funding.

- To provide a sense of cohesion and common purpose amongst the diverse community of participating neuroscience, behavior and health researchers.

Since I joined the faculty at the University of Vermont in 2006, this forum has always been a scientific highlight of my year. The goals listed above are very salient to me, as my own scientific career has benefited immensely from our community. I hope that you enjoy this year's meeting, and thank you so much for participating!

Sincerely,

Sayamwong E. Hammack "Jom" Ph.D.
President, Vermont Chapter of the Society for Neuroscience
Professor
Department of Psychological Science
University of Vermont

Constance Cepko, Ph.D.

Professor of Genetics in the Department of Genetics at Harvard Medical School and an Investigator of the Howard Hughes Medical Institute

Determination of cell fates in the retina and SABER-FISH, a new in situ hybridization method for the multiplexed detection of RNA and DNA in tissue.

The mechanisms that cells use when they choose their fate during development of the central nervous system is the main problem under study in our lab. We have focused our studies on the retina, a tractable model for the rest of the central nervous system. In addition, we are interested in why photoreceptor cells die in the many forms of retinal degeneration, and are developing a gene therapy that prevents their death and the subsequent loss of vision. We also enjoy developing new technologies that enable these studies as well as others.

NBH RESEARCH FORUM SCHEDULE OF EVENTS

Friday, February 8 – Grand Maple Ballroom

4:00 pm   Hors d'oeuvres

4:30 pm   Welcome and Introduction: **Jom Hammack, Ph.D.**, President, Vermont Chapter of the Society for Neuroscience.
Dr. Cepko introduction by **Bryan Ballif, Ph.D.**

4:35 pm   Keynote Lecture: **Connie Cepko, Ph.D., Professor of Genetics in the Department of Genetics at Harvard Medical School and an Investigator of the Howard Hughes Medical Institute.** "Determination of cell fates in the retina and SABER-FISH, a new in situ hybridization method for the multiplexed detection of RNA and DNA in tissue."

5:35 pm   Reception

Saturday, February 9 – Grand Maple Ballroom

8:00 am   Registration and light breakfast and Poster setup

8:40-8:45 am   Introductory Remarks: **Mark Bouton, Ph.D.,** Director, University of Vermont Neuroscience, Behavior and Health Research Initiative

Platform Session I   Session Chairs: Katharine Tooke and Riley St Clair

8:45-9:00   **Davi Bock, Ph.D., Department of Neurological Sciences, UVM** "Whole-brain electron microscopy of Drosophila melanogaster reveals nonrandom memory circuitry"

9:00-9:15   **Ashley Waldron, Department of Biology, UVM** "Knock-down of Histidyl-tRNA Synthetase causes cell cycle arrest and apoptosis of neuronal progenitor cells"

9:15-9:30   **Sarah Emerson, Department of Biology, UVM** "The Role of Shootin-1 in zebrafish neurodevelopment"

9:30-9:45   **Daniella Thorsdottir, Department of Pharmacology, UVM** "Role of BDNF-mediated neuroplasticity within the PVN in cardiovascular regulation"

9:45-10:00   **Zhaojin Li, Department of Neurological Sciences, UVM** "Role of Angiotensin II in leptomeningeal anastomosis vasoactive properties in chronic hypertension"

10:10-10:40   Coffee Break

Platform Session II   Session Chairs: Callum Thomas and Theresa Legan

10:45-11:00   **Matthew McCabe, Department of Neurological Sciences, UVM**
"Synaptic dysfunction in a mouse model of epileptic encephalopathy"

11:00-11:15   **Greg Johnson, Department of Psychological Science, UVM**
"PACAP/PAC1 in the dentate gyrus of the hippocampus modulates contextual fear conditioning and increases granule cell excitability through an extracellular regulated kinase dependent signaling cascade"

11:15-11:30   **Willie Curry, Department of Neurological Sciences, UVM**
"The effect of interneuron progenitor cell implantation on a task of hippocampus-dependent working memory in an animal model of temporal lobe epilepsy"

11:30-11:45   **S. Bradley King, Department of Psychological Science, UVM**
"Long duration anxiogenic effects of BNST PACAP are not due to conditioned anxiety"

11:45-12:00   **Megan Shipman, Department of Psychological Science, UVM**
Chemogenetic inhibition of prelimbic cortex projections to dorsomedial striatum attenuates operant responding"

Lunch and Posters

12:00-2:00   Lunch

12:35-1:10   Poster Session I (Odd Numbers)

1:10-1:55   Poster Session II (Even Numbers)

(Platform Session III on next page)

Platform Session III   Session Chairs: Megan Perkins and Noelle Michaud

2:00-2:15   **Jaeda Coutinho-budd, Ph.D., Department of Biology, UVM**
"Cellular and molecular mechanisms of neuron-glia interactions at neuronal cell bodies"

2:15-2:30   **Nicholas Klug, Ph.D., Department of Pharmacology, UVM**
"Manipulating pressure and flow in the retinal vasculature"

2:30-2:45   **Michael Dash, Ph.D., Department of Psychology, Middlebury College**
"Infraslow coordination of slow wave activity through enhanced neuronal synchrony"

2:45-3:00   **Emily Coderre, Ph.D., Department of Communication Sciences and Disorders, UVM**
"Predictive Abilities During Visual Narrative Comprehension in Individuals with Autism"

3:00-3:15   **Eric Thrailkill, Ph.D., Department of Psychological Science, UVM**
"Resurgence of extinguished operant responding in humans depends on lack of generalization from the treatment context"

3:15   Closing Remarks and Awards

POSTERS

1. Stress Narrative Favors Habit-Based Control of Instrumental Behavior in Humans

Remy Castella, Nathan Schwab, Heather Homberg, Kevin Walder, Eric Thrailkill, & Scott Mackey
Departments of Psychiatry and Psychological Sciences, University of Vermont

Instrumental behavior is governed by two brain systems: a habit-based controller and a goal-directed controller. Habit-based control is fast and efficient, and depends on learning related to previously reinforced behavior. Goal-directed control is slower and more deliberate, and flexibly adapts responding to moment-to-moment changes in the behavioral context. Specific conditions bias control of instrumental behavior to one system or the other. Stress, fatigue, overtraining and cognitive load bias behavior toward habit-based control. Devaluation paradigms in which the outcome of a trained behavior is suddenly devalued are used to assess which system is controlling behavior under different conditions. Here, we used a devaluation paradigm to determine whether a verbal narrative stressor would bias behavior toward habit-based control. Participants were exposed to either a stressful or a neutral nonstressful narrative. On average, the stressed participants continued to respond at a higher rate than the nonstressed participants after outcome devaluation indicating that the narrative stressor effectively biased behavior toward habit-based control. We also examined whether the narrative stressor would differentially affect behavior in smokers and nonsmokers but found that there was no difference between groups.

2. ENIGMA-Addiction: Neuroimaging Brain Phenotype

Scott Mackey, Hugh Garavan, and the ENIGMA Addiction Consortium
Department of Psychiatry, University of Vermont

ENIGMA-Addiction is an international, multi-site data pooling consortium that seeks to identify the neurobiological and genetic correlates of SUD. While it continues to expand, it currently contains over 15,000 participants from 14 countries and includes current and former addicts, recreational users, and longitudinal cohort studies. The motivation for the large sample size is to be able to identify gene-brain associations that are reliable and reproducible. The first study of the consortium examined whether there are brain volumetric differences between SUD cases and controls and if these are common or different across different drugs of abuse. A mega-analysis was performed on data pooled from 23 laboratories, including 3,240 individuals, 2,140 of whom had substance dependence on one of five substances: alcohol, nicotine, cocaine, methamphetamine, or cannabis. Lower volume or thickness was observed in many brain regions in individuals with substance dependence. The greatest effects were associated with alcohol use disorder. A set of affected regions related to dependence in general, regardless of the substance, included the insula and the medial orbitofrontal cortex. Furthermore, a support vector machine multivariate classification of regional brain volumes successfully classified individuals with SUD on alcohol or nicotine relative to nondependent control subjects. These results indicate that dependence on a range of different substances shares a common neural substrate and that differential patterns of regional volume could serve as useful biomarkers of dependence on alcohol and nicotine. Future aims include a systematic search for genetic correlates of these addiction-general and drug-specific putative biomarkers.

3. Transmitter co-expression in the peripheral and central nervous system of an invertebrate model system the wandering spider Cupiennius salei

Taylor Harris and Ruth Fabian-Fine
Department of Biology, Saint Michael's College

Co-transmission and neuromodulation in sensory circuits plays an important role in the ability of organisms to detect a vast array of external and internal stimuli and initiate appropriate behavioral responses. Pathologies in these circuits have been implicated in disorders leading to abnormal behavioral responses, emphasizing the importance to gain a better understanding of co-transmission and modulation in sensory circuits. Large, individually identifiable neurons in the spider, Cupiennius salei are exceptionally suitable to study the functional significance of co-transmission. Using in situ hybridization, electron microscopy, Western Blot analysis and immunohistochemistry we have demonstrated that most neurons in the CNS co-express up to five neurotransmitters. We observed co-expression of the fast acting transmitters GABA, glutamate and acetylcholine and provide evidence that these neurons also release FMRFamide and proctolin. The intensity of immunofluorescence is indicative of the transmitter amount expressed in individual neurons. We hypothesize that strongly labeled neurons represent projection neurons that send axons into different areas of the CNS. We further propose that neurons that are strongly labeled for one transmitter and show weak labeling for other transmitters utilize the weakly labeled transmitter as neuromodulator. We propose that neurons that show similar expression intensities for all co-expressed transmitters are likely modulatory neurons. Our findings reveal that the number of biochemically diverse neurons is far greater than previously suggested.

4. Co-localization of γ-aminobutyric acid and FMRFamide-related peptides in the central nervous system of Cupiennius salei

Noelle Picard, Luke Fournier, Ruth Fabian-Fine
Department of Biology, Saint Michael's College

Mechanosensory hair cells in the mammalian inner ear receive efferent innervation through neurons that co-express two or more transmitters. Due to the bony encasement around the hair cells and their difficult accessibility, our knowledge regarding the functional purpose of the efferent innervation is only fragmentary. To study efferent innervation of sensory neurons, we have identified an invertebrate model system - the wandering spider (Cupiennius salei) - in which the sensory and efferent neurons are more easily accessible. The efferent neurons in both the mammalian and arachnid systems consist of biochemically and morphologically diverse neurons that co-release a variety of transmitters including GABA, glutamate, and acetylcholine. Other transmitters include dopamine, octopamine and neuropeptides such as enkephalin and FMRFamide family members. We have recently demonstrated that ~10% of neurons in the CNS of C. salei express FMRFamide. Interestingly, the distribution of FMRFamide-expressing neurons is similar to that of previously described GABA-immunoreactive neurons. Using light microscopic immunohistochemistry, we demonstrate that ~92% of FMRFamide-expressing neurons are also GABA-immunoreactive. Our findings suggest that in C.salei, FMRFamide is mainly utilized as a neuromodulator in GABA-expressing neurons. These findings are supported by ultrastructural observations that show that GABAergic terminals contain small numbers of large electron dense vesicles, which are characteristic for neuropeptide containing vesicles. The functional significance if this co-expression is currently unknown and will be subject of future investigations.

5. Co-expression of proctolin and glutamate in the central and peripheral nervous system of Cupiennius salei

Hailee E. Poulin, Elizabeth E. Senior, Madison Dobecki, Bradley Anair, Ruth Fabian-Fine
Department of Biology; Saint Michael's College

Mechanosensory neurons in the invertebrate model system Cupiennius salei are modulated by efferent fibers that have been shown to express multiple neurotransmitters including GABA, glutamate, octopamine, and FMRFamide (Fabian-Fine et al., 1999 J Neurosci 19:298 pp.; Widmer et al., 2005 J Neurosci 25:1588 pp). Ultrastructural investigations reveal diverse vesicle populations within individual synaptic profiles indicating that some of the efferent neurons co-transmit two or more transmitters. Whereas small electronlucent vesicles contain smaller fast-acting transmitters, electron dense vesicles contain neuropeptides. A variety of both vesicle types are present within individual presynaptic profiles (Tarr et al., Cell Tissue Res 2018). The functional significance of this co-transmission on sensory neurons is unknown. For later electrophysiological investigations we are identifying the transmitters that are co-expressed within the efferent neurons. Using immunohistochemistry and Western Blot analysis we demonstrate that approximately 74.6% of proctolin-immunoreactive (proctolin-IR) neurons coexpress glutamate, including motor neurons. The majority of proctolin-IR neurons appeared weakly labeled (96.79%), 3.21% appeared strongly labeled. These findings suggest that proctolin is likely present at low concentrations as a neuromodulator within glutamatergic neurons. Less than 10% of glutamate-IR neurons lacked proctolin-IR. It is unclear if these neurons co-express FMRFamide that has been shown to be present in a subpopulation of glutamatergic neurons (Tarr et al., 2018). We conclude that most glutamatergic neurons co-release proctolin, which likely modulates the electrophysiological response pattern of glutamatergic synapses that are presynaptic to sensory neurons and muscle fibers.

6. Abl-dependent phosphorylation of SH family adaptors promotes their interaction with the CrkL-SH2 domain.

Brendan W. Chandler, Anna M. Schmoker, Jaye L. Weinhert, Charlotte A. Kearns, Warren T. Yacawych, Alicia M. Ebert, Bryan A. Ballif
Department of Biology, University of Vermont

Neuronal migratory and proliferation events are regulated through complex signaling pathways during embryonic development. The proteins CT10-regulator of kinase (Crk) and Crk-like (Crkl) are critical in acting as signal mediators, binding to proteins via their SH2 domains when those proteins are phosphorylated by Abl kinase at YxxP motifs. We have shown previously in a bioinformatics screen that proteins with a higher ratio of YxxP motifs to total length of sequence have a higher probability of candidacy to be bound by Crk or Crkl. The Src homology 2 domain containing family (SH proteins) are a group of four proteins with similar SH2 domains. A yeast two hybrid screen identified SHD and SHE to interact with Abl kinase. Utilizing a pulldown with a GST-Crkl-SH2 resin, we show that each of the four SH family members (SHB, SHD, SHE, SHF) bind to the Crkl-SH2 domain under Abl stimulated conditions. Tandem mass spectrometry analysis shows that YxxP motifs on SHB and SHD are phosphorylated by Abl. Mutating all YxxP sites of SHD to FxxP negates binding to the Crkl-SH2 under Abl stimulated conditions. In Situ hybridization techniques applied to the zebrafish eye exhibit SHDb expression in the nervous system, including the eye. With Crkl and Abl also known to be expressed at these time points, it is likely that this novel interaction plays a role in central nervous system signaling during embryonic development.

7. Inactivation of the Prelimbic Cortex attenuates Operant Responding in both Physical and Behavioral Contexts

Callum Thomas, Eric Thrailkill, Mark Bouton, and John Green
Department of Psychological Science, University of Vermont

The recognition of the role of context in the control of both voluntary (instrumental) and involuntary (Pavlovian) behavior has led to major changes in the ways that we approach altering behavior, such as addiction therapies and dieting. Generally, research has focused on the importance of the physical context; however, we now know that context can include things such as cues, internal states, time, etc. Recently, evidence from research using rats has suggested that when a sequence of two instrumental behaviors is required to earn a reinforcing outcome, the first response can be the "behavioral" context for the second response. That is, the second response is performed as a result of having just completed the first response, and the physical context, composed of the surrounding visual, tactile, auditory and olfactory stimuli, is important only for the first response. The present experiments aimed to determine if the prelimbic cortex (PL), which has previously been shown to be important for the effect of the physical, training context on instrumental responses, is also important for behavioral contexts. Rats first learned a heterogenous behavior chain in which the first response (i.e. pressing a lever or pulling a chain) was cued by a discriminative stimulus and led to a second stimulus which cued a second response (i.e. pulling a chain or pressing a lever); the second response led to a sucrose reward. Preliminary results indicate that, when the first and second responses are tested in isolation in the training context, pharmacological inactivation of the PL resulted in a reduction of the first response only. But when the second response was performed in the "context" of the first response (i.e., as part of a behavior chain), PL inactivation reduced the second response. Overall, these results support the idea that the PL is important for mediating the effects of a training context on instrumental responding, whether that training context is physical or behavioral.

8. AUTS2 and Epigenetic Mechanisms Underlying Alcohol Use Disorders

James M Stafford[1], Yann Pelloux[2], Pedro Lee[3], Nicolas Descostes[3], Zhonghua Gao[3], Adam Mar[2], Danny Reinberg[3]

[1]Dept. Neurological Sciences., UVM Larner College of Medicine [2]Dept. Neuroscience and Physiology., NYU Langone Medical Center [3]Dept. Biochem. and Mol Pharm., NYU Langone Medical Center

Alcohol (ethanol, EtOH) use disorders (AUD) are characterized by heterogeneous genetic and behavioral underpinnings. Indeed, growing evidence suggests that disruptions in the underlying gene sequence can only partially account for the molecular profile of AUD. An emerging theme is that the expression profile of large gene networks is markedly altered in the alcoholic brain. These aberrant transcriptional profiles in AUD are largely driven by epigenetic regulation. Preliminary data and recent literature suggest that autism susceptibility candidate 2 (AUTS2) may represent one such key epigenetic regulator that goes awry in AUD. There are converging lines of evidence from human and animal studies implicating brain expression levels of Auts2/AUTS2 as well as an intronic AUTS2 SNP in EtOH consumption. The goal of this work is to; 1) examine whether AUTS2 directly impacts AUD-associated phenotypes such as EtOH consumption in a brain region-specific manner, and 2) identify how AUTS2-associated chromatin dynamics shape gene expression and neuronal pathology in models of EtOH consumption. Auts2 conditional knock-out mice revealed that EtOH consumption and ataxia are differentially impacted by Auts2 deletion in the forebrain and purkinje cells. Combining biochemical and molecular assays with neuronal culture suggested a strong role for AUTS2 in the chromatin machinery underlying transcriptional programs and the formation of neural networks in cortical neurons. This work is beginning to reveal that AUTS2 impacts select AUD-phenotypes such as EtOH consumption and associates with chromatin machinery that drives transcriptional networks in discrete brain regions. Precisely how these molecular effects map into EtOH consumption and other behavioral phenotypes is a focus of ongoing work.

9. A Data-Driven Clustering of Subjects Based on Brain Activation Reveals Phenotypic Group Differences

Hannah M. Loso, BA, Nicholas Allgaier, PhD, Philip Spechler, MA, Nicholas Fontaine, Shana Adise, PhD., Alexandra Potter, PhD and Hugh Garavan, PhD
Department of Psychiatry, University of Vermont

Introduction: Traditional approaches to understanding the neural basis of neuropsychiatric disease, substance use and cognitive processes focus on between group analysis with groups determined by phenotypic criteria (e.g., symptom profiles, diagnoses and levels of substance use). This approach has revealed activation differences with effect sizes that are typically small and difficult to replicate. Data driven approaches to identifying individual differences in patterns of brain activity during cognitive tasks may have more power to detect neural differences that are clinically relevant. The objective of this study was to explore the utility of Data Spectroscopic Clustering (DSC) in identifying groups based on patterns of BOLD fMRI signal during the Stop Signal Task (SST) and to determine if these groups have distinct behavioral phenotypes.

Methods Analysis was conducted on a subset of the IMAGEN study, a multi-site longitudinal study of neurodevelopment in adolescents. Data analysis focused on subjects, ages 19-to-20-years old, who had complete mental health and substance use information (n=726; 374 males). We employed DSC to group subjects based on patterns of BOLD response during successful stop trials in the SST. Beta weights from the stop success contrast were extracted using the Shen-268 atlas and then DSC was applied. Resultant groups were examined for differences on mental health and substance use assessments (the Development and Well-Being Assessment (DAWBA) and the European School Survey Project on Alcohol and Drugs (EPSAD) questionnaires, respectively). ANOVAs were used to determine if the groups differed on substance use or psychiatric symptoms.

Results The DSC identified six groups of subjects (Table 1) defined by similarities in task activation during the SST. The groups did not differ by sex, handedness or behavioral performance on the Stop Signal Task. Although group membership was significantly related to site (p = .032), all sites had representation in all groups. Interestingly, one of the groups, group 2, had significantly higher binge drinking behavior in the 30 days preceding their study visit compared to group 1 ($F_{(1, 720)}$ = 21.7, p<.001, $\eta p2$ = .029), group 3 ($F_{(1, 720)}$ = 8.73, p = .003, $\eta p2$ = .012), group 4 ($F_{(1, 720)}$ = 15.1, p <.001, $\eta p2$ = .021), group 5 ($F_{(1, 720)}$ = 16.3, p <.001, $\eta p2$ = .022) and group 6 ($F_{(1, 720)}$, p<.001, $\eta p2$ = .027).

Conclusions Using DSC to identify groups of subjects with similar patterns of task-related brain activation may be useful for identifying groups that differ on clinically relevant variables. The next step in this approach focusses on investigating why the phenotypic characteristics of a group are related to that group's particular pattern of brain activation. Longitudinal studies will be important to determine the predictive utility of grouping subjects based on patterns of neural activity during cognitive tasks.

10. Identifying predictive brain structure features in alcohol dependent subjects

Sage Hahn, Nicholas Allgaier, Scott Mackey, Hugh Garavan
Department of Psychiatry, University of Vermont

Typical neuroimaging analysis tends to remain bounded in exploring linear effects between features and/or groupings of features. The objective of this study was to explore the merit of machine learning techniques, generally capable of modeling more complex nonlinear effects, in predicting alcohol dependence from measurements of brain structure, previously shown possible by (Mackey et al. 2018). Of particular interest was in isolating subsets of features responsible for accurate cross validated predictions. A dataset of 911 individuals, 640 diagnosed as alcohol dependent, was collected by the Enhancing Neuro-Imaging Genetics Through Meta-Analysis (ENIGMA) Addiction Working Group (Mackey et al. 2016). Freesurfer 5.3 was utilized to process each patients structural weighted T1 MRI scan extracting volume measurements for 7 bilateral subcortical regions and measurements corresponding to thickness and surface volume for 34 bilateral cortical regions. Measurements were then residualized according to age, sex, intra cranial volume and study site.

In order to reliably determine classifier performance repeated (n=50) random 3-fold stratified cross validation (CV) was employed, where specifically a support vector machine (SVM) with a radial basis function kernel was trained and evaluated on all available measurements, with SVM parameters chosen from a randomized parameter search (n=100) using further nested 3-fold CV (Suykens et al. 1999). Baseline SVM performance when trained on all 150 available measurements achieved an average area under the receiver operating characteristic curve (ROC AUC) of .779 +- .027, in comparison to when trained on only the 14 subcortical volume measurements with a ROC AUC .626 +- .032, 64 measures of surface area with a ROC AUC .605 +- .030, and 64 measures of average thickness with a ROC AUC .780 +- .027. These results suggest that only measurements corresponding to average thickness contribute to classifier performance, though notably there still remains $2^{34} - 1$ (17,179,869,183) possible combinations of features potentially responsible. A multi objective evolutionary search algorithm was designed with the goal of finding both the smallest set of useful thickness measurements possible as well as the most predictive. Outputted feature sets from the search were then thresholded, retaining only sets of features with a ROC AUC > .77 under the previously introduced evaluation methodology. After 4 searches, 28 separate groupings of 11 to 18 features met this criteria. These sets were then analyzed for predictive importance with the assumption that a particular features importance is directly related to the fraction of feature sets in which it appears. Two regions in particular, the right posterior cingulate cortex and right middle temporal gyrus appeared in 90+% of sets, along with a total of 10 features occurring in over 50% out of 45 which appeared at least once.

The ability of a machine learning classifier to predict alcohol dependence from measurements of cortical thickness alone represents an encouraging result towards the development of dependence related neuroimaging biomarkers. Likewise, efforts towards isolating the specific sets of thickness measurements responsible move closer towards that goal. Future experiments will run additional evolutionary searches as well as seek to replicate classifier performance on unseen datasets.

11. Neural Activation during Reward Outcomes is Associated with Inattentive Symptoms of Attention Deficit Hyperactivity Disorder

Max M. Owens[1,2], James MacKillop[2,3], Shannon McNally[2], Iris Balodis[3], Lawrence H. Sweet[2,4]
[1]Department of Psychiatry, University of Vermont [2]Department of Psychology, University of Georgia [3]Michael G. DeGroote Centre for Medicinal Cannabis Research and Peter Boris Centre for Addiction Research, St. Joseph's Healthcare Hamilton/McMaster University [4]Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University

Symptoms of attention-deficit/hyperactivity disorder (ADHD) and impulsivity have both been linked to the functioning of a network of brain regions that are implicated in reward processing. However, to date, many of these studies focus on the anticipatory phase of reward processing and are limited by small sample sizes. In the current study, a community sample of 1081 adults (54% female; mean age = 28.8, SD = 3.7) completed a computerized functional magnetic resonance imaging task in which participants experienced reward outcomes. During this task participants guessed whether a playing card appearing on a screen would be above or below 5. They were rewarded with $1.00 (U.S.) for successful guesses and lost $0.50 (U.S.) for unsuccessful guesses. Out-of-scanner, participants completed the Achenbach Self-Report Scale, which includes subscales for inattentive and hyperactive symptoms of ADHD and a delayed reward discounting task, a measure of decisional impulsivity. In the multiple regression analyses, neural response to reward in the ventral striatum, ventromedial prefrontal cortex, insula, dorsolateral prefrontal cortex, and lateral temporal cortex, as well as the bilateral occipital cortex, was inversely associated with inattentive symptoms of ADHD. No significant associations were found between neural response to reward and hyperactive symptoms of ADHD or delayed reward discounting. Results are consistent with the conceptualization of ADHD as a disorder of hypoactive reward processing, perhaps provoking a person to seek out greater stimulation, even at subclinical symptom levels.

12. Dopamine-Dependent Cognitive Processes after Menopause: The Relationship between COMT Genotype, Estradiol, and Working Memory

Julie A. Dumas[1], Jenna A. Makarewicz[1], Janice Bunn[2], Joshua Nickerson[3], Elizabeth McGee[4]
[1]Department of Psychiatry, [2]Department of Medical Biostatistics, [3]Department of Radiology, [4]Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Vermont Robert Larner, M.D. College of Medicine

Background: The prior literature on menopause and cognition has found large individual differences in whether or not women experience cognitive changes. In an effort to begin to disentangle the individual differences in cognition after menopause, the current study examined how a gene related to functioning of the dopaminergic system, catechol-O-methyltransferase (COMT) and estradiol were related to brain functioning in healthy postmenopausal women. The dopaminergic system may be important for cognition after menopause because age-related changes in the dopaminergic system have been implicated in normal cognitive aging (Braver & Barch 2002) and COMT and estradiol have been shown to influence cognition in pre-menopausal women (Jacobs & D'Esposito 2011).

Method: Participants were 118 healthy, cognitively normal postmenopausal women between the ages of 50-60. All women provided a blood sample for COMT and estradiol analyses and underwent an MRI scan on a 3 Tesla scanner. Working memory performance and related brain activation were measured with BOLD fMRI during the N-back task.

Results: Results were examined across each COMT genotype and a median split was performed on the circulating estradiol levels to create high and low estradiol groups for each genotype. COMT genotype and estradiol level were hypothesized to be proxy measures for brain dopamine levels with the Met/Met and high estradiol group having the most dopamine and Val/Val and low estradiol group having the least dopamine. The fMRI results showed that the N-back task activated the expected bilateral frontal and bilateral parietal working memory network. However, no main effects of COMT genotype or estradiol group were found. There was COMT-estradiol interaction found in a small area of decreased activation in the right precentral gyrus (Brodmann Area 6) that was related to the increasing hypothesized dopamine level. Specifically, women with a Met/Met genotype in the high estradiol group had the least activation in this frontal lobe working memory region. Women with a Val/Val genotype in the low estradiol group had greater activation in this region relative to the other groups. Performance on the N-back task did not show any group differences.

Conclusion: These data indicate that after menopause COMT genotype and potentially the menopause-related changes to the dopaminergic system are not related to cognition. Future studies should examine how the relationship between COMT, estradiol, and cognition around the menopause transition as there are appear to be differences in this relationship for pre and postmenopausal women.

13. Differences in Cognition and BOLD Signal Related to Early Stages of Puberty.

Philip Nguyen, Bader Chaarani, Hannah Loso, Shana Adise, Julie Dumas, Hugh Garavan, Alexandra Potter
Department of Psychiatry, University of Vermont

Introduction: Adolescence is a period of profound development during which the adolescent undergoes a myriad of physical and psychological changes such as an increase in reliance on peers for social support, and a rise of risk-taking behaviors. These changes have been linked to the onset of puberty, a process which brings about dramatic alterations in hormone levels that lead to physical, psychological, and neurodevelopmental maturation. Recent developmental MRI studies have shown that some aspects of brain function are related to pubertal maturation. However, few studies have investigated the relationship between pubertal stage, cognition, and brain activity during early pubertal development in large, diverse populations. Methods: This study examined the relationship between early pubertal stage and cognition using data from the Adolescent Brain Cognitive Development (ABCD) Study (release 2.0). 9583 participants (age 9 – 10 years) were administered neurocognitive assessments from the NIH Toolbox and completed cognitive tasks during functional MRI. Puberty scores were assessed via the Pubertal Development Scale (PDS) which was completed by both the parent and child. PDS total scores were calculated by averaging the parent and child ratings. Participants were then grouped by pubertal stage based on these scores. After filtering out participants with missing data 6875 (2932 female, 3943 male) subjects remained for the pubertal stage and cognition analysis. Pubertal groups were compared on NIH toolbox task performance using an ANCOVA, controlling for age, education level, income, and site. Next, pubertal scores were regressed against functional imaging data for the Stop Signal Task (SST). Results: Pubertal stage had significant main effects ($p< .005$ FWE corrected) effect of pubertal stage on task activation during successful response inhibition. Activation of bilateral inferior frontal gyri and middle frontal gyrus was negatively associated with pubertal stage. Conclusion: This study provides evidence for cognitive changes during early puberty and altered patterns of brain activity during a response inhibition task. These results suggest that certain facets of cognition are negatively associated with pubertal stage in 9 and 10 year old youth, a finding that is consistent with the dual system model of adolescent risk-taking.

14. Linguistic and Non-Linguistic Semantic Processing in Individuals with Autism Spectrum Disorder

Yu Han1 and DK Yuan2
Department of Communication Sciences and Disorders, University of Vermont

Applicant Individuals with autism spectrum disorders (ASD) struggle with language, especially higher-level functions like semantic integration. However, many studies indicate that semantic processing of non-linguistic stimuli is not impaired in ASD, indicating a language-specific deficit in semantic processing. Semantic priming tasks have been used to compare event-related potentials (ERPs) in response to lexico-semantic processing (written words) and visuo-semantic processing (pictures) in adults with ASD and adults with typical development (TD). In these tasks, ASD subjects shows successful lexico-semantic and visuo-semantic processing, as indicated by similar N400 effects between ASD and TD adults for word and picture stimuli. The current study implemented machine learning algorithms (e.g., logistic regression, SVM, random forests, neural networks) to classify ASD and TD subjects using signal magnitude covariates between each pair of electrodes as features (i.e., ERP signals). Multi-Layers perceptron model is able to efficiently classify ASD vs. TD groups, while random forest is a proper classifier for picture vs. word.

15. Quantifying Anxiety Behavior in Drosophila melanogaster.

Amanda Bozorgi, Kreager Taber and Amanda Crocker
Program in Neuroscience, Middlebury College

Anxiety disorders are the most commonly diagnosed psychiatric condition in the United States. Yet our understanding of the role genetics plays in the development and manifestation of anxiety behavior is poorly characterized (Cryan and Sweeney, 2012). In both humans and animals anxiety is considered an emotional response to stress (Wang et al. 2001). When organisms are exposed to an environmental stress they are likely to respond with fear and anxiety phenotypes, depending on the magnitude of the individual stressor. Repeated stress has far greater consequences than individual events. Studies indicate that repeated stress can reduce the brain's capacity for storing and retrieving memories (Gill and Grace, 2013). Here we outline how we study anxiety behavior in Drosophila melanogaster (henceforth: the fruit fly) using an open field test. Similar to rodents, naive flies will spend more time in the center of this assay, whereas flies having undergone a stress prefer to follow the walls (Mohammad et al. 2016). Previous work demonstrated that drugs such as diazepam and drugs targeting the serotonin system modulate wall-following anxiety behavior in the fly (Mohammad et al. 2016). Here we show that we can also modify this behavior through the octopaminergic system (Norepinephrine homolog in the fly). Using the Drosophila Genetics Reference Panel (DGRP- a collection of inbred recombinant wildtype flies (Mackay et al. 2012)) we demonstrate that anxiety behavior in the fly is a variable trait. Future work will use this data set to perform a genome-wide association study to identify genes involved in the manifestation of anxiety behavior in the fly.

16. Altered gastrointestinal motility in mouse models of Multiple Sclerosis

Friederike Uhlig, Emily A Holt, Melody M Haag, Brigitte Lavoie, Dimitry N Krementsov, Cory Teuscher, Gary M Mawe

Department of Neurological Science, University of Vermont

Multiple Sclerosis (MS) is an autoimmune disease of the CNS involving neuron and glia cell degeneration. In addition to the well-recognized somatic deficits, MS frequently involves autonomic dysfunction, including constipation. We and others have recently demonstrated that features of constipation are detectable in the animal model of MS, experimental autoimmune encephalomyelitis (EAE), indicating that the enteric nervous systems (ENS) could be affected. The current study was conducted to better understand the time course of GI symptomology and its relationship with clinical symptoms. EAE was induced with MOG (myelin oligodendrocyte glycoprotein) in B6 mice, and GI function was evaluated by assessing colonic motility, fecal water content and whole GI transit time. In male mice, clinical symptoms were first detected ~16-18 days, and GI dysfunction peaked at 21d, but GI function recovered by 28d. Female mice were less susceptible to MOG-induced EAE but also displayed GI dysfunction. Overall, murine EAE induced with the MOG protocol displayed a variable and transient GI symptomology. Next, we tested the mouse spinal cord homogenate (MSCH) model of EAE in B6 mice, which involves intraperitoneal injection of pertussis toxin (PTX). Disease onset was earlier and more rapid than with the MOG model, and changes in GI function (colonic motility slowed, number of pellets decreased compared to before immunization) were detected in MSCH animals as well as PTX controls. In summary, GI dysfunction was detected in both EAE models tested, but drawbacks, the transient nature of the MOG symptoms and the effect of PTX in the MSCH model, preclude the use of these models for mechanistic studies. Future studies will investigate alternative models and use transgenic animals with GI symptomology to perform calcium imaging. Supported by NIH grant DK113800.

17. Pericyte-to-Arteriole Propagation of Capillary Electrical Signals

Montana Gubrud, Albert L. Gonzales, and Mark T. Nelson
Department of Pharmacology, University of Vermont

The brain is one of the body's most complex organs, and it is made up of highly active neurons consuming a disproportionate share of the body's energy resources. As such, the brain is highly sensitive to even brief disruptions in blood flow. As information is processed, different neural circuits exhibit spatially and temporally distinct activity profiles and thus display varying metabolic demands. Functional hyperemia is the process by which these metabolically active neurons stimulate an increase in local capillary blood flow. Our recent work has shown that extracellular K+, a byproduct of neural activity, can initiate capillary endothelial Kir channel signaling, resulting in a retrograde hyperpolarizing signal that causes upstream arteriolar dilation and increased blood flow into the capillary network. These findings suggest a dynamic K+-sensing role for capillary networks which allows them to respond to regional brain activity. Furthermore, our work has centered around contractile pericytes found at capillary branch points most proximal to the feeding arteriole which have various projections that wrap around the capillary vessel. Each projection has been shown to be capable of independent Ca2+-induced constriction and control of blood flow. Using transgenic mice expressing optogenetic actuators, we examined the intra- and intercellular propagation of electrical or chemical signals between projections of a single capillary pericyte and between capillary pericytes and upstream arterioles. We will test the hypothesis that capillary electrical signaling associated with functional hyperemia is unidirectional, only propagating from capillary pericytes to the feeding arteriole. To test this, we isolated and pinned down (en face) retinas from transgenic optogenetic mice expressing the light-sensitive transmembrane domain of the G protein-coupled protein rhodopsin (Acta2-opto--α1AR-IRES-lacZ), or a light-activated cation channel (Acta2-CatCh-IRES-lacZ), allowing for the subcellular generation of secondary messengers inositol triphosphate (IP3) and diacylglycerol (DAG) or a local membrane depolarization, respectively. Light-dependent generation of IP3 and DAG within a single pericyte projection led to a local capillary constriction but had no effect on the contractile state of cell's other projections. However, light-dependent membrane depolarization and constriction of one capillary branch generated a step-wise constriction of the other pericyte projections, suggesting the presence of electrical, but not chemical, signaling between pericytes projections. Consistent with the retrograde capillary electrical signaling paradigm, light-induced
membrane depolarization and constriction of proximal capillary pericyte, resulted in the constriction of the upstream arteriole. However, light-induced membrane depolarization and constriction of the feeding arterioles had no effect on the contractile state of the most proximal pericyte, suggesting the absence of a propagating arteriole-to-pericyte electrical signal. Collectively, these data suggest that propagation of membrane depolarization is unidirectional from proximal pericytes to the feeding arteriole.

18. Long duration anxiogenic effects of BNST PACAP are not due to conditioned anxiety.

S. Bradley King[1], Victor May[2], and Sayamwong E. Hammack[1]
[1]Department of Psychological Science, University of Vermont, Burlington, VT, USA;
[2]Department of Neurological Sciences, University of Vermont College of Medicine

Anxiety associated with chronic or repeated stressors has been argued to result from long-term changes in plasticity within stress-responsive neural circuits. We have implicated pituitary adenylate cyclase activating polypeptide (PACAP) and its cognate PAC1 receptor in the bed nucleus of the stria terminalis (BNST) in mediating multiple physiological and behavioral consequences of chronic stress (Hammack et al., 2009; King et al., 2017; Roman et al., 2014). Recent data have suggested that PAC1 receptor signaling may engage several intracellular cascades that can produce long-lasting effects following PACAP binding, including both long-duration changes in membrane excitability and long-term trophic changes (May & Parsons, 2017). In line with this, we have previously shown that a single, sufficient dose of BNST PACAP can produce long-lasting increases in anxiety-like behavior that persist a week after infusion. However, since the behavioral effects of BNST PACAP were tested both immediately after and 7-days after infusion in our previous study, the long-term elevations in acoustic startle responding observed following intra-BNST PACAP may have been due to a PACAP-induced anxiety-like state that was conditioned to the startle chamber. In the current, study we demonstrate that BNST PACAP infusion can elevate acoustic startle responding in rats that were only tested 7-days following infusion (not tested immediately after infusion), suggesting that the persistent anxiogenic enhancement of PACAP is not mediated by anxiety previously conditioned to the startle chambers.

19. Characterization of Sema6A forward and reverse signaling in Zebrafish eye development

Caroline Dumas, Riley St. Clair, Bryan Ballif and Alicia Ebert
Department of Biology, University of Vermont

Semaphorin6A (Sema6A) and PlexinA2 (PlxnA2) are a receptor/ligand pair involved in cell migration and axon guidance of neurons and blood vessels, among other cell types. We previously demonstrated Sema6a and PlxnA2 as an essential signaling pair for zebrafish eye development, as knockdown of either leads to cell adhesion and proliferation defects. It is known that Sema6A can act both as a ligand in canonical downstream signaling through the PlxnA2 receptor, and as a receptor in reverse signaling. In order to determine the importance of the reverse Sema6A-PlxnA2 signaling in zebrafish eye development, we knocked down Sema6A with an antisense oligonucleotide and rescued with full length human Sema6A (FL-Sema6A) or a truncated Sema6A without the intracellular domain (ΔC-Sema6A) incapable of reverse signaling. Using biochemistry techniques, we have shown that FL-Sema6A and ΔC-Sema6A are localized similarly in the cell but are processed unevenly leading to a soluble protein that is released into the media. We are currently investigating the ability of ΔC-Sema6A and the soluble Sema6A to rescue the eye phenotypes observed with loss of endogenous Sema6A. These experiments will lend insight into how reverse signaling and the soluble Sema6A are involved in development of the zebrafish eye.

20. Cortical zeta inhibitory peptide injections reveal the complex influence of synaptic strength on sleep quality and quantity

Abigail A. Green, Lexie Lessing, Michael B. Dash
Department of Psychology, Middlebury College

Though we spend a third of our lives asleep, decoupled from our sense of the environment, we still know very little about what drives our need for sleep. Synaptic strength has been suggested to significantly impact sleep need, as hypothesized in the Synaptic Homeostasis Hypothesis (SHY). SHY suggests that sleep downscales net synaptic strength, which is accumulated throughout the day from plastic learning processes, allowing the brain to return to a metabolic and morphological baseline for proper functioning (Tononi and Cirelli, 2006). To test whether synaptic homeostasis drives sleep need, zeta inhibitory peptide (ZIP), a protein kinase Mζ (PKMζ) inhibitor, was locally injected into the cortex of Sprague-Dawley rats to reduce synaptic strength. By recording slow wave activity (SWA) during non-REM sleep, cortical sleep need was measured (Vyazoviskiy et al., 2007). Previous results from single ZIP injections into the right motor cortex suggested that pharmacological depotentiation decreases SWA at the injection site but does not significantly alter time spent in each behavioral state (Carroll 2019). Thereby, local synaptic strength appears to locally regulate sleep need but not sleep quantity. To determine whether a more extensive reduction in synaptic strength throughout the cortex would alter behavioral state in addition to local SWA, we injected ZIP into four cortical sites instead of one. Contrary to expected, analysis of electroencephalographic (EEG) signals (n=6) revealed that multiple ZIP injections increased local SWA at injection sites and had no significant effect on total time spent in non-REM sleep. Our results suggest that the effects of synaptic depotentiation on sleep quality may vary as a function of the spatial extent of cortical depotentiation induced. Together, they highlight the importance of local and global regulators of sleep quality and additionally raise the possibility that sleep quantity and quality are independently regulated.

21. The Effects of Tryptophan-Modulating Bacteria on Serotonin Signaling

Theresa Legan, Joy Cohen, Brigitte Lavoie, and Gary M. Mawe
Department of Neurological Sciences, University of Vermont

A growing body of research on the integral role of the microbiome in health and disease provides evidence for potential impacts on virtually every physiological system. An emerging approach to manipulating the microbiome is through the administration of "probiotic" bacteria. Indeed, there is evidence to suggest that dietary supplementation of probiotic bacteria can improve gut dysfunction, as well as influence psychiatric symptoms such as anxiety- and depressive-like behavior, but the mechanism of action is not understood. One way in which probiotics may exert their effects could be by altering serotonin (5-HT) levels indirectly through modulation of the 5-HT precursor, and essential amino acid, tryptophan. We therefore tested the hypothesis that administration of bacteria with the capacity to metabolize or synthesize dietary tryptophan will result in a decrease or increase, respectively, in colonic mucosal 5-HT levels in mice, and result in altered colonic motility and fecal composition, since 5-HT is a key mediator of propulsive motility in the intestines. We administered either tryptophan-modulating bacteria or placebo in the drinking water of CD-1 mice. We found that three of the four bacterial strains produced effects that were opposite of our hypothesis. Mice treated with the tryptophan-consuming strains B. infantis R0033 and B. animalis ssp. lactis R0421 B94 displayed accelerated whole GI transit time. The B. infantis R0033 treated group also exhibited greater colonic and duodenum 5-HT levels compared to placebo. In contrast, treatment with the tryptophan-synthesizing strain P. freudenreichii ssp. shermanii HA182 slowed whole GI transit time. Consistent with our hypothesis, mice treated with the tryptophan-synthesizing strain B. subtilis R0179 displayed higher fecal water content, indicative of faster motility, as well as accelerated GI transit time. Taken together, these findings suggest that tryptophan-modulating bacteria have the capacity to influence GI physiology and function, and further highlight the importance of elucidating the properties of specific bacterial strains moving forward.

22. Stimulus salience and reinforcer predictability in the formation of habits

Noelle Michaud, Melissa Rifkin, Nicholas Murphy, Eric A. Thrailkill, and Mark E. Bouton
Department of Psychological Science, University of Vermont

Instrumental (operant) behavior provides a laboratory method for studying processes that influence voluntary behavior. Recent research suggests that an instrumental behavior can be either a goal-directed action or a habit, but there is little information about how goal-directed actions eventually become habitual. The present experiments examined the role of both the salience of the stimulus that potentially triggers a habit and reinforcer predictability as factors that might encourage habit formation. Rats received discriminated operant training in which a lever press was reinforced only in the presence of a specific stimulus (S). The status of the behavior as action or habit was then determined by the results of reinforcer devaluation tests. In Experiments 1a and 1b, we compared the effectiveness of two stimuli at encouraging habit formation: The insertion of a Lever into the chamber versus presentation of an auditory stimulus (Tone). In either case, the fifth lever press after S was initiated was reinforced. Despite prior speculation in the literature, the "salient" lever insertion S was no better than the tone at supporting the development of habit. Experiment 2 then examined the role of reinforcer predictability with a Tone S. Lever pressing during the tone was either reinforced during every trial or 50% of trials. Habit was observed only when training arranged the highly predictable relationship between the S and the reinforcer, rather than the partially reinforced relationship. These results have important implications for the understanding of how habits form in the laboratory as well as in everyday life.

23. Deconstructing habit formation in female rats

Hannah L. Schoenberg, Emily X. Sola, Caleb Winn, Donna J. Toufexis
Department of Psychological Science, University of Vermont

In early stages of instrumental learning, behavior is goal-directed, but over the course of learning can become habitual, such that performance of the behavior becomes insensitive to changes in the value of the behavior's outcome. We have previously found that this progression is accelerated in female compared to male rats. In order to investigate a variety of manipulations that might accelerate or attenuate the progression from goal-directed to habitual behavior, it was first necessary to identify parametrically the range of training in our behavioral paradigm within which male and female rats transition from goal-directed to habitual behavior. To begin this endeavor, we trained female rats on a variable interval 30-s schedule to nose-poke for sucrose with decreasing degrees of training (response-reinforcer pairings), starting at 200 reinforcer exposures. We found that female rats show an insensitivity to reinforcer devaluation down to 140 response-reinforcer pairings, but remain goal-directed at 120 reinforcers. Thus, the habit-threshold range in females is between these two levels of reinforcer exposure. We are currently using this information to investigate the contributions of the direct and indirect pathways of the basal ganglia to habit formation in female rats. We hypothesize that enhanced activation of the direct pathway at the habit sub-threshold range of 120 reinforcer pairings will accelerate habit formation, and to test this we are using viral vectors to selectively upregulate the excitatory serotonin 6 receptor (5-HT6R) in the direct pathway within the dorsolateral striatum (DLS). Preliminary data support this hypothesis, such that female rats transfected with this viral vector display insensitivity to reinforcer devaluation at 120 reinforcers, while controls remain goal-directed.

24. Optogenetic entrainment of the septo-hippocampal circuit is state conditional and attenuates spatial accuracy

Michelle Kloc
Department of Neurological Sciences, University of Vermont

The manipulation of pattern generators in order to impose temporal organization on target nodes while accounting for dynamic changes in behavior and cognitive demand remains a significant challenge for the use of neurostimulation as a therapeutic treatment option. While perturbation through optogentic stimulation can reveal circuit mechanisms that create and locally integrate temporal organization, it is unclear whether superseding endogenous signals with artificial oscillations would benefit or impede hippocampus-dependent cognition or how cognitive demand might affect artificial septo-hippocampal entrainment. Optogenetic MS stimulation in wild-type rats in 3 conditions showed that septal input is more likely to supersede endogenous hippocampal LFP oscillations when animals are at rest or performing a hippocampus-dependent spatial accuracy task. Stimulation during a hippocampus-independent task, however, resulted in compensatory endogenous oscillations. Although stimulation effects on the inter-spike interval of hippocampal pyramidal cells mirrored task-conditional theta entrainment of the LFP, place field properties were unaffected. Analyses of spatial behavior indicate that optogenetic stimulation can attenuate performance and specific measures of goal zone estimation accuracy but otherwise does not affect the rat's ability to navigate to the target quadrant. The results suggest that the behavioral effect of temporally organizing the septo-hippocampal circuit relative to an artificial theta signal is limited to the accuracy of the rat's approximation of the goal zone location. These results have significant implications for the therapeutic use of optogenetic stimulation as a means of attenuating cognitive deficits associated with temporal discoordination.

25. Effect of testosterone dose on spatial learning strategies and BDNF in young male rats

Kevin J. Zhang, Rajan Ramdev, Nicholas Tuta, Mark D. Spritzer
Department of Biology and Program in Neuroscience, Middlebury College

Studies suggest that on some spatial tasks, males tend to outperform females. This may be due to the effects of sex steroids on spatial strategy preferences. Past studies in rodents suggest that low estradiol levels bias females toward a striatum-dependent response strategy, whereas high estradiol levels bias them toward a hippocampus-dependent place strategy. Work in our laboratory indicates a similar pattern in that low levels of testosterone bias male rats toward a response strategy, whereas high testosterone levels bias them toward a place strategy. In this experiment, we tested the effect of different testosterone doses on the ability of male rats to effectively employ these two spatial learning strategies. Furthermore, brain tissue from the prefrontal cortex, hippocampus, and striatum was collected 24 h following behavioral testing, and ELISA assays were used to quantify the levels of brain-derived neurotrophic factor (pro- and mature-BDNF). All rats were castrated and assigned to one of three daily injection doses of testosterone propionate (0.125, 0.250, or 0.500 mg/rat) or a control of the drug vehicle. Using a plus-maze protocol, we found that a lower testosterone dose (0.125 mg) significantly improved a rat's performance on a response task, while a higher testosterone dose (0.500 mg) tended to improve a rat's performance on a place task. In addition, ongoing BDNF analysis suggests heightened hippocampal pro- and mature-BDNF levels, relative to the cortex and striatum, but no significant effect of testosterone dose within the three brain regions. Taken altogether, these results suggest that different doses of testosterone can effect performance place and response tasks, but such differences cannot be explained by pro- and mature-BDNF levels in brain tissue.

26. Investigating Sema6A-PlxnA Signaling Mechanisms in Development: Identification of Key PlxnA Phosphorylation Sites and the Discovery of a Novel Secreted Sema

Riley M. St. Clair, Sarah E. Emerson, Kristen P. D'Elia, Marion E. Weir, Anna M. Schmoker, Kori S. Williams, Matthew T. Goldstein, Elizabeth Stant, Alicia M. Ebert, and Bryan A. Ballif
Department of Biology, University of Vermont

Semaphorins (Semas) are a family of secreted and transmembrane proteins that play critical roles in the developing nervous system, cardiovasculature, and immune system. Semas signal predominantly through Plexin (Plxn) receptors to regulate cellular processes such as cytoskeletal dynamics, proliferation, and differentiation. Although several cellular players governing Sema-Plxn signaling have been identified, the molecular mechanisms that initiate signaling are only partially understood. Therefore, we aimed to investigate the receptor-proximal events of Sema-Plxn signaling and we report here two main findings towards a better understanding of the early events of Sema-Plxn signaling: 1) PlxnA receptor phosphorylation at two tyrosine sites is critical for zebrafish eye development and 2) Sema6A has a functional naturally-released ectodomain, sSema6A. We used mass spectrometry-based approaches to identify highly-conserved, Fyn kinase-mediated PlxnA tyrosine phosphorylation sites. Mutation of these sites to phenylalanine results in significantly decreased Fyn-dependent PlxnA tyrosine phosphorylation and this phosphorylation is critical in zebrafish eye development. Interestingly, while investigating whether or not these sites are phosphorylated upon Sema6A ligand binding, we serendipitously discovered that a functional soluble Sema6A, sSema6A, is naturally released from cells expressing the full-length transmembrane Sema6A. Using zebrafish eye explants, we show that sSema6A promotes early eye field cohesion, a process known to be Sema6A-dependent. While other soluble Sema ectodomains have been identified, we describe here the first soluble ectodomain from the Sema6 class. Together these data suggest that Sema6A may have long-range effects in addition to its canonical contact-mediated functions and that Fyn-dependent phosphorylation is a key feature of vertebrate PlxnA signal transduction. Future work will investigate if the transmembrane and secreted forms of Sema6A can induce Fyn-mediated PlxnA tyrosine phosphorylation.

27. Investigating the pathogenic mechanisms responsible for the spectrum of neurological diseases caused by dominant and recessive mutations affecting ARS function.

Patrick Mullen[1], Pryce Patterson[1], Ashley Waldron[2], Jamie Abbott[1], Christian Fjeld[1], Mahafuza Aktar[3], Aleksandra Siekierska[4], Peter de Witte[4], Hannah Stamberger[5], Peter De Jonghe[5], Reza Maroofian[6], Alicia Ebert[2], Christopher Francklyn[1]

[1]Department of Biochemistry, University of Vermont [2]Department of Biology, University of Vermont [3]Department of Neurological Sciences, University of Vermont [4]Laboratory for Molecular Biodiscovery, Department of Pharmaceutical and Pharmacological Sciences [5]Department of Neurology, Antwerp University Hospital 6Institute of Biomedical and Clinical Science, University of Exeter Medical School

The aminoacyl tRNA synthetase (ARS) gene family encodes ubiquitously expressed enzymes that catalyze the aminoacylation reaction, in which an amino acid is attached to its corresponding tRNA molecule. Recently, loss-of-function mutations in ARS have been linked to a diverse spectrum of neurological diseases. Dominant mutations are associated with the peripheral neuropathy known as Charcot-Marie-Tooth disease (CMT), while recessive mutations cause either sensorineural disorders, or severe neurodevelopmental abnormalities often characterized by microcephaly, epilepsy, and cognitive impairment. Understanding the pathogenic mechanisms underlying each of these phenotypic classes may facilitate the generation of novel therapies. Here, we characterize disease-associated mutations in the histidyl- and valyl-tRNA synthetases (HARS & VARS), as well as the ARS-associated protein AIMP2. Our future work will focus on developing a novel therapeutic strategy for targeting splice-site mutations in AIMP2.

28. Neurochemical expression and function of interstitial cells (ICs) in the urinary bladder of mice with cyclophosphamide (CYP)-induced cystitis

Megan E. Perkins, Beatrice M. Girard and Margaret A. Vizzard
Department of Neurological Sciences, The Larner College of Medicine, University of *Vermont*

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a painful, debilitating lower urinary tract (LUT) disorder characterized by pelvic pain and increased urinary frequency. Bladder overactivity is a hallmark of IC/BPS; however, the exact etiology of IC/BPS is still unknown. We have recently begun to characterize a population of interstitial cells (ICs) in the lamina propria (LP) of mouse bladder that express PDGFRα- and TRPV4-immunoreactivity (IR) and exhibit increased Ca^{2+} activity in response to TRPV4 agonist. ICs have been implicated in contributing to bladder pathophysiology including detrusor overactivity. Reductions in detrusor overactivity following spinal cord injury have been reported with imatinib, an inhibitor of PDGFR-α signaling. Using a mouse model of CYP-induced bladder inflammation, we now demonstrate increases in PDGFRα- and TRPV4-IR and transcripts in ICs in the LP. We hypothesize that ICs in the LP contribute to increased voiding frequency observed with CYP-induced cystitis. We examined the functional role of ICs using a tyrosine kinase inhibitor, imatinib mesylate, with acute (4 hr) CYP-induced cystitis as a model of IC/BPS. In these experiments, mice were treated with imatinib (200-250 mg/kg; gavage) for six, consecutive days. On the third day, we surgically implanted a bladder catheter to evaluate bladder function using conscious cystometry. On the sixth day, mice were treated (4 hr) acutely with CYP (200 mg/kg; i.p.) and bladder function was then evaluated with continuous intravesical instillation of room temperature saline. We evaluated various imatinib doses (50-250 mg/kg) and delivery routes (chronic oral gavage, chronic intraperitoneal injection, acute intravesical instillation) of imatinib. We have determined that imatinib (200-250 mg/kg) delivered by oral gavage is the most effective dosage and route, of those evaluated, in reducing effects of acute CYP treatment. Acute (4 hr) CYP treatment in mice (male and female) significantly ($p = 0.0025$) reduced bladder capacity and intermicturition interval with minimal effects on bladder pressures. Oral gavage of imatinib mesylate (200-250 mg/kg), in female mice with CYP-induced (4 hr) cystitis, significantly increased intermicturition intervals ($p = 0.0005$) and bladder capacity ($p < 0.0001$) compared to mice treated with CYP-induced (4 hr) cystitis and saline gavage. However, these changes were not observed in male mice treated with CYP. Interestingly, control (no CYP) mice treated with imatinib (200-250 mg/kg; gavage), exhibited significantly decreased intermicturition intervals (male: $p = 0.0467$) and bladder capacity (male: $p = 0.0016$; female: $p = 0.0136$) compared to control mice (no CYP) and saline gavage. Effects of imatinib on bladder pressure (e.g., maximum, minimum, threshold) are also being evaluated in CYP-treated and control (no CYP) mice. In conclusion, imatinib (200-250 mg/kg; gavage) significantly increased bladder capacity and intermicturition intervals in female mice treated acutely (4 hr) with CYP suggesting that imatinib may be an effective treatment to improve bladder function following urinary bladder inflammation. In addition, these results demonstrate differential effects of imatinib on mouse bladder function depending on the presence of bladder inflammation (CYP vs. control). Future studies will investigate changes in inflammatory mediators that may underlie a mechanism of action of imatinib in the LUT.

29. Neuropeptide-like precursor 3 in ethanol behavioral plasticity

Nicole Amagliani, Kelsey Butler, Jessica Lisk, El Phillip, Eric Thomas, Weslee Thompson, & Gregory Engel
Department of Psychological Sciences, Castleton University

Recent evidence suggests that the gene Neuropeptide-like precursor 3 (Nplp3) is involved in behavioral plasticity in the fruit fly, Drosophila melanogaster. Behaviors affected include courting/mating and aversive learning. Our work shows that Nplp3is also involved in ethanol tolerance. In behavioral tests Nplp3 mutant flies show significant perturbation of ethanol tolerance. These are the first findings reported based upon direct manipulation of Nplp3, suggesting that it may serve an important role in learned behaviors in the fly.

30. Expression of pro-inflammatory cytokine during chemotherapy in taste buds and the use of Amifostine as a cytoprotective agent

Anish Sarkar, D. Allyn, Rona Delay, *E. R. Delay
Department of Biology, University of Vermont

Chemotherapy is a predominant mode of cancer treatment in patients, often inducing adverse effects such as taste dysfunctions when the drug also affects normal tissues. The taste sensory system is an important modality developed to differentiate nutrition from poisonous substances. Disturbances in taste can result in malnutrition, weight loss and further aggravate the condition of the patient during recovery. There could be various reasons for drug-induced taste disturbances such as loss of cells within taste buds, disruptions in taste cell renewal, and tissue inflammation. Our lab has been studying the molecular, cellular and behavioral effects of the chemotherapy drug, cyclophosphamide (CYP). CYP is an antineoplastic, which is a pro-drug and inactive in its native state. Once it is metabolized in the liver by the P450 enzyme complex, its primary metabolite, phosphoramide mustard, functions as an alkylating agent. Our current research is focused on potential CYP-induced inflammation. Specifically, this study is examining the expression of the cytokine TNFα in the taste bud during the 72 h immediately after injection as well as determine if Amifostine offers any protection to taste buds. Previous research using TUNEL and caspase-3 assays suggests CYP-induced cell loss in fungiform and circumvallate papillae peaks at about 8 and again 18-24 h, post CYP administration (75 mg/kg, IP). Our present investigation using immunohistochemical analysis suggests that the peak expression of the pro-inflammatory cytokine, TNF-alpha occurs about 8 and 24 hrs post CYP injection in both fungiform and circumvallate papillae. Pre-treatment (100 mg/kg, SC) with Amifostine, appears to decrease the expression of TNF-alpha, indicating the drug can protect the taste system from the alkylating effects of CYP metabolites.

31. Blockade of VEGR2 in the urinary bladder increased bladder capacity in control rats and in rats with cyclophosphamide (CYP)-induced cystitis.

Katharine Tooke and Margaret A. Vizzard
Department of Neurological Sciences, University of Vermont

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic, inflammatory pain syndrome characterized by urinary urgency, frequency, and pelvic pain. Using a rat CYP model of urinary bladder inflammation, previous studies demonstrated increased vascular endothelial growth factor (VEGF) expression in the urinary bladder with acute (4 hr) and chronic (10 day) CYP-induced cystitis as well as expression of VEGF receptors including VEGFR1, VEGFR2, Npn1 and Npn2. Translational studies demonstrated elevated levels of VEGF in the urinary bladder of women with IC/BPS. Furthermore, high levels of VEGF are associated with immature angiogenesis and vascularization in the bladder as well as visceral hyperalgesia, and pelvic pain. We have determined the effects on bladder function of VEGFR2 receptor blockade using a potent, selective VEGFR2 tyrosine kinase inhibitor (Ki 8751, 1 mg/kg) in the urinary bladder in male and female Wistar rats with 4 hr CYP-induced cystitis as well as littermate controls (no CYP). We used intravesical infusion of the VEGFR2 antagonist coupled with conscious, open outlet cystometry where each rat (control or CYP treated) was evaluated before and after VEGFR2 receptor blockade. With VEGFR2 receptor blockade, bladder capacity increased 31.7% in control female rats ($p \leq 0.01$) and 41.9% in control male rats ($p \leq 0.01$). Voided volume increased 24.8% in control female rats ($p \leq 0.01$) and 33.0% in control male rats ($p \leq 0.05$). After infusion of the VEGFR2 antagonist in female rats treated with CYP, bladder capacity increased by 44.6% ($p \leq 0.05$) and voided volume increase by 32.7% ($p \leq 0.05$). Infusion of the VEGFR2 antagonist in male rats with CYP-induced cystitis exhibited increased (49.2%) bladder capacity ($p \leq 0.05$), although no change in void volume was observed. The magnitude of change in void volume following VEGFR2 receptor blockade was comparable between control and CYP treatment groups and male and female rats. In contrast, the magnitude of change in bladder capacity in female rats treated with CYP was significantly ($p \leq 0.05$) greater than that in control female rats. The magnitude of change in bladder capacity following VEGFR2 receptor blockade was comparable between male and female control and CYP-treated rats. These data suggest that pharmacological targeting of VEGF/receptor signaling may be a possible intervention for individuals with IC/BPS.

32. The Budapest Reference Connectome 3.0: brain network analysis

Yu Han and Ali Javed
Department of Computer Science, University of Vermont

The social brain network (SBN) consists of the superior frontal gyrus (SFG), amygdala, fusiform gyrus and precuneus. The SBN directly regulates many social behaviors and processes, such as emotion regulation, face recognition, fear conditioning and theory of mind. Deficits in the SBN directly lead to many neurological, psychiatric and developmental disorders. In addition, comobidities arise from disrupted connections between the SBN and other brain regions. In order to examine how impairments in brain areas with extensive connections to the SBN lead to specific disorders (e.g., autism spectrum disorder) and their comorbid symptoms (e.g., obsessive compulsive symptoms), a computational network analysis method using the Budapest Reference Connectome 3.0 was adopted. The shortest paths connecting each node in the SBN was investigated. The frequency of occurrence of nodes in the shortest paths, but outside the SBN, were tested both in the original network and in 1000 random networks to identify regions significantly associated with the SBN. The results suggest that comorbid symptoms are not caused by simultaneously occurring deficits within multiple brain areas. Rather, it is the disruption of connectivity between the SBN and other brain regions that leads to co-appearing symptoms.

33. Contributions of dorsal hippocampus to renewal of conditioned suppression

Armin Tavakkoli, Danielle I. Fournier, David J. Bucci, & Travis P. Todd
Department of Psychological and Brain Sciences, Dartmouth College

Extinction of fear to a conditioned stimulus (CS) is a context-dependent; removal from the extinction context results in renewal of conditioned fear to the CS (Bouton & Bolles, 1979). Prior experiments have demonstrated a critical role for the dorsal hippocampus (DH) in fear renewal. However, the majority these studies examined renewal in conditioned freezing procedures. The role of the DH in renewal is less clear in other procedures, such as conditioned suppression. For example, pre-training lesions of the fornix or the DH have no impact on ABA renewal of conditioned suppression (Frohardt et al., 2000; Wilson et al., 1995). Likewise, post-extinction lesions of the DH do not weaken ABA renewal of conditioned suppression (Todd et al., 2017). Since all prior conditioned suppression experiments examined ABA renewal, which involves a return to the original conditioning context, the current study examined the impact of pre-training DH lesions on ABC renewal. ABC renewal isolates the contextual retrieval of extinction, because it does not involve a return to the original conditioning context. In experiment 1, both Sham and DH lesioned rats received light-shock pairings in Context A, followed by extinction in Context B. Fear was reduced to the CS in Context B, and renewed when presented in an equally familiar Context C. Although Sham lesioned rats demonstrated ABC renewal, DH lesioned rats did not. Similarly, in experiment 2, another group of naïve rats received light-shock pairings in Context A, followed by extinction in Context B. Rats then received DH and Sham lesions after extinction training. Once again, although Sham lesioned rats showed intact renewal, DH lesioned did not. Summation testing in both experiments revealed that the extinction context was not a conditioned inhibitor. Overall, these experiments suggest that the DH is necessary for renewal when it occurs in a neutral context.

34. Predictive Approach to Social Psychology: Using Machine Learning to Predict the Five Factor Personality Traits

Jessica E. Kobsa and Armin Tavakkoli
Department of Psychological and Brain Sciences Dartmouth College, Hanover

The Five Factor Model of personality (FFM) includes the five traits that underly human personality. Previous literature has correlated these traits with various demographic and social measures. However, recent findings suggest that correlations are susceptible to overfitting and collinearity of variables, which may seem to support false relationships. This study aimed to (1) test the replicability of previous findings on the associations between personality traits of the Five Factor Model and various outcomes on a new dataset and (2) test an approach focused on prediction rather than on explanation using machine learning techniques. This study collected a new dataset consisting of measures of personality traits and measures of various outcomes and developed predictive models for each personality trait. For each trait, one model was developed using traditional multiple linear regression, and another regression model was developed using variables selected by LASSO cross-validation, a machine learning technique. The models were then tested on out-of-sample data and the error of their predictions compared. For four of the five personality traits, the LASSO-based model predicted out-of-sample data with less error than the traditional model, suggesting that machine learning techniques can be used to build better predictive models in psychology.

35. Pro-Kinetic Actions of Intraluminally Acting 5-HT4 Receptor Agonists

Melody M. Haag & John Konen, Colleen B. Kerrigan, Brigitte Lavoie, Jill Wykosky, Grant W. Hennig, Gary M. Mawe
Department of Neurological Sciences, University of Vermont

5-HT4 receptor (5-HT4R) agonists are known to be an effective treatment for intractable constipation; however, adverse side effects, including cardiovascular complications, have limited their use. Although these agonists were thought to act via a presynaptic faciliatory effect on enteric nerve terminals, we discovered that 5-HT4 receptors are extensively expressed in the epithelial layer of the colon, and that intraluminal infusion of 5-HT4 agonists accelerated colonic motility *in vitro* (Hoffman et al., *Gastroenterology* 142:844-854 2012). The current investigation was conducted to test whether intraluminally-acting formulations of 5-HT4R agonists can promote intestinal motility *in vivo.* For in vivo studies, mice received oral gavage of either vehicle or an intraluminally acting 5-HT4R agonist. Outcome measures included whole gut transit, colonic motility (bead expulsion assay), fecal output and water content, gastric emptying and small intestinal transit. Mice gavaged with an intraluminally acting 5-HT4R agonist had significantly faster whole GI transit time versus vehicle treatment trials in the same mice. This effect was blocked by pretreatment with an antagonist (GR-113808), and it was not detected in 5-HT4 null mice. Mice receiving treatment gavage exhibited a 5-HT4 antagonist-sensitive acceleration of colonic motility, as compared to vehicle trials in the same mice. Fecal output and water content were increased in mice receiving treatment gavage versus vehicle. No changes in gastric emptying were detected, but a slight acceleration of small intestinal transit was noted with one of the test compounds. Overall, these findings demonstrate that administration of intraluminally acting 5- HT4R agonists promotes propulsive motility. These outcomes support the concept that intraluminally acting 5-HT4Rs agonists represent a novel therapeutic target for the treatment of constipation that would offer an improved safety profile compared to systemically absorbed compounds.

36. PACAP/PAC1 in the dentate gyrus of the hippocampus modulates contextual fear conditioning and increases granule cell excitability through an extracellular regulated kinase dependent signaling cascade

Gregory C. Johnson[1], Victor May[2], Rodney L. Parsons[2], and Sayamwong E. Hammack[1]

Pituitary adenylate cyclase activating polypeptide (PACAP) and the PAC1 receptor (PAC1R) are associated with several behavioral pathologies that implicate fear and anxiety behaviors such as post-traumatic stress disorder (PTSD). The hippocampus is critical for spatial-mapping and contextual memory and PAC1R transcript is highly expressed in the dentate gyrus (DG) of the hippocampus. Rodent studies have identified impairments in contextual memory and DG long-term potentiation in PAC1R knockout mice, an effect mimicked by inactivating the DG. Here we examined the role of PACAP infusion directly into the DG in the acquisition, expression, and extinction of contextually conditioned fear. Our results show that PACAP enhances expression of contextual fear at test, while not affecting acquisition. Furthermore, patch clamp recordings from granule cells in the DG show that PAC1R activation significantly increases their intrinsic excitability, although not through cyclic-AMP nor phospholipase C mediated signaling, but through activation of the extracellular regulated kinase signaling pathway likely initiated through PAC1R endocytosis/endosomal signaling

37. The effect of interneuron progenitor cell implantation on a task of hippocampus-dependent working memory in an animal model of temporal lobe epilepsy

Willie J. Curry[1], Amanda E. Hernan[1], Greg Richard[1], Matt Weston[1] & Rod C. Scott[1, 2]
[1]Department of Neurological Sciences, University of Vermont, [2]Institute of Child Health, University College London

Epilepsy is associated with a very high incidence of cognitive and behavioral comorbidities that are detrimental to overall quality of life. Current treatments for epilepsy involve anti-seizure pharmacological agents that generally increase the available amount of inhibition to counteract the hyperexcitability observed in the disorder. However, this often only treats the seizures characteristic to epilepsy in approximately 30% of patients with epilepsy, pointing to a need for novel treatment approaches to target both seizures and cognition. Previous and ongoing research points to a more complex story than the excitation/inhibition imbalance that has become dogma. Rather, specific patterns of neuronal loss and synaptic reorganization are believed to lead to modifications in the firing properties of surviving neurons. Interneurons are critical for temporally regulating the firing of neuronal networks. Through the implantation of interneuron progenitor cells obtained from the medial ganglionic eminence (MGE), we sought to investigate changes in cognitive outcome and performance on tasks of working memory. We found that epileptic rodents receiving grafts of MGE-derived progenitor cells in the dorsal hippocampus performed better on the Morris Water Maze, a task of spatial navigation and cognition, when compared to animals receiving only vehicle injections. Additionally, *in vivo* single-unit recordings in CA1 of the hippocampus revealed differences in firing parameters such as mean firing rate and spike width. These encouraging results will be further explored in future studies.

38. Hippocampal and Prefrontal Cortical Temporal Coding in a Model of Cortical Malformation

Hernan AE, Mahoney JM, Curry W, Mawe S, Scott RC
Department of Neurological Sciences, University of Vermont

Malformations of cortical development (MCDs) are the result of an insult during the neuronal migration process that leads to structural and functional abnormalities in neural networks. In humans, MCDs are often associated with intractable epilepsy and cognitive deficits. In this study we used the embryonic day 17 methylazoxymethanol acetate (MAM) model to examine the impact of these MCDs, independently of seizures, on neural networks that subserve cognition. Previous work by our group has shown that MAM rats can acquire spatial and non-spatial learning and memory tasks with significant over-training, however the neural mechanism underpinning this learning is unknown. To this end, we utilized an extensive over-training protocol in order to ensure that MAM rats were able to perform a delayed non-match to sample (DNMS) working memory task while recording single unit and local field potential activity from prefrontal cortex (PFC) and CA1 of the hippocampus simultaneously. In line with previous observations, MAM rats take significantly longer to reach criterion in the training phases of the task. Once they are trained, MAM animals perform the working memory component of the DNMS task as well as controls, however they make significantly more omissions errors and take longer to correctly complete each trial. Using a generalized linear modeling approach (GLM), we investigated temporal and rate coding of PFC and CA1 neurons during DNMS. We find that MAM neurons in the hippocampus are less temporally regulated than those in controls, and that this reduced modulation predicts overall performance by session. We also examined rate coding in response to task parameters through the GLM. We found that MAM rats' encoding of the sample and match levers was less precise than control rats' encoding. Fewer neurons were comodulated in MAM rats. Finally, neurons that were well temporally modulated and neurons that were encoding the sample and match phases were more likely to be connected, showing for the first time that rate coding to task parameters is directly related to temporal coding of fine spike timing. Temporal and population coding parameters alone significantly predict session accuracy in both groups. Understanding the systems-level mechanism of learning in the context of abnormal neural networks in animals with MCDs could lead to novel therapeutic targets that maximize cognition in patients with epilepsy.