

1-19. Travel Award Winners

1. Rapid dopamine signaling in response to a short-acting opiate, remifentanyl

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Fast-scan cyclic voltammetry (FSCV) measures dopamine neurotransmission on a sub-second time scale and this technique has been used to extend our understanding of the mechanisms that mediate drug motivation and reward. Here, we use FSCV provide the first subsecond assessment of fluctuations in extracellular dopamine concentration within the nucleus accumbens core and shell during intravenous (i.v.) administration of the short-acting opiate, remifentanyl. The primary, unique feature of remifentanyl is its short half-life of 0.3 – 0.7 minutes. We have found that doses of remifentanyl that maintain self-administration (1.25 µg/kg, 2.50 µg/mkg, 5.0 µg/kg) robustly increase extracellular dopamine concentration within the nucleus accumbens just seconds following infusion and remain elevated for 1 minute before falling back to basal levels around 1.5 minutes. A dose of remifentanyl that does not maintain self-administration (0.625 µg/kg) does not cause a significant increase in dopamine. The effects of remifentanyl on behavior are short-lived as well. Doses that maintain self-administration induce catalepsy characteristic of opioid drugs but this state lasts only minutes before rats become ambulatory again. Our data suggest that remifentanyl may be an excellent tool for future studies that wish to use i.v. drug delivery as a reinforcer in studies of ‘drug learning’ because of its brief effects on dopamine neurotransmission.

2. Heterosynaptic interaction of the sprouted crossed entorhinal and septal inputs to the hippocampus following unilateral entorhinal cortex lesion in rats

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The central nervous system exhibits a capacity for structural and functional reorganization following injury. Within the hippocampal formation, for example, several of the projections to the dentate gyrus proliferate extensively following the unilateral destruction of the entorhinal cortex, the major projection to the dentate. While the majority of neural projections from the entorhinal cortex to the dentate gyrus project ipsilaterally to form the perforant pathway, a small number of fibers emerging from the entorhinal cortex terminate in the contralateral dentate to form the crossed temporodentate (CTD) pathway. Following a unilateral lesion of the entorhinal cortex in rats, axonal sprouting has been observed to occur in the CTD fibers as well as in those fibers arising from the septum that terminate in the dentate gyrus to form the septodentate pathway. With long-term survival after unilateral entorhinal lesions, the extensive proliferation of the CTD renders it capable of discharging the granule cells of the dentate gyrus (which is uncharacteristic of the normal CTD) and enhances field excitatory postsynaptic potentials in the dentate. In contrast, granule cell discharge is rarely, if at all, observed after short-term survival periods of 15 days or fewer. The present study examined whether stimulation of the proliferated septodentate pathway followed by CTD stimulation (i.e. heterosynaptic paired-pulse stimulation) would potentiate granule cell responses at 15 days post-lesion. Male, Sprague-Dawley rats were either given unilateral entorhinal lesions or sham operations. In an acute anesthetized preparation, stimulating electrodes were placed in the medial septum and intact entorhinal cortex 15 days following surgery. Evoked potentials were recorded with a glass microelectrode placed in the dentate gyrus. A “conditioning pulse” elicited in the septum was paired with a subsequent “test pulse” elicited in the entorhinal cortex at inter-pulse intervals of 30-500 ms. We assessed the dentate response to the test pulse either with or without stimulation by the conditioning pulse. Whereas stimulation of the CTD rarely evoked granule cell discharge, pairing the CTD with septodentate stimulation produced granule cell discharge in a greater number of cases. These findings suggest that the heterosynaptic

interaction of the sprouted CTD and septodentate inputs to the dentate gyrus of the hippocampus has the capacity to produce granule cell discharges.

3. Neonatal Alcohol Exposure via Intraperitoneal Injections Affects Ultrasonic Vocalizations and Activity Levels in Rats

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Developmental exposure to alcohol is known to cause many physical, behavioral, and social deficits in humans as well as in rodents. The third trimester of pregnancy is a period of rapid brain development in humans; this period of growth is analogous to the first postnatal week in rodents. Previous studies using rodents as a model for Fetal Alcohol Syndrome (FAS) have administered alcohol via gastric cannula or oral intubation. These are time consuming techniques that are difficult for undergraduate students to learn. Intraperitoneal injections of alcohol have been used in mice, with these mice showing similar behavioral effects to children with FAS, but this technique had yet to be validated in rats. The purpose of this study was to validate this intraperitoneal alcohol administration technique in rats through the assessment of ultrasonic vocalizations (USVs) and activity levels, which previously have been shown to be affected by neonatal alcohol administered via gastric cannula or intubation. When young rat pups are isolated from their dam, they emit 40 kHz USVs as a signal for retrieval by the dam. Previous studies have shown that neonatal alcohol results in a longer latency to first USV and decreased USV frequency. Furthermore, it is well established that neonatal alcohol results in increased locomotor activity in rodents. In this study, alcohol-exposed rats were administered 4.5 g/kg/day of ethanol by intraperitoneal injection on postnatal days 1-7. Injected control pups received saline injections, while suckle control pups never received an injection. On postnatal day 14, the pups were individually isolated and their USVs recorded for 6 minutes using a bat detector. Rat pups developmentally exposed to alcohol emitted significantly fewer USVs and had a significantly longer latency to first USV than control pups receiving no treatment. On postnatal days 20-21, rat pup activity levels were recorded in a circular open field. Rats previously exposed to alcohol were significantly more active compared to injected and suckle controls on both days of testing. Since these findings are similar to those caused by other methods of neonatal alcohol administration, this study supports the validation of intraperitoneal injections in rat behavioral models of Fetal Alcohol Syndrome.

4. The neuroprotective efficacies of various botanical extracts, Rue chalapensis, Hibiscus sabdariffa, and Panax Ginseng species against neurotoxic-induced Parkinson's disease in neuroblastoma cells in vitro

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Common neurodegenerative disorders, such as Parkinson's disease (PD), may show neuronal cell loss as an accumulation of reactive oxygen species (ROS) due to increased oxidative stress. Many extracts, containing anthocyanins, flavonoids, or phenolic compounds, have been shown to be strong antioxidants and possible neuroprotective agents. Various *Panax* species, such as Korean, American, and Chinese Red or White Ginseng, have been shown to enhance memory and stimulate the immune system. Ginseng extracts have also been considered as adaptogens, natural substances that aid in homeostatic balance. Roselle extract from *Hibiscus sabdariffa* L. contains primarily anthocyanins and protocatechuic acid, which can exhibit both antioxidant and antitumorigenic properties. Rue extract, or *Ruta chalepensis* L., has been shown to protect erythrocytes from oxidative stress-induced free radicals. To determine the neuroprotective efficacies of these extracts with relationship to the oxidative stress-induced *in vitro* PD model, pretreatments of B35 and SK-N-

SH neuroblastoma cells with these individual and combination agents against the neurotoxic insults, MPP+ and 6-OHDA were undertaken. The cells were pretreated in 96-well plates to formulate dose-response curves, with each of the serially-diluted extracts added for 24 hours before a potent dose of MPP+, a mitochondrial complex I inhibitor, or 6-OHDA, a potential ROS generator. The cells were exposed to each insult first for 24 hours for posttreatment studies, followed by the extracts for 24 hours. Cotreatments with each agent and the neurotoxic insults were performed to elucidate possible preconditioning or gene activation versus actual mechanisms of action. Cell viability/cell proliferation of triplicate data sets was assessed through the MTT mitochondrial and Neutral Red lysosomal assay. Pretreatments of American Ginseng against MPP+ showed neuroprotection from 10-100ng/ml. Under posttreatment conditions, rescue occurred against MPP+ in both nanogram and microgram ranges. Korean Ginseng is more effective under posttreatment conditions than in the pretreatment trials. In combination treatments, the Chinese Red/Chinese White Ginseng extracts were most effective overall. Preliminary dose responses for *R. chalapensis* and *H. sabdariffa* extracts show effective doses of 10^{-3} - 10^{-5} g/ml for B-35 neuroblastoma cells. In SK-N-SH cells, the effective dose for each extract was tenfold less than the lowest dose in the B-35 cells. The neuroprotective efficacies of the various extracts against the neurotoxin-induced PD model may indicate their successful use in the prevention or treatment of Parkinson's Disease.

5. Social preference and social novelty behavior in zebrafish

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Zebrafish (*Danio rerio*) have an innate tendency to gather with other conspecifics in shoaling groups. Based on this instinctive response, we developed two new visual choice tests of preference for social interaction and social novelty. These tests are amenable for undergraduate thesis research and in graduate or undergraduate neuroscience or psychology courses. They are conducted during the day in a brightly-lit (940 lux) room, in mazes with a white background designed to induce anxiety. The tests are based upon, and the type of data collected are similar to murine three-chambered sociability tests. Initially, we compared performance among different zebrafish lines, as was done for the three-chambered social interaction test for mouse strains. We compared inbred (AB) and wild-crossbred (WIK) lines, from the Zebrafish International Resource Center (Eugene, OR) to albino and standard zebrafish from Petco (San Antonio, TX). AB fish spent more time in the chamber of the testing arena containing a clear box with another zebrafish inside, while Petco standard fish spent more time near a an empty blue box ($p < 0.05$, $N=9-12$).

Involvement of serotonergic and cannabinoid systems has been implicated in mammalian social behavior, and perhaps through their activation, high doses of the pain reliever acetaminophen (paracetamol) can enhance social behavior in rodents. Equivalentents of both cannabinoid CB₁ receptors and serotonin 5-HT_{1A} receptors are expressed in the zebrafish brain. We thus examined the effects of acetaminophen in comparison to the CB₁ receptor agonist WIN55,212 or 5-HT_{1A} partial-agonist buspirone on shoaling tendency, or social interaction, in zebrafish. Fish were exposed by bath to either 1 g/L acetaminophen, 10 mg/L buspirone dissolved in home tank water, or 1 mg/L WIN 55,212 dissolved in 0.1% DMSO (WIN 55,212) or drug-free tank water (+/- 0.1%DMSO) in a volume of 250 ml contained in a 600 ml beaker for 10-15 min. Fish were then placed in a social interaction and novelty test for 10 min each following 20 min of acclimation to test the effect of these drugs on shoaling tendency. We found that WIN 55,212 and buspirone both increased shoaling tendency ($p < 0.05$), which is consistent with their targeting of neural circuits that might be involved in social interaction. Acetaminophen failed to do so at this dose, but we are currently testing lower doses. Future studies will involve exposure of young-juvenile zebrafish to these same compounds and testing as adults. This structured social behavior test may be useful for

to compare effects of drug or toxicant exposures and genetic manipulations, and may substitute for rodent studies in undergraduate labs.

6. Complex Regulation of α -Synuclein Properties in Yeasts by Endocytosis Pathway Genes

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Parkinson's disease (PD) is an incurable and fatal neurodegenerative disease linked to the death of midbrain dopaminergic neurons. The accumulation and impaired degradation of the aggregated α -synuclein protein is thought to contribute to this cell death. Therefore, to develop the ability to selectively accelerate α -synuclein degradation is of therapeutic interest. Increasing evidence points to the lysosome as a site for α -synuclein degradation, but the exact route(s) are still being determined. In a budding yeast (*Saccharomyces cerevisiae*) model, we tested the hypothesis that the multivesicular body (MVB)/endosome pathway is a route for degradation of wildtype (WT) and familial mutant E46K α -synuclein. Specifically, we evaluated if three PD-related α -synuclein characteristics (subcellular localization, accumulation, and cellular toxicity) altered or worsened in yeast strains that were individually deleted for genes that encode for proteins that form the pre-ESCRT and post-ESCRT steps and the ESCRT-I, -II, and -III complexes of the MVB pathway. We report several findings. First, all seventeen MVB genes that were evaluated affected at least one α -synuclein characteristic examined, thus providing genetic evidence for the endosome pathway as a regulator of α -synuclein pathobiology. Secondly, each gene regulated each α -synuclein property to differing extents. α -Synuclein localization was the most widely altered property affected by at least fourteen gene deletions. Its accumulation was enhanced by at least nine gene deletions. Lastly, only the lack of one gene (*vps28*) enhanced α -synuclein-dependent toxicity. Together, our data suggests that both WT and E46K α -synuclein are degraded by the lysosome via the endocytosis route (Supported by NIH R15 048508-02, NSF MRI 0115919, NSF CCLI 0310627).

7. Mutations in palmitoyl protein-thioesterase 1 alter exocytosis and endocytosis at synapses in *Drosophila* larvae.

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Infantile-onset Neuronal Ceroid Lipofuscinosis (INCL) is a severe pediatric neurodegenerative disorder produced by mutations in the gene encoding palmitoyl-protein thioesterase 1 (Ppt1). This enzyme is responsible for the removal of a palmitate group from its substrate proteins, which may include presynaptic proteins like SNAP-25, cysteine string protein (CSP), dynamin, and synaptotagmin. The fruit fly, *Drosophila melanogaster*, has been a powerful model system for studying the functions of these proteins and the molecular basis of neurological disorders like the NCLs. Genetic modifier screens and tracer uptake studies in Ppt1 mutant larval ganglion cells have suggested that Ppt1 plays a role in endocytic trafficking. We have extended this analysis to examine Ppt1's involvement in synaptic function at the *Drosophila* larval neuromuscular junction (NMJ). Mutations in Ppt1 genetically interact with temperature sensitive mutations in the *Drosophila* dynamin gene *Shibire*, accelerating the paralytic behavior of *shibire* mutants at 27°C. In addition, Ppt1-deficient and Ppt1 point mutant larvae display defects in locomotion; these defects were not observed in *Df(1);UAS-PPT1*-rescued larvae. Electrophysiological work in NMJs of Ppt1-deficient larvae has revealed an increase in miniature excitatory junctional potentials (EJPs) and alterations in response to repetitive (10 Hz) stimulation. In particular, synapses in Ppt1 mutant larvae exhibited a significant increase in vesicle depletion in response to the 10 Hz stimulation, and impairment in vesicle recovery. Similar results were obtained in larvae containing a point mutation

in Ppt1 encoding an alanine→threonine substitution within the substrate binding site. Endocytosis was further compared in Ppt1-mutant vs. wildtype larvae using FM1-43 uptake assays, which demonstrated significantly less FM1-43 uptake at the mutant NMJs. Taken together, our genetic, cell biological, and electrophysiological analyses suggest a direct role for Ppt1 in synaptic vesicle exo- and endocytosis at motor nerve terminals of the *Drosophila* NMJ.

8. Latent inhibition of a conditioned taste aversion (CTA) in fetal rats is age-dependent.

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CTAs may be acquired when an animal consumes a novel taste (Conditioned Stimulus = CS) and then experiences the symptoms of poisoning (Unconditioned Stimulus = US) (Garcia et al., 1955). When later re-exposed to the CS, the animal will avoid the taste or reduce consummatory oral-facial movements (Grill & Norgren, 1978). In the current studies we sought to determine if a CTA could be diminished by non-reinforced pre-exposure to a CS (i.e., latent inhibition; LI) in fetal rats. We injected E17 or E18 pregnant Sprague-Dawley rats with 100% allicin (pure garlic extract; i.p.) or an equal volume of physiological saline. The taste/smell of garlic has been shown to cross the placental barrier (Gruest et al., 2004) and we were able to measure it (via HPLC) in the amniotic fluid during pilot studies. One day later the pregnant rats received a second injection of the CS allicin (i.p.) followed by either LiCl (81 mg/kg, i.p.; the US) or a control injection of saline. Forty-eight hours later (either E20 or E21) a spinal block was performed on the dam producing complete abdominal analgesia while pups were removed (still attached via umbilical cord), and tested in a temperature-controlled isotonic saline bath. Pups received oral lavage with 10µl, 0.1% allicin (i.e., similar to the concentration experienced in the amniotic fluid days earlier). Observations of ingestive orofacial motor responses (mouthing and licking) were recorded during the oral lavage of the garlic taste. If allicin had been paired with LiCl in utero, E21 fetuses exhibited a conditioned suppression of orofacial movements, indicative of an aversion to this taste (Grill & Norgren, 1978). However, pre-exposure to the garlic taste on E18 produced a latent inhibition of this CTA. Rats one day younger during conditioning (E18) did not exhibit signs of a CTA when they were tested ex utero on E20. LI of a CTA is a non-associative form of learning that requires the animal to remember the non-reinforced CS if it is going to be effective in diminishing the CTA acquisition. Thus, our data provide the first demonstration that fetal rats can acquire a LI. Our data also suggest that this ability emerges when pre-exposure to the CS occurs on E18 but not E17.

9. The Effects of Nicotine on Egocentric Spatial Navigation in Zebrafish

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Zebrafish are a versatile laboratory model that has been widely employed by many genetics and molecular biology labs. It is only recently that the value of zebrafish in behavioral pharmacology studies has been realized. Previous research has shown that zebrafish (*Danio rerio*) form egocentric-based, or viewpoint dependent, representations of their environment. Recent findings also suggest that psychostimulants, especially nicotine, have some beneficial effects such as cognitive enhancement in zebrafish. The aim of the present study was to further investigate the effects of nicotine on egocentric spatial navigation in zebrafish. Fish were divided into three groups: control (0 mg/L nicotine), 100 mg/L nicotine, and 200 mg/L nicotine. Egocentric spatial navigation was assessed using a three-axis maze that measures non-cue based spatial memory. It was hypothesized that low doses of nicotine would enhance while high doses would inhibit spatial memory performance. The 200 mg/L concentration significantly enhanced while the 400 mg/L

nicotine concentration significantly impaired spatial memory performance as compared to the control group. Nicotine significantly reduced the number of errors in the spatial task. Furthermore, female fish significantly outperformed males in spatial navigation ability in both the control and nicotine conditions.

10. Quantification of serotonergic receptors and calcium channels in the sublesional mouse spinal cord after spinal cord injury

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The mammalian hindlimb central pattern generator (CPG) for locomotion is located in the lumbar spinal cord, and coordinates contralateral alternation of the hindlimbs, as well as intralimb flexor/extensor muscle alternations. Serotonin (5HT) plays an important role in enabling the CPG to function. All serotonergic input to the lumbar cord descends from the medullary Raphe nuclei; these inputs are lost after a complete spinal cord lesion. We are investigating the compensatory responses of neurons below the lesion that result from this loss of serotonergic input. We used immunohistochemical methods to determine whether spinal cord injury (SCI) affects the expression levels of 5HT_{2C} receptor clusters and Ca_v 1.3 channel clusters. Four weeks after a complete lesion at T8-9, mice were sacrificed and processed for immunolabeling of these two molecules. A combination of ImageJ and Matlab routines was used to determine the number, size, and intensity of 5HT_{2C} receptor clusters after SCI, as well as the percentage of the frame area covered by Ca_v 1.3 channels and their average brightness. After SCI, there was a significant 2.2-fold upregulation in the number of 5HT_{2C} receptor clusters, and 5HT_{2C} receptor clusters were significantly 1.9-fold larger in SCI mice. There was no significant difference in the average brightness of 5HT_{2C} receptor clusters between intact and SCI spinal cords. This suggests that SCI evokes an increase in 5HT_{2C} receptor expression, but not an increase in packing density of the receptors at synapses. After SCI, the area and intensity of Ca_v 1.3 channels were significantly 1.7-fold and 1.6-fold larger, respectively, than in intact mice. We also tested whether treatment with the 5HT₂ partial agonist quipazine could prevent these compensatory responses, as quipazine treatment has led to improved locomotor recovery after SCI in previous behavioral experiments. Half of the SCI mice were given daily i.p. quipazine while the other half were given i.p. saline vehicle. We saw no significant differences between the quipazine- and saline-treated animals in the upregulation of 5HT_{2C} receptors or Ca_v 1.3 channels. These results suggest that daily activation of 5HT₂ receptors is insufficient to prevent the SCI-induced increase in 5HT_{2C} receptors and Ca_v 1.3 channels. Supported by NIH grant NS057599.

11. Pathological axonal transport II: binding cooperativity, ATP, and tau

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Impaired axonal transport has been implicated as the cause of numerous neurodegenerative disorders, including Amyotrophic Lateral Sclerosis (ALS), Charcot -Marie-Tooth, Alzheimer's, Parkinson's, and Huntington's diseases. In experimental studies, imaging of both in vivo and in vitro anterograde and retrograde transport by the molecular motors kinesin and dynein, respectively, has revealed several possible mechanisms leading to deficient transport that may be synonymous across these various pathologies. Beyond specific and isolated gene mutations and protein aggregation, general hypotheses of transport disturbance have included metabolic changes that reduce ATP availability, changes in motor-motor and motor-cargo interactions and binding cooperativity, and the effects of ubiquitous motor signals or chemical mediators, such as tau. In this exploratory study, we combine a theoretical model with experimental data to investigate these

hypotheses. Using our previously developed methods for analyzing the distribution of the number of cargos versus the distances they are transported in a motor neuron, we analyze the effect of individual and combined changes in ATP, motor binding cooperativity, and tau. By modeling the relationships between other experimental measures such as pause length and duration, binding rate and ratio, and cargo size, we distinguish the impact and identities of the hypothesized mechanisms for impaired transport. Finally, we address the important implications of said mechanisms in neuropathology

12. Protection against glutamate toxicity in HT22 neurons by a novel phosphodiesterase inhibitor

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Glutamate toxicity is a major contributor to neuronal cell death following an ischemic stroke. Ischemic stroke is characterized by focally decreased blood supply to the brain and results in a deficiency of glucose and oxygen transport to the surrounding tissue. Deprivation of these essential nutrients results in the inability to produce ATP which prevents ionic pumps from transporting K⁺ into and Na⁺ out of neurons. The reversal of ion gradients results in an increased depolarization and release of glutamate into the extracellular space. In addition to the generation of excitotoxicity via NMDA receptors, this abundance of extracellular glutamate decreases cystine uptake through the xCT antiporter, which depletes intracellular supplies of glutathione. Glutathione is the primary antioxidant in the brain, and its decrease is associated with increased reactive oxygen species and cell death. Previous research has shown that cell signaling cascades downstream of cAMP can influence glutathione levels and prevent toxicity by inhibiting apoptotic signaling cascades. Through collaboration with Dr. Charles Hoffman of the Boston College Biology Department, we have evaluated the effect of a novel phosphodiesterase inhibitor, BC27, on glutamate-induced toxicity in HT22 neurons. Assays measuring radiolabeled cAMP hydrolysis suggest that most of the PDE activity in HT22 neurons is PDE4 specific and that BC27 is a PDE4 inhibitor. While BC27 significantly protects against glutamate toxicity in HT22 neurons, it surprisingly does not block the decrease in glutathione in glutamate treated cells. Using viability assays in conjunction with specific pathway activators and inhibitors, we have found evidence suggesting protein kinase C and extracellular signal-regulated kinase as possible effectors of BC27. We are currently investigating the involvement of transcription factors, transcribed genes and their translated proteins further downstream that may be responsible for BC27's protection against glutamate toxicity.

13. Immunofluorescence restaining of previously processed experimental tissues reveals preservation of antigenicity

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Immunofluorescence is a light microscopic technique for visualization of proteins in biological tissues. One drawback to the procedure involves the inability to perform further analysis on the tissue after it has been stained and coverslipped. This can pose expense- and time-related problems when a sample has been stained for a given protein, but subsequent analysis of a different protein must be performed on a new set of tissue. In the present study, we demonstrate that tissues previously processed to tag a protein using immunofluorescence can be successfully 'restained' for a different protein, thereby preserving the tissue and reducing costs, time, materials, and animal usage. We first examined the perivascular axonal density of tyrosine hydroxylase (TH) immunoreactive axons associated with the rat middle cerebral artery, an extracerebral blood vessel on the surface of the brain. We quantified the TH axonal density of 'control' vessels (n=8) that were analyzed only for rabbit anti-TH (Millipore) and that were tagged with donkey anti-rabbit Alexa-

594 (Molecular Probes). The TH perivascular axonal density of these vessels was then compared to the TH axonal density of a separate set of vessels (n=3) that was initially stained for a different protein, analyzed using confocal microscopy, and then 'restained' with anti-TH antibody. In order to 'restain' the samples, free floating vessels first were incubated with goat anti-vesicular acetylcholine transporter and then tagged with donkey anti-goat Alexa-488, followed by standard mounting on glass microscope slides with Vectashield (Vector Labs). After imaging with confocal microscopy, coverslips were floated off and vessels were retrieved, placed into fresh buffer, and processed for rabbit anti-TH and tagged with donkey anti-rabbit Alexa-594. Quantitative analysis of TH density revealed no statistical differences in circumferential, longitudinal, or total TH axonal density between vessels stained only once and 'restained' vessels. Similar results were obtained when testing 'restaining' properties of 12-18 μ m cryostat sections of peripheral nervous tissues and spinal cord tissues processed on microscope slides. In conclusion, we show that, for free-floating vessels as well as for cryostat sections that have been mounted on glass slides, the initial staining process does not degrade the tissue enough to prevent reuse, and that 'restaining' the tissues provides results that are equivalent to tissues processed only once. These are promising results, for it suggests that biological samples may be preserved for future use of additional immunofluorescence procedures using confocal microscopy.

14. Expression of endocannabinoid biosynthesizing enzymes in hippocampal CA1 neurons

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The hippocampus mediates short-term memory formation in the brain. Within the region, two cell types comprise the neuronal network involved in learning and memory; excitatory pyramidal cells, which make up the pathway of information flow, and inhibitory interneurons, which modulate pyramidal cell activity. Interneurons display an amazing range of heterogeneity, suggesting that they affect pyramidal cells and thus learning and memory in unique ways. The cellular mechanism that underlies learning and memory is synaptic plasticity, which is defined as synaptic changes that either strengthen or weaken (long-term depression, LTD) synapses. Recently, hippocampal interneurons were shown to undergo a novel form of interneuron LTD, mediated by retrograde endocannabinoid (eCB) neurotransmission. Because the involvement of interneurons in eCB production is debated, and due to the large heterogeneity among interneuron subtypes suggesting eCB synthesizing enzymes are not expressed equally by each subtype, our goal was to identify the expression of eCB synthesizing enzymes within interneurons and correlate them to interneuron subtypes. To do this, we extracted single interneurons from rat CA1 stratum radiatum or pyramidal cells from stratum pyramidale using patch clamp electrodes and analyzed the expression of eCB signaling components using quantitative real-time PCR. GAD65 and GAD67 expression were used as interneuron markers. The calcium binding proteins parvalbumin, calbindin, calretinin, and the neuropeptide cholecystokinin were used to determine interneuron subtype. The expression of several components involved in eCB neurotransmission, including TRPV1, NAPE-PLD, DAG lipase alpha, and CB1 were also examined. Our results demonstrate that eCB biosynthetic enzymes are expressed by interneurons, suggesting that interneurons can synthesize eCBs. Interestingly, these enzymes are not expressed ubiquitously among interneurons, with several enzymes confined to particular interneuron subtypes. CCK/CB-expressing basket cells were identified for the first time to also express NAPE-PLD, an enzyme that synthesizes anandamide, while other interneuron subtypes do not. Therefore, these cells could produce anandamide, a CB1 agonist, and thus activate their own CB1 receptor. We also tested CA3 and CA1 pyramidal cells for eCB biosynthetic enzyme expression and found that there is no difference between eCB biosynthetic enzyme expression in individual cells, nor between CA3 or CA1 cells. These results will provide a greater understanding of hippocampal interneurons' putative involvement in eCB production and thus likely roles in learning and memory.

15. Relationships between behavioral abnormalities and set-shifting impairments in the neonatal ventral hippocampal lesion model of schizophrenia.

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Rats with a neonatal ventral hippocampal lesion (NVHL), a developmental model of schizophrenia, exhibit behavioral abnormalities, such as disrupted prepulse inhibition (PPI), reduced social interaction, increased spontaneous locomotion, and potentiated locomotor response to stimulant drugs, that have been linked to clinical symptoms. NVHL rats also demonstrate executive function impairments on a T-maze strategy set-shifting task. In patients with schizophrenia, weak relationships exist between negative symptoms and executive function deficits, both of which are governed by the prefrontal cortex. Here, we examined performance in an operant-based set-shifting task, and explored potential correlations between set-shifting and behavioral abnormalities. Rats received bilateral hippocampal infusions of ibotenic acid (NVHL group) or artificial cerebrospinal fluid (sham group) on postnatal day 7. At adulthood, animals were tested on PPI, spontaneous locomotion, and social interaction with an unfamiliar partner. Rats were then trained on an operant set-shifting task where they were required to learn either a position-based or a visual cue-based rule on the first day of testing (Set), and then shift to the other rule on the second day of testing (Shift). Finally, animals were tested for amphetamine-induced (1.5 mg/kg, i.p.) locomotion. As previously observed in the T-maze task, NVHL rats were able to reach criterion performance on the first day's rule (Set) as easily as shams, but took more trials to reach criterion and made more errors than shams on the second day's rule (Shift). Unlike in the T-maze task, this deficit was dependent on the order of testing; the NVHL impairment was most clearly evident when rats shifted from a position-based rule to a visual cue-based rule. Set-shifting performance did not correlate with social interaction behavior, as might have been predicted from the clinical relationship between executive function and negative symptoms. However, unexpected correlations were found between set-shifting performance and rearing in the spontaneous locomotion task. In particular, the number of regressive errors was positively correlated with the number of rears. As regressive errors are governed by striatal areas, this correlation supports a dysfunction in corticostriatal circuits in the NVHL rat. Together, these results suggest that assessment of executive function deficits in the NVHL model may depend on the parameters of the particular set-shifting task, and that relationships between behavioral and cognitive abnormalities in NVHL animals are complex and do not necessarily follow patterns observed in patients with schizophrenia.

16. Ca_v1.3 but not Ca_v1.2 L-type calcium channels co-localize with GABA_B receptors in neonatal rat hippocampus

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In the mammalian hippocampus, current enhancement through L-type calcium channels, via activation of GABA_B receptors, was previously shown to be a developmental phenomenon, with peak enhancement occurring at postnatal day 7 (Bray, J. and M. Mynlieff. 2009). This L-type calcium current enhancement has been demonstrated to be dependent on protein kinase C activation either directly, or through an intermediary. Two types of L-type calcium channels, Ca_v1.2 and Ca_v1.3, are expressed in the superior region of neonatal hippocampus. We have demonstrated that expression of both isoforms is low at birth, with expression of Ca_v1.2 peaking around 1 week of age, followed by a rapid decline. Expression of Ca_v1.3 gradually increases to an adult steady state level by postnatal day 21. Ca_v1.2 and Ca_v1.3 are present in all layers of the superior region of the

hippocampus, with the highest concentrations found in the pyramidal cell layer and the proximal dendrites. $Ca_v1.2$ and $Ca_v1.3$ both demonstrate consensus phosphorylation sequences, and thus, may be modulated by metabotropic receptors such as the GABA_B receptor. The goal of this project was to determine the subcellular location of voltage gated L-type calcium channel isoforms, 1.2 and 1.3, in relation to GABA_B receptors in the neonatal rat hippocampus. Close proximity of GABA_B receptors to a specific L-type calcium channel isoform is important for the modulation of current that has been demonstrated. The hippocampi of postnatal day 6-8 rats were removed, frozen, sectioned at 25 μ m, and mounted onto slides. The sections were stained with primary antibodies against $Ca_v1.2$, $Ca_v1.3$ (polyclonal rabbit antibodies, Santa Cruz Biotechnology, Inc., Santa Cruz, CA), and GABA_B receptors (monoclonal mouse anti-GABABR1, Neuromab, UC Davis, CA), followed by secondary antibodies conjugated to Dylight® 488 or 549. Confocal microscopy was employed to determine the proximity of L-type calcium channels and GABA_B receptors in the hippocampus. Image analysis demonstrated co-localization between GABA_B receptors and $Ca_v1.3$ channels, but not $Ca_v1.2$ channels. These results suggest that the calcium current enhancement established in postnatal day 6-8 rat hippocampi is due to $Ca_v1.3$ channel modulation by GABA_B receptors rather than modulation of $Ca_v1.2$ channels.

17. Subcellular localization and protein interactions of PTL-1 in *Caenorhabditis elegans*

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PTL-1, a microtubule-associated protein of the structural MAP2/tau family, is the sole member of this gene family in *Caenorhabditis elegans*. Structural MAPs of the MAP2/tau family include the vertebrate proteins MAP2, MAP4 and tau, and homologs like PTL-1 (Protein with Tau-like repeats-1) in other animals, including *Caenorhabditis elegans* (*C. elegans*) and *Drosophila melanogaster*. MAP2 and tau are expressed almost exclusively in neurons in mammals and are thought, by virtue of their microtubule-stabilizing activity *in vitro*, to regulate microtubule networks in dendrites and axons. MAP2, restricted to the somatodendritic compartment of vertebrate neurons, may be involved in the establishment or maintenance of dendritic polarity. Tau, localized to the axonal subcompartment in vertebrate neurons, may provide a similar function in axons. Tau hyperphosphorylation has been associated with a number of neurodegenerative conditions, so-called tauopathies, including Alzheimer's disease. In addition, this group of proteins may also function in the regulation, formation or maintenance of protein assemblies. Understanding the normal functions of this protein in less complex model organisms than mammals will shed light on the processes affected by its dysfunction in disease. Sequence analysis of available invertebrate genomes revealed a number of single, putative tau-like genes with high similarity to *ptl-1*. The *ptl-1* gene is expressed in a number of cells, most notably mechanosensory neurons and knockout worms exhibit a touch response deficit. *ptl-1* is also expressed in cells during the comma stage of development and knockout mutants exhibit an egg hatching defect. We examined the subcellular protein localization of PTL-1 using immunocytochemistry; PTL-1 protein is present both in the cytoplasm throughout the mechanosensory neuron, as well as localized to discrete puncta. Interacting proteins were identified using immunoprecipitation followed by MALDI-TOF analysis of trypsin-digested peptides.

18. Ethanol induced axon pathfinding defects in the zebrafish, *Danio rerio*.

Andrew Ross, Cecilia Culp, Aleksander Krazinski, Zachary Knecht, and Jennifer Bonner

In utero exposure to ethanol during human pregnancy can lead to birth defects characterized as Fetal Alcohol Spectrum Disorder (FASD). Individuals affected by FASD can experience a spectrum of conditions that include impaired motor function, physical deformities, and cognitive deficits as a

result of ethanol interactions with neuro-developmental pathways. To investigate mechanisms that underlie FASD impairments, we are using zebrafish (*Danio rerio*) as a model organism to investigate the disruptions to nervous system development that arise from ethanol exposure. Zebrafish embryos were treated with ethanol during embryogenesis and then analyzed for axon pathfinding abnormalities. Immunofluorescence techniques were implemented to visualize commissural spinal neurons, motor neurons, and forebrain commissures. We demonstrate that commissural spinal neurons of embryos exposed to alcohol failed to grow dorsally after crossing the midline of the spinal cord. Additionally, motoneuron axon growth was severely shortened. Importantly, ethanol induced specific axon guidance defects, rather than generalized disorganization, suggesting ethanol-induced impairments may be due to direct interactions with known axon guidance signaling systems.

19. Selectively bred highresponder and lowresponder rats differ in “affective” responsiveness to a novelty seeking test

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Vulnerability to addiction has been broadly related to a combination of traits termed “externalizing” behavior, including sensation-seeking, risk-taking and impulsivity. We have shown that rats selectively bred for locomotor response to novelty differ on a number of these dimensions. Bred high-responder (bHRs) rats show greater risk-taking behavior, are more impulsive, and are more prone to addictive behavior compared to bred low-responder (bLR) rats. Outbred high-responder rats with an increased locomotor response to a novel environment also exhibit an increased propensity for drug self-administration. However, recently, it has been shown that “novelty-seeking”—a trait thought to be more akin to sensation seeking in humans—is associated with an increased propensity for compulsive drug use in rats, but increased locomotor response to novelty is not. Here we utilized our two lines of rats that have been selectively bred based on locomotor response to an inescapable novel environment to determine whether they also differ in “noveltyseeking”. Given the constellation of addiction-related traits that differ between these phenotypes, we hypothesized that bHR rats would exhibit increased novelty-seeking behavior relative to bLR rats. Yet, when given the choice to explore a novel vs. a familiar environment, we found no differences between bHRs and bLRs. Both exhibited a preference for the novel environment and there were no differences in the latency to explore either side of the testing chamber. The test elicited a corticosterone response in both phenotypes, and the shape of the hormonal response differed slightly, with the area under the curve greater for bHRs. Ultrasonic vocalizations (USVs) were recorded and analyzed as an index of “affective” response. Interestingly, only bHRs emitted detectable USVs in either the ‘positive’ (50 kHz) or ‘negative’ (22 kHz) range during the novelty-seeking test. bHRs emitted a greater number of ‘positive’ than ‘negative’ calls in both the familiar and novel sides of the chamber and the total number of calls was the same on both sides. bHRs also emitted more non-frequency modulated calls than frequency modulated calls on both sides of the chamber. Thus, the behavioral data from bHR and bLR rats indicate similar preferences for the novel environment, but the USV data suggest the affective response was quite different for each phenotype. Given that locomotor response to novelty is dissociable from the novelty-seeking trait in our selectively bred lines, these data do not support the notion that ‘noveltyseeking’ is a better predictor of addictive behavior.

20-24. SOMAS Winners

20. Characterization of Estrogen Regulation of Oxytocin Neurons and Release in Female Prairie Voles

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Oxytocin (OT) is a neuropeptide hormone secreted by the posterior pituitary that has implications in social bonding, mating, parenting behaviors, the stress- response, and birthing and lactation within the female members of mammalian species. Estrogen is known to modulate the OT system, and it is widely assumed that estrogen (due to regulation of gene expression) upregulates the OT system. This purpose of this study is to investigate how estrogen affects the synthesis and release of oxytocin, particularly the release of oxytocin in response to stress. Understanding the manner in which estrogen regulates the synthesis and release of oxytocin will help us understand social- and stress-related diseases that show sexual dimorphism or hormone-related effects, including autism and schizophrenia. The current study examines the effects of chronic estrogen (estradiol benzoate, EB) on OT peptide expression in the hypothalamus, levels of OT in plasma under basal conditions, and temporal OT release in plasma following a stressor. The subjects chosen for the study, female prairie voles (*m. ochrogaster*), were housed in same-sex sibling pairs and underwent ovariectomies to remove endogenous sources of estrogen. They were then assigned to either estradiol bezoate (EB) or control treatment groups. According to treatment group, the animals received a subcutaneous (S.C.) capsule containing either EB or vehicle treatment. After 14 days of treatment, the animals were assigned to either stress or no stress groups. Stress animals underwent a resident intruder (R-I) test lasting five minutes. They were then sacrificed 0, 10, 30, or 60 minutes following the R-I stressor, and brains and trunk blood were collected for immunohistochemistry and enzyme immunoassay analysis respectively. Immunohistochemistry will allow us to analyze how much oxytocin is being made in the brain. Enzyme immunoassay will allow us to measure oxytocin content in the bloodstream.

21. Effects of maternal protein intake during gestation on offspring energy balance regulation in rats.

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Prenatal nutritional perturbations can produce long term effects on offspring physiology and behavior. One way that impaired nutrition during gestation affects developing offspring is by affecting the development of neuroendocrine systems which control energy homeostasis. Pregnant rats from days 5-21 of gestation were placed in either a control group, given a diet of 20% protein, or low protein, group given a diet of 6% protein. All offspring were cross-fostered to control (20% protein) dams at postnatal day 1 (P1). At P1, P7 and P14, size and weight were determined, and at P14 offspring milk ingestion was measured. In addition, body weight was measured weekly and subsets of animals were sacrificed at P30 and P60 to measure hypothalamic neuropeptide Y (NPY) protein expression via immunohistochemistry. Low protein offspring had a lower birth weight ($5.23g \pm 0.2$ vs. $6.34g \pm 0.1$, $p < 0.05$), smaller crown-rump length at birth ($38.1mm \pm 1.2$ vs. $40.7mm \pm 0.4$, $p < 0.05$), and increased milk ingestion at P14. As adults, low protein offspring had higher body weights and altered hypothalamic NPY protein expression. Therefore, offspring from low protein fed rats undergo intrauterine growth restriction which affects neuroendocrine development, potentially predisposing them to become hyperphagic and obese in adulthood.

22. Oxytocin and the neuroanatomy of sociality in degus and coruros

Heather Osorio, Annaliese K. Beery

The neurohypophysial peptide oxytocin (OT) plays a role in maternal attachments, aggression, and anxiety, and studies have suggested that it may promote social tolerance and the ability to live in groups. We examined the neuroanatomical distribution of oxytocin receptors (OTR) as a possible marker of social behaviors in the degu, *Octodon degus*, and the coruro, *Spalacopus cyanus*. Nine frozen brains were sliced at 20 microns (μM). Neuroanatomical stains (Acetylcholinesterase and Nissl stain) and autoradiography will be used to visualize the density of oxytocin receptors in key areas previously associated with social behaviors. I expect the degu and coruro to show similar OTR distributions due to their similar social organizations. I also predict that the degu and coruro will show similar OTR distribution as other non-monogamous rodents, with high density in the amygdala and low density in the nucleus accumbens and lateral septum. Findings from this study will help us to evaluate the hypothesis that a specific pattern of OTR is associated with sociality.

23. Characterizing the phenotype of progesterone receptor expressing cells in the postnatal rat lower rhombic lip

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Steroid hormones play a critical role in neural development, mediating processes such as migration, apoptosis and phenotypic differentiation. In addition to testosterone and estrogen, the perinatal brain is exposed to progesterone, and sensitivity to progesterone is evident by progesterone receptor (PR) expression in many regions of the brain. One such area is the lower rhombic lip (LRL); PR expression is present at high levels in the LRL on the day of birth (postnatal day 1; P1) and terminates sometime after P7. The LRL is a developmentally transient structure and a site of neurogenesis. Prenatally, neurons born in the LRL migrate to form precerebellar structures that, along with the cerebellum, coordinate sensorimotor functions. PR expression is present as early as embryonic day 18 and as late as P8 in the LRL and demonstrates an age-related increase prenatally, and an age-related decrease postnatally. The high level of PR expression in the perinatal LRL suggests that progesterone may potentially influence LRL function. Prenatally, the LRL serves as a source of neurons for precerebellar structures. Although the postnatal LRL is mitotically active, we wanted to determine the potential influence that PR may have on this function. We used double immunofluorescence for PR and the thymidine analog bromodeoxy-uridine (BrdU) to examine this potential. Only a small percentage (on average 15%) of PR positive cells also contained BrdU suggesting that it is unlikely that PR is directly influencing cell birth in this structure. Since newly synthesized cells migrate following birth, we examined whether PR could be influencing migration in the LRL. We observed that roughly double the percentage (>30%) of PR positive cells were colocalized with the radial glial marker, vimentin. These findings suggest that PR has the potential to influence migration, rather than neurogenesis, in the developing LRL. Future experiments will examine the functional significance of PR in the LRL radial glia.

24. Frontal-parietal gamma coherence as a possible correlate of attention in rats

Linnea Herzog, Kia Salehi, Mike Wiest, Ph.D

What types of electrical events in the brain underlie the process of attention to relevant stimuli in our outside environment? One phenomenon that has been singled out as a possible neural correlate of attention is coherence, or a constant phase relationship between two neural signals that originate from different areas of the brain. In electrophysiological experiments that involve coherence analysis, the raw signals (often local field potentials, which represent the postsynaptic activity of groups of neurons from a particular region of the brain) are split up into their different

frequency components so that coherence is always specified at a particular frequency range. Previous findings by Womelsdorf et al. suggest that increased coherence in the gamma range (40-70 Hz) preceding a stimulus may be involved in attending to relevant stimuli (1). Our study sought to determine if increased gamma coherence between the frontal and parietal cortex, two areas that have been implicated in attention and perceptual processes (2), correlates with rats' performance in an attentional task. In this study, auditory stimuli were presented to rats through a speaker in a standard operant chamber while local field potentials were recorded in frontal and parietal cortex for 30-45 minutes using pairs of 32-channel microelectrode arrays. Rats were trained to perform a lick-on-beep task for which licks that occurred within a brief (2-3 s) window after auditory stimuli were presented were categorized as hit trials and received a water reward, and all other trials were categorized as miss trials that did not receive a water reward. Matlab was used to calculate frontal-parietal coherence at 0-100 Hz for hit or miss trials 500 ms before auditory stimuli were presented. More coherence in the gamma range was observed before hit trials than before miss trials. These preliminary results indicate that the neural signals that initiate attention to relevant stimuli may involve increased gamma coherence between neurons in frontal and parietal cortex.

25. Frontal-parietal gamma coherence as a possible correlate of attention in rats

Linnea Herzog, Kia Salehi, Mike Wiest, Ph.D

What types of electrical events in the brain underlie the process of attention to relevant stimuli in our outside environment? One phenomenon that has been singled out as a possible neural correlate of attention is coherence, or a constant phase relationship between two neural signals that originate from different areas of the brain. In electrophysiological experiments that involve coherence analysis, the raw signals (often local field potentials, which represent the postsynaptic activity of groups of neurons from a particular region of the brain) are split up into their different frequency components so that coherence is always specified at a particular frequency range. Previous findings by Womelsdorf et al. suggest that increased coherence in the gamma range (40-70 Hz) preceding a stimulus may be involved in attending to relevant stimuli (1). Our study sought to determine if increased gamma coherence between the frontal and parietal cortex, two areas that have been implicated in attention and perceptual processes (2), correlates with rats' performance in an attentional task. In this study, auditory stimuli were presented to rats through a speaker in a standard operant chamber while local field potentials were recorded in frontal and parietal cortex for 30-45 minutes using pairs of 32-channel microelectrode arrays. Rats were trained to perform a lick-on-beep task for which licks that occurred within a brief (2-3 s) window after auditory stimuli were presented were categorized as hit trials and received a water reward, and all other trials were categorized as miss trials that did not receive a water reward. Matlab was used to calculate frontal-parietal coherence at 0-100 Hz for hit or miss trials 500 ms before auditory stimuli were presented. More coherence in the gamma range was observed before hit trials than before miss trials. These preliminary results indicate that the neural signals that initiate attention to relevant stimuli may involve increased gamma coherence between neurons in frontal and parietal cortex.

26. MicroRNA-Mediated Control of Oligodendrocyte Differentiation in *Danio rerio*

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MicroRNAs (miRNAs) are short ribonucleic molecules (approximately 22 nucleotides) that act as posttranscriptional regulators of target messenger RNA (mRNA) transcripts. miRNAs, bind to target mRNAs, acting as negative regulators of gene expression by targeting specific transcripts for degradation. miRNAs are processed by a RNase-type enzyme called Dicer to form mature miRNAs.

Once mature, they are incorporated into the RNA-induced silencing complex (RISC) that ultimately causes posttranslational repression. miRNAs regulate various biological processes, however little is known about their role in the disease multiple sclerosis. A common neural cell type that has been observed to be affected by miRNA is oligodendrocytes. Oligodendrocytes are among a well-dispersed neuronal cell type called neuroglia that function to produce multilamellar myelin membranes which surround the neuronal axons of the CNS. Like most glial cells, the purpose of oligodendrocytes is the generation of a myelin layer to insulate and protect the axons, while increasing the speed at which nerve impulses propagate and flow along the cell myelinated fibers. The myelin is targeted for degradation by immune cells within the brain during an episode of MS. Since the etiology of the MS is not fully understood, investigating the differential expression of microRNAs in MS brains might provide the elusive clues to understand how this disease progresses. miRNAs present in higher levels in the brains of MS patients were identified through microarray analysis. miRNAs play a vital role in oligodendrocyte differentiation and overall CNS development. In order to determine the role of the miRNAs associated with the MS brain, we microinjected morpholinos generated against miRNAs of interest in *Danio rerio* embryos at the one cell stage. The findings in this study illustrate the fundamental role of miRNAs in oligodendrocyte differentiation, providing insight into early CNS development, differentiation, and repair. As a result of 2 of the 3 morpholinos microinjected, each showed apparent influences in overall CNS development. Specifically, morpholino 27a injections resulted in a decrease of oligodendrocytes. While injection of morpholino 150, resulted in a large brain phenotype with a curved tail and myotome disorganization. Additionally, around 50% of the surviving injected fish displayed the morphant phenotype. The findings in this study illustrate the fundamental role of miRNAs in oligodendrocyte differentiation, providing insight into early CNS development, differentiation, and repair.

27. The comparison of BTBR and B6 mouse strains on a quantitative measure of social motivation: relevance for mouse models of autism

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Much advancement has been made in the understanding and treatment of human disease through studies on animal models. For human disorders involving abnormal social behavior such as autism, research on mouse models will benefit from the development of novel assays of complex social behavior including social motivation. The goal of this research is to develop and validate new tasks of social motivation and social avoidance for mouse models of autism and other disorders involving social deficits. The proposed tasks involve the use of original operant conditioning paradigms programmed through a computer system that will allow a test mouse to control access to another mouse within an operant box. The access to the stimulus mouse will serve as a social reward for mice with prosocial tendencies but may serve as an aversive stimulus for mice with nonsocial tendencies. Research has been carried out with the C57BL/6J (B6) mouse, a prosocial inbred mouse strain, and on the BTBR T + tf/J (BTBR) mouse, an inbred mouse strain with well-documented social deficits. Comparisons were made between mouse strains and between individually- and group-housed B6 mice. In the first paradigm, the test mice were trained to press a lever for a social reward in the form of access to an unfamiliar stimulus mouse for 15 sec. The social reward was set on a progressive ratio schedule with a step size of three. The number of lever presses achieved in the final trial of a testing session (breakpoint) was used as an index of social motivation. In the second paradigm, motivation for a food reward was compared to a social reward. The mice were conditioned to associate one lever consistently with a food reward and another consistently with the same social reward described in the previous paradigm. All 12 B6 mice tested thus far (6 group-housed and 6 individually-housed) acquired the learned association with most of them reaching the

criterion (10 rewarded lever presses per session for 3 consecutive sessions) by the 9th shaping session. On the other hand, the BTBR mice took longer to initially learn the task. Only 5 of 7 BTBR mice tested thus far acquired the task, each reaching criterion on average by the 16th shaping session. Results indicated that there was no difference in social motivation between group-housed and individually-housed B6 mice for both paradigms. However, early results indicate that the BTBR mice may display reduced social motivation compared to the B6 mice in this task. In the second paradigm, all B6 mice showed a preference for the food reward versus the social reward. Results are currently being obtained from the BTBR mice on this same paradigm, but are hypothesized to have a higher ratio of food versus social rewards than observed in the B6 mice. Overall, our preliminary results suggest that these operant conditioning paradigms may be valuable tools to assess social motivation and will be expanded to include other mouse strains with nonsocial tendencies including purported models of autism.

28. Effects of acute prenatal ethanol exposure on axon tract development

Jennilyn Weber, Kacie Dougherty, and Carlita Favero
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Fetal Alcohol Spectrum Disorder (FASD) is the umbrella term used to describe the broad range of cognitive and physical defects resulting from prenatal exposure to alcohol. The cognitive deficits observed in children affected by FASDs likely result from malformations during axon tract development. Studies of chronic (i.e. multiple days during gestation) prenatal ethanol exposure in animal models recapitulate the defects seen in humans and show disrupted axon tract development, but less is known about acute (i.e. single day during gestation) effects or underlying mechanisms. We are particularly interested in the effects of acute prenatal ethanol exposure on development of the axon tracts connecting the thalamus and cortex because they are essential for normal sensation and perception. In this study, we will administer ethanol via injection to pregnant Swiss Webster mice between embryonic days (E) 10.5 and E14.5, when the axons connecting the thalamus and cortex are forming. Age-matched controls will be injected with phosphate-buffered saline. We will analyze axon tract development at E18.5 or postnatal (P) day 0 using immunostaining and dye tracing. We will also use immunostaining to investigate brain cytoarchitecture for abnormalities due to acute prenatal ethanol exposure.

29. Light effects on VIP and VPAC2R levels in the mammalian SCN

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The suprachiasmatic nucleus (SCN) coordinates daily circadian rhythms, states of vigilance, locomotor activity, and hormone release and functions as a mammal's master pacemaker. Vasoactive intestinal polypeptide (VIP), a candidate synchronizing neuropeptide in the SCN, signals through a G-coupled protein receptor, VPAC2R, to synchronize behavioral rhythms in wild type mice. Studies have shown that a population of SCN neurons is responsive to retinal illumination, and constant light serves to produce a phenotype similar to mice lacking VIP signaling: arrhythmic locomotor activity and desynchrony among SCN neurons. This study investigates light's effect on VIP and VPAC2R levels in the SCN. To address this question, we used ABC immunohistochemistry to measure staining intensity of VIP and VPAC2R in SCN brain sections of C57 wild type mice. Brains from mice maintained in constant light for one month were collected 5 hours after subjective dawn and brains from mice maintained in a light-dark cycle were collected 5h after dawn. *Vip*^{-/-} and *Vipr2*^{-/-} knockouts were used as negative controls. We found that constant-light treated mice showed increased levels of VIP in the SCN and unchanged levels of VPAC2R compared to mice from

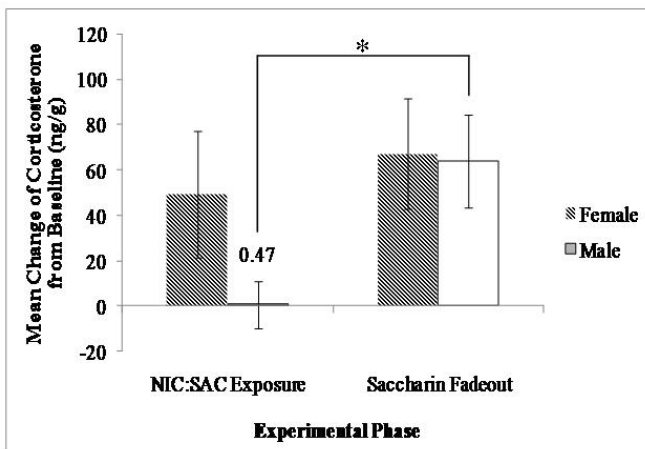
a light-dark cycle. We conclude that levels of VIP depend on luminance, and that the loss of circadian rhythms in constant light may result from increased changes in VIP and changes in VPAC2R above a certain threshold. This data suggests a relationship between light and the VIP/VPAC2R mechanism, an association that elucidates the dysfunction of circadian rhythm, hindered neural development, and the mental illness, Schizophrenia.

30. Sex differences in response to inherent stressors in a rodent model of nicotine oral self-administration.

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The relationship between sex, stress, and nicotine is intricate, cyclic, and paramount to developing improved treatment strategies for addiction. This study employed a rodent model to explore sex differences in stress response to nicotine oral self-administration. Adolescent male and female Sprague-Dawley rats had 24hr access to a nicotine:saccharin (NIC:SAC) solution (40µg/ml:0.01% w/v) as their sole source of water for 7 days. Initial NIC:SAC exposure was followed two weeks later by an 8 day saccharin fadeout phase during which the consumption of either a saccharin-only (SAC) or NIC:SAC solution was measured via a lickometer in daily 20 minute sessions. Across the saccharin fadeout, the amount of saccharin in both solutions decreased by half every other day. Fifteen hours of water restriction preceded each session. Stress was monitored via assessment of corticosterone (CORT) levels using enzyme linked immunosorbent assay of ethanol-extracted fecal samples taken at baseline, after NIC:SAC exposure, and after saccharin fadeout. Compared to males, females showed significantly greater consumption of NIC:SAC during the phase of initial 24hr exposure. Females also had elevated levels of CORT compared to baseline during this phase. Whereas CORT levels among males had not changed from baseline during initial NIC:SAC exposure, CORT levels rose above baseline in response to the saccharin fadeout ($p < .01$; Fig. 1). CORT levels among females during this phase were no different than they had been during initial NIC:SAC exposure. During saccharin fadeout, females consumed more than males, whether they were



consuming NIC:SAC or SAC. These results indicate that sex differences exist in the nature of inherent stressors within the nicotine oral self-administration paradigm. This has implications for animal studies employing self-administration models in general and development of different intervention strategies for treatment of nicotine addiction in men and women.

31. The Effects of CMS on Hippocampally-Dependent Spatial Memory in Adolescent Female Rats: A Behavioral Study

Samantha Shapiro and Eric Wiertelak

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The chronic mild stress (CMS) paradigm has been used for the past two decades as a way of

modeling anhedonia and depression in the rodent model. Although CMS studies have generally involved male rats, there is a small amount of research that has looked at the effects of CMS on female rats. Research conducted on adult female rats has found that – unlike male rats of all ages – when adult female rats are exposed to CMS, their performance on spatial memory tests improves. This improvement in spatial memory can possibly be explained by the presence of the hormone estradiol, which is known to inhibit glucocorticoid receptor expression and reduce CMS-induced atrophy in the hippocampus. While adult female rats generally produce large quantities of estradiol, estradiol is present in relatively low concentrations in juvenile and adolescent rats. Thus, it is possible that non-adult female rats will not show improved spatial memory after CMS. The present study was designed to address this issue, and to examine how CMS affects spatial memory in adolescent female rats. In order to analyze spatial memory, this study used a Morris water maze as a behavioral measure of how mild stress affects hippocampally-dependent spatial memory in adolescent female Sprague-Dawley (SD) rats. Rats underwent a 30-day CMS paradigm in which various mild stressors were applied on a randomized basis; Morris water maze trials were conducted both before and after the CMS paradigm. In order to ensure that the CMS was inducing anhedonia, saccharine consumption was measured and compared across groups every 15 days. Results of the study revealed that the CMS caused anhedonia and effectively stressed the rats, and that the rats' Morris water maze performance (i.e., spatial memory) improved after exposure to the CMS. This finding indicates that adolescent female rats are able to resist the hippocampal atrophy that CMS has been found to cause in male rats. Future research should investigate the neural mechanisms behind this sex difference and further analyze the extent to which hippocampal estradiol functions during chronic stress.

Keywords: CMS, spatial memory, adolescent females, Morris water maze, anhedonia, estradiol

32. Characterization of Alcohol Modulation of Vanilloid Receptor 1 (TRPV1)

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Alcohol abuse has long been a source of economic, social and health-related problems in our society. National trauma centers are overwhelmed by the numbers of drunk-driving accident victims and drivers that enter their hospital rooms each week; substantial government dollars are allocated towards welfare programs that provide support and foster care for children and victims of alcohol abusive parents or relatives; direct costs of loss of productivity by alcoholic citizens affect our economy as less money is put into circulation. However, alcohols' simplicity in structure and transient low-affinity effects make them difficult to characterize by classic techniques such as radiolabeled ligand-binding assays or spectroscopy. Recent evidence suggests a connection between alcohol and vanilloid receptor 1 (TRPV1), an ion channel responsible for transducing chemical and thermal stimuli into neurological responses such as pain. To test the hypothesis that TRPV1 is a direct pharmacologically relevant target for alcohol in the nervous system, I have measured TRPV1 function using two-electrode voltage clamp of *X. laevis* oocytes. I first characterized a simple TRPV1 agonist (protons), whose chemical properties are unlikely to be influenced by alcohol, and selected an intermediate point in the proton activation curve at which the effects of modulators such as alcohol should be straightforward to detect. Under these conditions, proton-activated TRPV1 currents were enhanced by concentrations of ethanol as low as 50 mM—slightly above the legal limit of intoxication for driving a car in Texas. Other ion channels implicated in direct alcohol interactions exhibit increasingly potent modulation by primary alcohols as their chain lengths increase, up to a “cutoff”—a property also observed for immobilization of organisms. Therefore, I have begun to characterize the modulation of proton-activated TRPV1 channels by primary alcohols, whose potency indeed increases with chain length. In the long term, characterization of TRPV1 as a pharmacologically relevant alcohol target should place an important

new piece in the puzzle of alcohol effects in the nervous system. Moreover, a more complete understanding of alcohol's molecular targets will eventually aid clinicians in identifying individuals with genetic pre-dispositions to alcohol-use disorders, and fuel the development of pharmaceutical tools for the study and treatment of alcohol use and abuse.

33. Netrin-1 activates integrins on neural growth cones: evidence for a direct ligand-receptor mechanism of activation

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During development, growth cones integrate numerous environmental cues, including netrin-1, to navigate to their precise targets. Recent evidence suggests that netrin-1 interacts with integrins. Integrin receptors are traditionally known to bind to extracellular matrix molecules, such as laminin. However, our results show that netrin-1 also interacts with integrins on growth cones of cultured chick DRG neurons. Immunocytochemical data show that netrin-1 induces integrin activation (e.g. induces a shift to a high ligand-affinity state) on growth cones. Netrin-induced integrin activation can be blocked by treating neurons with specific function-blocking integrin antibodies and competitive integrin peptides prior to netrin-1 application. To test if this netrin-integrin interaction is a direct one, we examined the ability of netrin-1 to bind to specific integrin peptides. Recombinant chick netrin-1 was incubated with select integrin peptides and subjected to a 30kD size exclusion column. The column collected molecules larger than 30kD. These >30kD samples were run on a 4-12% gradient Bis-Tris gel and stained with Simply Blue. Results show that the 65kD recombinant netrin-1 was collected by the column as well as a 2kD integrin peptide. However, scrambled integrin 2kD peptides were not seen. These results suggest that netrin-1 can bind directly to a specific region of integrins that is unique from the known laminin-binding region. Together these studies imply that integrins can serve as a netrin-1 receptor. Future studies will continue using RNAi to decrease integrin receptor and netrin receptor expression in Neuro2A cells and to observe their resultant netrin-induced growth cone behavior.

34. The Role of Nitric Oxide and Microglia in Anesthetic Preconditioning in vitro.

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Background: Anesthetic preconditioning (AP) is a budding preventative treatment for patients undergoing neurosurgical and cardiovascular procedures that are at risk for post-operative ischemic stroke damage. AP is a phenomenon by which tissues are pre-treated with clinical concentrations of a general anesthetic (a minor insult), resulting in the upregulation of endogenous protective measures that can protect against subsequent more extreme insults (e.g. ischemic damage). Our lab has hypothesized a mechanism for this phenomenon in brain whereby exposure to a volatile anesthetic (e.g. isoflurane) activates nitric oxide synthase, resulting in the production of the signaling molecule nitric oxide (NO). In particular, high concentrations of NO are released from microglia as part of their role in inflammatory responses. In the current study, we investigated whether the general anesthetic isoflurane caused an increase in NO release from microglia. In the future, we plan to determine whether an increase in this microglial NO release is essential for anesthetic preconditioning.

Methods: A microglial cell line (EOC-20), 129 murine primary neuronal cultures, and 129 murine organotypic slices were exposed to 1.5% isoflurane for 2 hrs in a dedicated anesthetic chamber at 37 C (95% air: 5% CO₂). Six hours post-exposure, a Griess Reaction was used to assess the level of

nitrites (conversion products of NO) in control and isoflurane-exposed samples. Using a Spectramax M5/M53 microplate reader, the absorbance (550 nm) was measured after a diazotization reaction.

Results: Preliminary results demonstrated that microglia exposed to isoflurane produced significantly elevated levels of nitrite by $15.7 \pm 1.7 \%$ ($p < 0.05$) in comparison to control cells suggesting increased NO release as result of the anesthetic exposure. Based on these results, future experiments will involve the deactivation of microglia in primary cultures and organotypic slices to see whether or not anesthetic preconditioning effects can be attenuated. Subsequently, we plan to co-culture the microglia with other cell lines to determine whether AP can result through activation of microglial protection mechanisms.

Conclusion: We conclude that NO production increases during anesthetic preconditioning in microglia and that this effect may contribute to anesthetic preconditioning in brain.

35. “Where’s the mind control switch?” Specificity of parasitic infection of nervous systems

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Parasites often manipulate the behavior of their hosts, but how they do so is often unclear. Larval tapeworms (*Polypocephalus* sp.) embed themselves within the nervous systems of decapod crustaceans, including white shrimp (*Litopenaeus setiferus*). We hypothesized that living in the neural tissue allows the tapeworms to manipulate their host’s behaviour. Shrimp behavior is correlated with the degree of infection: heavily infected shrimp are more likely to be actively walking. If this behavioral difference results from parasitic manipulation rather than pathology, the tapeworms should preferentially infect specific regions of the nervous system, rather than being distributed randomly throughout all tissue, or randomly throughout neural tissue. Tapeworm larvae are routinely found in nervous tissue, but not in the digestive gland. Tapeworm larvae are found significantly more often in the abdominal ganglia and thoracic ganglia than the brain or subesophageal ganglia after controlling for the different sizes of these regions. We are currently examining the position of larvae within the three dimensional structure of single abdominal ganglia.

36. Dendritic Spines Over Lifespan Development in Layer VI Barrel Cortex Neurons

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Dendritic spines are small protrusions that serve as the principal source of excitatory inputs onto cortical pyramidal cells. Alterations in spine density and morphology have been correlated with both developmental maturity and changes in synaptic strength. It is well known that environmental conditions can influence the developmental trajectories of dendritic spines, specifically in the sensory cortices. In order to better understand the developmental profile of dendritic spine morphology and density over the first post-natal year in CD-1 mice, we utilized the Golgi staining technique to label neurons and their associated dendritic spines in a relatively unbiased fashion. We focused on quantifying the density and morphology of the spines of layer VI pyramidal neurons residing in barrel cortex using the computer assisted reconstruction program Neurolucida. We classified spines into five morphological classes (thick-neck mushroom, thin-neck mushroom, stubby, branched, and filopodia) at six developmental time points P(postnatal day) 15, P30, P60, P90, P180, and P360. Our findings suggest that the dendritic spines in layer VI barrel cortex pyramidal neurons are not static and their density and relative morphological distribution change over time. We observed a significant increase in mushroom spines and a decrease in filopodia as the animals matured. Further analysis show that as the animal aged there was a reduction in the

branching pattern of dendrites, as well as a decrease in overall spine densities. The ratio of apical spine density to basilar spine density decreased as well. Characterizing the profile of dendritic spines within layer VI over the first post-natal year will provide better understandings of the impacts of the environmental influences and developmental maturation on spine dynamics.

37. Differential Modulation of Nociceptive versus Non-Nociceptive Synapses by Endocannabinoids

Alexandra Higgins and Brian Burrell, PhD

Chronic pain is a major health concern that affects approximately thirty-percent of the population in the United States (Johannes et al. 2010). Endocannabinoids, which are modulatory lipid neurotransmitters, have been proposed as a potential therapy for chronic pain, but recent evidence has suggested that endocannabinoids may have pro-nociceptive effects and actually enhance the perception of pain (Pernia-Andrade et al. 2009). Because sensitization processes that contribute to chronic pain can involve changes in both nociceptive and non-nociceptive afferents, it is possible that endocannabinoids have different effects on these pain versus non-pain pathways. To test this hypothesis, experiments using the central nervous system of the medicinal leech were carried out in which it is possible to perform intracellular recordings from identifiable nociceptive (N cell) and non-nociceptive (pressure or P-cell) sensory neurons and their postsynaptic targets. Specifically, the effects of the endocannabinoid transmitter 2-arachidonoyl glycerol (2AG) were tested on both nociceptive synapses (N-to-AP and N-to-L) and non-nociceptive synapses (P-to-AP and P-to-L). Consistent with previous experiments from our laboratory (Yuan & Burrell 2010), 2AG treatment elicited long-term depression of the nociceptive synapses. Non-nociceptive synapses, however, were potentiated by 2AG treatment, demonstrating that this endocannabinoid transmitter did in fact have opposing effects on nociceptive versus non-nociceptive synapse. One possible mechanism for 2AG-induced potentiation of non-nociceptive synapses is disinhibition; that is, 2AG depresses inhibitory input regulating P-cell synaptic transmission. Consistent with this hypothesis the non-nociceptive P-to-L synapse was found to be enhanced when the GABA receptor antagonist bicuculline was applied. Furthermore, potentiation of the P-to-L synapse by 2AG occludes subsequent enhancement that would normally occur following bicuculline treatment. Interestingly, bicuculline treatment depressed the N-to-L synapse, suggesting that GABAergic modulation had an excitatory effect on this nociceptive synapse. These results demonstrate that endocannabinoids can differentially modulate nociceptive vs. non-nociceptive synapses and these opposing effects are likely to be important when considering how drugs that act on the endocannabinoid system should be applied to treat various forms of chronic pain.

38. Isolation and expression of *rem2* isoforms and *arpc1b* in the adult teleost fish brain in response to injury

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Unlike adult mammals, adult teleost fish have a tremendous capacity to repair and regenerate neural tissue. However, the underlying molecular mechanisms of this ability are not fully understood. We began examining the temporal expression patterns of two genes, *rem2* and *actin-related protein 2/3 (Arp2/3) complex 1b (arpc1b)* in the brain of the adult rainbow trout, (*Oncorhynchus mykiss*) during its response to injury. Rem2 is a member of the RGK (Rem, Rad, and Gem/Kir) subfamily of the Ras superfamily of GTP-binding proteins. Among RGK members, Rem2 is unique in structure and is also found at high levels in neuronal tissue. Vertebrate Arpc1b is a subunit of the Arp2/3 complex and mediates interaction between the Arp2/3 complex and protein activators leading to actin nucleation. It is also a regulator of centrosome integrity during mitosis. Preliminary differential display results in our lab indicated these genes as putatively regulated in

the rainbow trout brain response to injury. We used real-time polymerase chain reaction (real-time PCR) to examine the expression of *rem2* (isoforms *rem2a* and *rem2b*) and *arpc1b* in the brain of adult rainbow trout (n = 5). A mechanical lesion was focused on one side of the midbrain and the fish were allowed to recover. At 24 hr post-lesion, both the lesioned side of the midbrain and the intact, contra-lateral side were separated and the total RNA of each was isolated and assayed in One-Step real-time PCR (*eef1a1* was used as a normalizing gene). Non-operated and sham-operated (trepanation only) animals were assayed as well (n = 5 for each group). Of the *rem2* isoforms, *rem2a* indicated a slight increase in expression in both the injured and intact sides of the midbrain. Unlike *rem2a*, the *rem2b* isoform showed no change in expression pattern. In contrast, a marked decrease in *arpc1b* expression was seen in both injured and intact sides of the midbrain. The observed changes in expression indicate that differential regulation is likely occurring despite the lack of significant change. Additional time point assays (currently underway) will allow complete characterization of *rem2* and *arpc1b* temporal expression patterns during the teleost brain response to injury. These and future studies intend to better understand the role of Rem2 and Arpc1b in adult vertebrate brain repair. Supported by NIH Grant Number P20 RR-016461.

39. Oxytocin Mediates Ghrelin-Induced Eating in the Ventromedial Nucleus of the Hypothalamus

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The orexigenic peptide ghrelin is known to stimulate food intake following microinjection into various hypothalamic nuclei. In contrast, oxytocin is an anorectic nonapeptide and recent work suggests that it may mediate ghrelin's effects on food intake. The present study investigated the effects of oxytocin pretreatment on ghrelin-stimulated eating. Adult male Sprague Dawley rats were injected with oxytocin (0.4 nmol and 4.0 nmol) and ghrelin (300 pmol) directly into the ventromedial nucleus (VMN) and food intakes were measured at 2 and 4 h postinjection.

Testing was conducted during the initial 4 h of the nocturnal cycle. VMN injections of oxytocin potently increased ghrelin-induced eating at 2 h postinjection. However, at 4 h postinjection, oxytocin suppressed the orexigenic effect of ghrelin. Our findings indicate that oxytocin and ghrelin signaling interact within the VMN to alter food intake and that the effect of oxytocin on ghrelin-induced eating is bidirectional.

The CB1 Inverse Agonist AM251 Attenuates the Orexigenic and Metabolic Effects of Paraventricular Nucleus Anandamide

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Endocannabinoids are proposed to control food intake via both central and peripheral mechanisms. Within the brain, the endocannabinoid anandamide (N-arachidonoyl ethanolamine; AEA) is believed to increase food intake through on-demand activation of hypothalamic circuits. In the present study we examined the effects of hypothalamic paraventricular nucleus (PVN) injections of AEA (25-400 pmol) administered at the onset of the nocturnal cycle on food intake and energy substrate oxidation (respiratory quotient; RQ). PVN administration of AEA increased eating behavior and elevated RQ. The latter finding is consistent with enhanced carbohydrate oxidation and the preservation of fat stores. The orexigenic and metabolic effects of AEA also paralleled the effects of PVN injections of ghrelin and NPY. Further, the inverse CB1 receptor agonist, AM251 (5-10 mg), administered directly into the PVN 10 min prior to AEA (100 pmol), attenuated both eating and RQ responses. AM251 administered alone did not alter food intake or RQ. Overall, these findings

demonstrate that CB1 receptors localized to the hypothalamic PVN play a role in eating and energy homeostasis.

40. Mild Traumatic Brain Injury and Its Effect on Contextual Fear Conditioning and Anxiety States Similar to Post-Traumatic Stress Disorder

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Mild traumatic brain injury (mTBI) is the most common type of brain injury, which may cause emotional and cognitive effects including difficulty in concentration, amnesia and anxiety (Henninger, 2005; *Experimental Neurology*, 195, 447). Over 40% of individuals that suffer an mTBI meet the diagnosis criteria for post-traumatic stress disorder PTSD; Hoge, C.W., et al. (2008). *The New England Journal of Medicine*, 453-463.). Neurologically, PTSD can be associated with the hyperfunction of the amygdala paired with the hypofunction of the prefrontal cortex and hippocampus (Rauch, S.L., et al. (2006). *Biol Psychiatry*, 372-382.). The goal of this study was to determine whether mTBI in an animal model resulted in neurological and associated behavioral changes similar to PTSD. No large-scale structural brain damage was visible 4 or 9 days after inducing closed head mTBI in male Sprague-Dawley rats, and there was no difference in motor function or pain response compared to controls. However, rats undergoing mTBI showed significant cell loss in the CA1 region of the dorsal hippocampus as well as an increase of neurons in the amygdala at 9 days post-mTBI. The dorsal CA1 hippocampus and the amygdala are linked to retrieval of contextual fear conditioning (Hunsaker, M.R. & Kesner, R.P. (2008). *Neurobiol Learn Mem.*, 61-69.). During contextual footshock, mTBI rats showed increased freezing behavior on conditioning test day, but similar extinction on the two test days following. Hyperactivity of the amygdala is also related to high anxiety (Goosens, K.A. & Maren, S. (2001). *Learn. Mem.*, 148-155.). Consistent with this, mTBI rats showed increased latency to enter open arms as well as decreased time spent in open arms of the elevated plus maze, indicative of increased general anxiety. Overall, results of cell counting as well as fear conditioning and anxiety testing show a neurobiological link between mTBI and anxiety states similar to PTSD. Supported by: South Dakota Board of Regents Competitive Research Grant, Department of Defense Grant # W81XWH-10-1-0578

41. Impact of perineuronal nets on barrel cortex neurons

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Perineuronal nets (PNN) are a phenotype of extracellular matrix that encapsulates cell bodies and proximal neurites in a lattice-like structure. The PNN has numerous roles in the central nervous system including neuroprotection, water homeostasis, modulation of neuronal excitability, and modifying memory consolidation. Its development coincides with the closing of the critical period of development, but sensory deprivation from birth can reduce PNN density. Furthermore in the mouse visual system, enzymatic digestion of PNN components can reactivate the period of developmental plasticity. In the current study we sought to mimic the effect of reactivation plasticity with an in vitro enzymatic digestion model. Our results demonstrate that a 65% decrease of Wisteria Floribunda Agglutinin detected PNN occurs at 1 hour incubation and complete elimination occurs at 2 hours (0.02 units/ ml, Chondroitinase ABC). Consistent with other studies, hemisphere controls showed the highest density of PNN in layer 4. Whole cell patch clamp recordings were conducted in acute slices after digestion to determine the intrinsic properties of neurons in the barrel field region. Our preliminary results show alterations in firing thresholds and

after-hyperpolarization amplitude at 65% digestion. Consistent with previous research done in culture, our results might be explained by the removal of a highly electronegative Chondroitin Sulfate proteoglycans cation buffering system. Because previous studies have demonstrated similar levels of reduction after sensory deprivation whisker trimming, our results provide introductory evidence for the effects of controlled PNN digestion on single cell physiology in the mouse barrel cortex. These results demonstrate that single cell recordings can be conducted from cortical slices after perineuronal net digestion and supports the potential utility of a graded digestion in vitro model.

42. Dopamine injections to the midbrain periaqueductal gray rapidly and reversibly inhibit vocal production in a teleost fish.

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Dopamine circuits are well known for their roles in modulating motor control and reward. Related to these functions, dopamine also modulates certain social behaviors, including courtship, aggression, and social bonding. Dysregulation of dopamine (DA) circuits has been implicated in several neuropsychological disorders characterized by social dysfunction. We are interested in understanding how DA shapes social behavior, the specific circuits involved, and the evolution of those circuits. To this end, we are exploring the role of DA in modulating vocal circuit function in a teleost fish, the plainfin midshipman (*Porichthys notatus*). Midshipman fish employ sexually dimorphic vocal calls in different social contexts, including courtship and territorial defense. Previous data from our lab have demonstrated the presence of tyrosine hydroxylase (TH) at various levels in the midshipman vocal circuit, including the midbrain periaqueductal gray (PAG), and differences in TH distribution between males and females. Here, we used a fictive vocal preparation, stimulating the ventral tuberal hypothalamus to elicit naturalistic vocal-motor output from the hindbrain vocal pattern generator of territorial male midshipman. Dopamine (5 mg in a total volume of 0.25-1 ml of saline, with 4% tetramethylrhodamine to mark injection sites) was focally injected into the PAG, and effects on ongoing fictive vocal production were monitored. DA injections to the PAG rapidly and reversibly inhibited vocal production, relative to size-matched control injections in the same locations (2-Way ANOVA, treatment and treatment x time interaction both significant, $p < .01$). Effects appeared within 1 minute of injection, and lasted up to 30 minutes ($p < .05$, post hoc t-tests). Duration of vocal output, the main parameter distinguishing courtship “hums” from agonistic “grunts”, was unaffected by DA injection. These data suggest that DA in the PAG does not modulate shifts in vocal output from humming to grunting, or vice versa, in different social contexts, but do imply that DA generally inhibits vocalization. DA could thus play a role, for example, in the cessation of humming that occurs when a female enters the nest of a courting male. Such a function would be consistent with DA release triggered by appetitive reward, and with the PAG playing a role in switching between behavioral output modes (i.e., from courting to mating), both of which are hypotheses supported by experimental evidence in other systems. Ongoing and future experiments will address the role of DA antagonists, including receptor-type specific antagonists, and sexual dimorphisms, in the effects of DA on vocalization.

43. The Use of Melatonin to Prevent the Structural Misfolding of the Alzheimer's Disease Wild Type Peptide (A β 22-35)

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Neurodegenerative disorders such as Alzheimer's disease (AD) are perpetuated by the neurotoxicity created by the misfolding of proteins, leading to amyloid formation. Plaques accumulate in AD-afflicted brains as a result of beta-amyloid (A β) fibril aggregation. The

intermediates that have formed during these aggregations have led to neural synaptic impairment, particularly in the hippocampus region, and an increased loss of neurons due to oxidative stress, resulting in cognitive dysfunction. Past studies on the A β (1-40) strand have shown that melatonin may have an inhibitory effect on the aggregation of A β peptides in addition to its established neuroprotective potential. Our previous research has focused on the accumulation of beta-sheets associated with the beta amyloid peptide A β (1-40) and A β (1-42), specifically the Wild Type (WT) fragment A β (22-35) that contains the ionic salt bridge. Point mutations in this “hair-pin” turn significantly affect the rate of fibril aggregation as well as the solubility of the toxic intermediates. By incubating the WT A β (22-35) with various concentrations of melatonin, it is hypothesized that fibril accumulation will be hindered. Using Attenuated Total Reflectance Infrared Spectroscopy (ATR-IR) and Ultraviolet Visible Spectroscopy (UV-Vis), we will be able to monitor the structural changes of the peptide within the mixture from monomer to beta-sheet. The Congo Red dye used in the UV-Vis trials relies on pentameric binding to visualize aggregated fibrils to serve as a quantitative measurement. Conclusions may then be made after comparisons to unaltered WT A β (22-35) beta-sheet formation. Results from this study may pave the way for future preventative treatments of AD and other neurodegenerative disorders.

44. Optimizing the Experience-Dependent Modification of Head Direction Cell Activity.

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Head direction (HD) cells are thought to represent the animal’s sense of spatial orientation. In a given environment, a HD cell will fire maximally at a particular “preferred direction” specific to that environment, and there is evidence that this environmental specific directional preference is developed during the first exposure to that environment. While there are many reports of this experience dependent modification of HD cells, little has been done to elucidate the experimental parameters that affect this type of learning. Anterior thalamic HD cells were isolated in female Long-Evans rats. On Day 1, animals were given a training exposure to a novel recording enclosure to determine the preferred direction of the recorded cell in this enclosure. On Day 2 the animals were returned to the enclosure to determine if the preferred direction established on Day 1 was maintained (i.e. learned about on the initial exposure). Some of the animals were given disorientation treatment prior to exposure to the novel enclosure on Day 1 in order to disrupt their preexisting spatial reference. In addition, for some animals the exposure to the novel enclosure on Day 1 was limited to a single 12-minute training session, while others received two 12-minute sessions with the landmark rotated between sessions. We found that the largest influence on the development of a stable directional reference in the HD system was the number of training sessions on Day 1. Cells from animals that received only one training session showed poor development of landmark control regardless of the disorientation variable, often showing changes in preferred direction relative to landmarks between Days 1 and 2. In contrast, cells from animals receiving two training sessions showed strong development of landmark control, as indicated by preferred directions that were stable between training and test. In conclusion, while HD cells are commonly described as showing experience-dependent modification of directional preference, we have found that this form of learning can be affected by the procedure utilized.

Dose-Dependent Effect of MK801 on the Head Direction Cell Network

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Head direction (HD) cells carry information regarding the head direction of the animal in space. Each HD cell possesses a specific preferred firing direction relative to spatial landmarks in the recording enclosure and this network has been proposed to form the basis of navigational behavior. Dizocilpine (MK801), a noncompetitive NMDA receptor antagonist, has been shown to disrupt

navigational behavior and spatial learning. Given the view that HD cells are important for navigational behavior, we sought to determine if MK801 would disrupt the directional sensitivity of the HD network. Anterior thalamic HD cells were isolated in female Long-Evans rats. Initially, HD cells were monitored for baseline preferred direction and landmark control. The animals were then administered i.p. injections of isotonic saline, a low dose of MK801 (.05 mg/kg), or a high dose of MK801 (0.1 mg/kg) and cells were re-examined for changes in directional specificity and landmark control. As expected, HD cells showed no changes in preferred direction and landmark control following saline injection. In contrast, after administration of the high dose of MK801, the activity of HD cells changed dramatically relative to baseline, becoming largely insensitive to the head direction of the animal and position of the visual landmarks. In addition, these animals showed marked behavioral alteration from drug administration, including hyperactivity and aimless locomotor behavior. Finally, administration of the low dose of MK801 resulted in no significant changes in directional specificity or landmark control of recorded cells, and no obvious changes in the behavior of the animals. These findings provide evidence for a dose-dependent effect of MK801 on the HD network and behavior. It is notable that the effect on the HD network appeared to correspond with the behavioral disruption observed in the animals. In addition, our lack of effect of the low dose of

MK801 on the HD network departs from previous behavioral studies that have found impaired navigation at this dose.

45. Adolescent risk taking and cocaine self-administration: A vicious circle

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Chronic cocaine use is associated with deficits in cognitive function, including maladaptive decision making and elevated risk taking. Adolescents also tend to show poor decision making skills, including elevated risk taking, which may contribute to and/or result from drug use. The causal relationships among adolescent development, risk taking, and drug use are difficult to disentangle in humans; however, these relationships can be investigated experimentally using animal models. We used a behavioral task developed in our laboratory (the Risky Decision-making Task) to assess relationships between adolescent risk taking and cocaine self-administration in rats.

Adolescent male Long-Evans rats (P25) were trained in the Risky Decision-making Task in standard operant chambers. In this task, they were given discrete trial choices between pressing one of two levers, the first which delivered a small, "safe" food reward and the second which delivered a large, "risky" food reward accompanied by the risk of a mild footshock, the probability of which increased over the course of the test session in consecutive blocks of trials (0, 25, 50, 75, 100%). Upon completion of the Risky Decision-making Task (P57), rats were allowed to mature and then half were implanted with an intravenous jugular catheter. Following recovery, rats were allowed to self-administer cocaine HCl (0.3-0.5 mg/kg/infusion) for 2 h/day for 10 days. Rats then shifted to a high-dose, long access cocaine self-administration regimen in which they self-administered 1.0 mg/kg/infusion cocaine HCl for 6h/day for 14 days. The other half of the rats underwent sucrose self-administration as a control procedure. Upon completion of self-administration, rats remained abstinent from cocaine for 3 weeks before being retested in the Risky Decision-making Task.

We have previously reported substantial individual variability in the Risky Decision-making Task, such that performance in adult rats can be reliably characterized as "risk taking" or "risk averse". Similar variability was observed in adolescent rats, suggesting that the task is adaptable for this younger age group. Importantly, preliminary data indicate that during the first four days of cocaine self-administration, there was a significant relationship between performance in the Risky Decision-making Task and cocaine intake, such that rats that chose the large, risky reward more often in adolescence ("risk takers") acquired cocaine self-administration more rapidly than their

risk averse cohorts. In addition, following self-administration procedures, rats that self-administered cocaine showed greater risk taking compared to the controls that had comparable experience self-administering a sucrose solution.

These data indicate that adolescent risk taking may be predictive of acquisition of cocaine self-administration, and that cocaine self-administration in turn may also cause long lasting elevations in risk taking, indicating a possible “vicious circle” between risk-taking and cocaine use.

Decision-making, Risk, Cocaine, Adolescence

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46. Effects of acute administration of a 5HT reuptake inhibitor (citalopram) and 5-HT_{2A} (M100907) and 5-HT_{2C} (SB242084) receptor antagonists on risky decision-making in a rat model.

Kenneth Vera, Marci R. Mitchell and Barry Setlow

Abnormal risk-taking is characteristic of several psychiatric disorders including addiction, schizophrenia, and depression, all of which also share the involvement of central serotonergic (5HT) systems; however, little is known about the involvement of 5HT systems in risk-taking. The purpose of this experiment was to assess the acute effects of drugs targeting different components of the 5HT system on risky decision-making in an animal model. Male Long-Evans rats (n = 16) were tested in standard operant chambers in the Risky Decision-making Task, in which they choose between two response levers, one which delivers a small “safe” food reward and the other which delivers a large food reward accompanied by the risk of a mild footshock, the probability of which increases over the course of each test session in consecutive blocks of trials (0, 25, 50, 75, 100%). Once task performance stabilized, rats received i.p. injections of the 5HT reuptake inhibitor citalopram, at doses of 0.1, 0.3, and 1.0 mg/kg, following an ABABABAB design for 8 days; each rat received each drug dose and a vehicle in pseudorandom order. Following drug washout, rats received the 5HT_{2A} antagonist M100907 (0.01, 0.03, and 0.1 mg/kg, i.p.) followed by the 5HT_{2C} antagonist SB242084 (0.1, 0.3, and 1.0 mg/kg, i.p.) using the same design, with a stable baseline performance re-established between each drug. Neither citalopram nor M100907 had any effects on rats’ preference for the large risky reward. SB242084 appeared to increase rats’ preference for the large risky reward, but this effect did not reach statistical significance. When combined with previous data from our lab showing no effects on the Risky Decision-making Task of either the 5HT_{1A} agonist 8-OH-DPAT or the 5HT_{1A} antagonist WAY100635, these data suggest that the 5HT system has only a minimal influence on risky decision-making.

47. Attenuated Motivation for Palatable Foods in Rats on High-Fat Diets

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Obesity is a prevalent condition that creates health risks for a significant part of western populations. Animals with high-fat diet (HFD) induced obesity display decreased motivation for rewarding, palatable foods (Davis et. al, 2008). The present research investigated the mechanism by which this occurs. In three separate experiments, rats were maintained on a diet of either standard rodent chow or high-fat diet (40% fat) for six or more weeks. All three studies employed operant conditioning and progressive ratio (PR) schedules of reinforcement to operationalize motivation. The first experiment found that HFD duration has an accumulative, negative effect on motivation for sucrose reinforcers. The second experiment found that pre-diet exposure to sucrose decreased motivation for those reinforcers in lean and obese animals. The third experiment found that HFD-induced obese animals also exhibit attenuated motivation for high-fat pellets when food deprived

and food sated. The results of these studies demonstrate that attenuated motivation for palatable foods in rats is affected by duration of HFD but not satiety or type of food reinforcer.

High-Fat Diet and Hippocampal Leptin Resistance

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Leptin is a hormone released by adipocytes in proportion to body fat content that signals to the hypothalamus to lower food intake and increase energy expenditure. Leptin resistance is characterized by high serum levels of leptin but a decreased response in the brain and failure to reduce food intake, and often occurs with chronic obesity. Along with obesity and negative medical outcomes that can occur with consumption of a high-fat diet, there are also associated learning and memory defects. Leptin resistance in the hippocampus (a brain region involved in learning and memory) of diet-induced obese (DIO) animals has not been studied and this could begin to explain the correlation between obesity and learning defects we observe in humans. In the current study, rats had 12 weeks exposure to a high-fat diet, then we performed intracerebroventricular cannulation (lateral ventricle) infused them with exogenous leptin and collected hippocampal and hypothalamic tissue. As a measure of leptin activity, phospho-signal transducer and activator of transcription 3 (pSTAT3) and phosphorylated ribosomal S6 (pS6) in the hippocampus and hypothalamus were quantified using Western blot. Consistent with other observations, lack of pSTAT3 signaling was observed in the hippocampus, however, pS6 was observed and is currently being quantified to assess leptin activity and possible leptin resistance via this pathway in the hippocampus.

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48. Persistent reduction in food self-administration following eticlopride-facilitated extinction responding.

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Dopamine receptors are implicated in the primary and secondary reinforcing effects of food and drug reinforcement. The purpose of this study was to evaluate whether blocking D2 dopamine receptors during extinction (secondary reinforcement) would affect reacquisition of responding for food pellets (primary reinforcement). Food restricted rats self-administered (FR1) food pellets in 1-h daily sessions for seven days. For the next seven days rats responded in extinction conditions. Prior to each daily extinction session rats were injected with saline or the dopamine D2 antagonist eticlopride (0.03 mg/kg, SC). After the extinction phase, rats were allowed to reacquire food pellet self-administration in seven daily sessions. Rats received saline or eticlopride prior to each session such that four treatment groups were represented: saline extinction, saline reacquisition; eticlopride extinction, saline reacquisition; saline extinction, eticlopride reacquisition; eticlopride extinction, eticlopride reacquisition. Eticlopride decreased lever pressing on the first day of extinction compared to saline-treated rats. There was also an overall acceleration of extinction in eticlopride-treated rats. Eticlopride delayed reacquisition of food self-administration compared to saline-treated rats, although eticlopride-treated rats responded for similar numbers of food pellets by the fifth day of reacquisition. Locomotor activity did not differ between eticlopride-treated and saline-treated rats throughout the study. Interestingly, rats administered eticlopride during extinction showed delayed reacquisition and a decreased overall response rate for food regardless of whether they receiving eticlopride during the reacquisition phase. These results support a role for dopamine D2 receptors not only in the primary reinforcing effects of a food, but in the association of food reinforcement with environmental context. Specifically, memory of a D2 antagonist-devalued food context carried over as a persistent devaluation of primary food

reinforcement even though food pellets were never explicitly paired with D2 antagonist. Indirectly devaluing a reinforcer in this way may provide a novel approach for reducing food or drug self-administration behavior relevant to addiction.

49. Exploration of the Differential Roles of the Entorhinal Cortex and the Fimbria-Fornix in Performance of a Delayed-Non-Matching-to-Sample Task in Rats.

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Because of the prevalence among the elderly of Alzheimer's disease, which impairs memory, efforts to understand the underlying neural mechanisms contributing to memory and cognitive function are important. Here, we aim to discern the roles of key structures associated with memory and learning impairment. The fimbria-fornix and entorhinal cortex are two structures contributing to the proper function of the hippocampal system – a system implicated in learning and memory. The fimbria-fornix is the primary fiber bundle connecting the hippocampus to subcortical structures. The entorhinal cortex gives rise to the perforant pathway which relays signals from cortical structures into the hippocampus. To test the role of these structures in working memory, male Sprague-Dawley rats were trained on a Delayed-Non-Matching-to-Sample (DNMTS) paradigm in an operant chamber. After reaching criterion on the DNMTS task, the rats received bilateral entorhinal cortex lesion (BECX), bilateral fimbria-fornix transection (BFFX), or sham craniotomy. Rats were given a 5-12 day recovery period before resuming behavioral testing. Post-operative behavioral testing began with 14 consecutive days of testing followed by ten weeks of testing on weekdays only. In both experimental groups, behavioral impairments on the DNMTS occurred early in pre-operative testing. Preliminary data analysis indicates that rats in the BECX condition recovered to preoperative levels of performance within 4 weeks of testing, whereas the BFFX rats showed a persistent impairment for 12 weeks postoperatively. In addition, histological analysis of the hippocampus indicates lesion-induced cholinergic sprouting in the BECX group in contrast to the rats in the BFFX condition that show a high level of cholinergic deafferentation. These differences in behavioral and histological results suggest that the entorhinal cortex and fimbria-fornix differentially contribute to working memory in the DNMTS task.

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50. Effects of chlorpromazine on the discriminative stimulus effects produced by 22 hours food deprivation.

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We have developed and refined a food-deprivation discrimination paradigm that may serve as an animal model of 'hunger'. The dopamine antagonist chlorpromazine has been demonstrated to decrease food intake in several species. We examined the ability of chlorpromazine to reduce the effects of acute food deprivation in rats trained to discriminate between 2 and 22 hrs of acute food deprivation in an operant choice paradigm. Generalization testing began after the discrimination was acquired (~90 daily sessions). During generalization tests, subjects were food deprived for 22 hours. Thirty minutes before the tests, subjects were administered saline or chlorpromazine (0.32 – 3.2 mg/kg, i.p). Chlorpromazine did not affect the discriminative stimulus effects of 22 hour deprivation, although chlorpromazine did decrease response rates at the largest dose examined (3.2 mg/kg). Chlorpromazine also decreased food intake at larger doses tested (1.0 and 3.2 mg/kg). These findings suggest chlorpromazine alters food consumption by mechanisms other than those

related to 'hunger.' Supported by a University of Wisconsin – Eau Claire Faculty/Student Research Collaboration grant

51. Exposure to attractive men reduces ultimatum game offers in women.

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Morality can be rudimentarily characterized in terms of empathy, fairness, and generosity. The neurochemical basis of these emotions seems to have evolved to ensure the survival of the species; oxytocin in particular is responsible for these emotions. Intrasexual competition for mates seems to have a negative effect on generosity and fairness. To test these ideas, we divided forty female college-age students into three groups and exposed them to different stimuli: attractive males (competition), babies (oxytocin), and a control nature group. Participants then played the ultimatum game to see whether their monetary offers/acceptance were affected by these stimuli. Women exposed to attractive males offered less money, while the performance of women in the babies or control group was not significantly affected.

52. White Matter Abnormalities in ADHD Subjects and their Siblings

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Previous voxel-based and regions-of-interest (ROI)-based diffusion tensor imaging (DTI) studies have found decreased fractional anisotropy (FA) and increased mean diffusivity (MD) in ADHD subjects, though findings remain relatively mixed. Given the shortcomings associated with registration for voxel-based analysis, and that most previous studies have employed a relatively limited diffusion gradient directions, we used 64-direction DTI data and refined tractography methods to examine FA, MD and tract volume of the arcuate fasciculus, anterior thalamic radiation, cingulum, corticospinal tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, forceps major, forceps minor, superior longitudinal fasciculus and uncinate fasciculus in children and adolescents with ADHD (n=61), unaffected siblings of ADHD probands (n=33) and demographically similar healthy controls (n=15). While we found no significant FA differences between ADHD subjects and controls, ADHD subjects showed significantly increased MD in the anterior thalamic radiation, forceps minor, right inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus and right superior longitudinal fasciculus. Unaffected siblings of ADHD subjects displayed similar differences in MD. Together these findings suggest that disruptions in white matter microstructure occur in several large white matter pathways in association with ADHD and a genetic predisposition for the disorder. Further, MD may reflect these abnormalities more sensitively than FA.

53. Contusion Size is Significantly Decreased in Calpain-1 Knockout Mice Following a Controlled Cortical Impact (CCI)

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An effective pharmacological treatment for individuals suffering from a traumatic brain injury (TBI) has remained elusive. One challenge has been the characterization of numerous proteins that are integral components in the death of neurons following a TBI. Recent research has indicated that calcium-activated neutral proteases, otherwise known as calpains, are essential mediators of cell death in numerous chronic and acute neurodegenerative disorders. Following TBI, calpain activation has been demonstrated in both dendrites and axons of the cortex and hippocampus. Additionally, calpain activation has been linked to TBI-induced pathology. General inhibition of calpain activity following TBI resulted in cytoskeletal protection and behavioral improvement. Two isoforms of calpain exist in the brain, m-calpain (calpain-2) and μ -calpain (calpain-1), yet the specific roles of each enzyme following TBI are not well understood. Using calpain-1 knockout mice, the current study examined the role of calpain-1 in TBI-induced neural degeneration following the controlled cortical impact (CCI) rodent model of TBI. Calpain-1 knockout mice were generated using mice with a pure C57BL/6 genetic background by first producing heterozygotes that contained the mutant calpain-1 allele. Through PCR based analysis, mice containing the mutant calpain-1 allele were identified and mated with one another to produce the homozygote calpain-1 knockout mice (Cpn1-/-). Both Cpn1-/- and wild type mice (n=6-8) received a CCI unilaterally over the forelimb sensorimotor cortex. Mice were sacrificed three days post-CCI and their brains were sliced coronally and stained with Nissl. Contusion size was examined with an analysis of remaining cortical volume utilizing computerized microscopy (NeuroLucida). Our results demonstrate that the calpain-1 knockout mice exhibit a significantly smaller contusion when compared to the wild type mice ($p < 0.02$). This finding suggests that calpain-1 is a mediator of cell death and the down-regulation of this enzyme following a TBI may result in neuroprotection in vivo. This work was supported by the DePaul University (DAK) and NHLBI (AHC).

54. Sex Differences in the Corpus Callosum: Comparing Two Partitioning Schemes

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The Witelson (1989) partitioning scheme divides the length of the corpus callosum at the half, anterior and posterior thirds, and posterior fifth. The Hofer &

Frahm (2006) partitioning scheme uses diffusion tensor imaging and divides the length of the corpus callosum at the half, posterior third, posterior fourth and anterior sixth. The latter scheme ostensibly partitions the corpus callosum such that fibers within subsections are more homogeneous in projection and function while a sex difference in the isthmus of the corpus callosum has been reported using the Witelson scheme, there is no literature on callosal sexual dimorphism using the Hofer & Frahm scheme. In this study, we applied and compared both schemes to determine if similar sexual dimorphisms exist in respective callosal subsections.

Thirty males and thirty females were scanned in a three-tesla MRI scanner. Midsagittal T1-weighted MRI section of the corpus callosum were selected for use based on the presence of the fornix and anterior cerebral artery, and the absence of exposed white matter in the cerebral cortex. The sections were partitioned and analyzed blind with regard to sex. For each subject, we measured the midsagittal cortex area (as an index of overall brain size), maximal length of the corpus callosum, total callosal area, and subsectional areas from each scheme. A t-test of the raw data gather for the Witelson scheme revealed a significant sex difference in the isthmus area, with males being larger, $t(58)=2.101$; $p < 0.05$. This result was also obtained with an ANCOVA equating for midsagittal cortex area, $F(1, 57)=4.45$; $p < 0.05$. No sex differences were found in the corpus callosum subsections partitioned by the Hofer & Frahm scheme (all $p < 0.152$).

To understand the discrepancy in results between these partitioning schemes, we first examined the possibility that there was proportionately more variance in measurements of the isthmus when

using the Hofer & Frahm scheme examined relative to the Witelson scheme. The two schemes, however, generated similar coefficients of variation. Alternatively, when the two schemes were examined in light of data from Luders et al. (2006), we found that the Witelson scheme included more segments within the isthmus that were sexually dimorphic (longer in males than females) than did the Hofer & Frahm scheme. Although the Witelson scheme defines the isthmus to include a more functionally heterogeneous set of fibers than does the Hofer and Frahm scheme, the isthmus is only sexually dimorphic in the Witelson scheme.

55. Cognitively grounded Cooperative Decision making in Capuchins: Evolution of prosocial behavior

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Humans made a switch from the traditional approach of 'self-preservation' into 'prosocial' behavior, but the reason for this is unknown. In order to model relevant social behaviors in humans, research is often conducted with the closest living relatives, non-human primates. The current study mimics the conditions of early humans by allowing capuchin monkeys to engage in a species-typical behavior (tool use), with full control over the decision to participate and/or cooperate with a partner. This experiment uses a pair of capuchins consisting of a tool monkey and a pulling monkey. The monkeys were subjected to 6 tests, consisting of 12 2 minute trials with varying food reward. The tool monkey was presented with a tool in the back of the primary enclosure and then had to make a decision between a mutualistic cooperative task or an independent task. In a control condition, the tool monkeys were given the option to do the cooperative task even when no partner was present. The results show that Capuchins cooperated when it was necessary to achieve the higher value food reward; however, they were sensitive to their partner's presence and almost exclusively went to the solo site during partner-absent conditions. Thus, they seem to trade off the traditional notions of 'self-preservation' with the costs of doing so in a very rational way. These results imply that the evolution of prosocial behavior was the result of cognitive decision making.

56. Mapping cortical visual areas in alert mice using optical imaging

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Representations of the visual world are built by the early visual system, transformed by higher visual areas, and distributed to the rest of the brain in order to guide behavior. To study area specific computation and selective routing of visual information we have developed a system for multi-area mapping using intrinsic signal imaging of neural responses in running mice. Our chronic imaging preparation features a replaceable 5mm cranial window which allows for simultaneous observation of over 9 anatomically identified visual areas, a titanium head-post for stabilization, and implanted EEG for monitoring brain state. The surgery takes less than 3 hours, can be performed as early as post natal day 20, and results in an imaging window that remains clear for over six months. We can successfully replace the cranial window at least 3-5 times per mouse when repeated access to the brain is required. In comparison with most previous studies using anesthetized mice, the strength of responses across visual areas is larger in awake, running mice, allowing for accurate retinotopic and feature mapping. These techniques will help make it possible

to carefully examine sensory representations in targeted visual areas using calcium imaging or electrophysiological recordings in combination with injections of anatomical tracers and post-hoc histological analysis.

Characterization of astrocytes expressing chondroitin sulfate proteoglycans in the human brain.

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Previous work identified an increase in the number of glial cells expressing chondroitin sulfate proteoglycans (CSPG+) in the amygdala of patients with schizophrenia (SZ). In the healthy human medial temporal lobe, the majority of these cells were found to express glial fibrillary acidic protein (GFAP), although they represented a small percentage of all GFAP+ cells, characterized by a distinct and highly segregated distribution. These findings suggest that CSPG+ glial cells may represent a distinct subpopulation of astrocytes. As a first step toward testing this hypothesis, we are using double and triple immunofluorescence to neurochemically characterize CSPG+ cells. Markers such as calcium binding protein S100b and water channel protein Aquaporin-4 (AQ4) are known to label subpopulations of astrocytes and were chosen for this study. Our main goal is to better understand the functional role of CSPG+ astrocytes and their implications in SZ and other neurological disorders. Immunohistochemistry will be performed on free-floating medial temporal lobe sections from healthy human subjects. Number of single-, double-, and triple immunolabeled cells will be quantified using multiple-marker fluorescence immunohistochemistry. Anatomical distributions are characterized by single antigen immunolabeling in combination with light microscopy. Our observations thus far show that S100b and AQ4 have a distribution similar to that of CSPG+ cells in the normal human amygdala and entorhinal cortex. However, despite morphological similarities, AQ4+ and CSPG+ astrocytes appear to represent distinct cell populations. While the population of S100b+ is larger than that of CSPG+ astrocytes, preliminary results suggest that a subpopulation of S100b+ astrocytes may also express CSPGs. Given the role of S100B in intracellular calcium-dependent signaling, evidence for the involvement of S100B and CSPG+ cells in SZ, these results raise the possibility that these factors may interact and contribute to the pathophysiology of this disease.

57. Gap Activity and Palmitoylation of Regulator of GProtein Signaling (RGS)10 are required for protection against Tumor Necrosis Factor (TNF) toxicity in MN9D cells.

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Parkinson's disease (PD) is the most common progressive neurodegenerative movement disorder. The motor symptoms of PD (resting tremor, bradykinesia, rigidity, and postural instability) are thought to be caused by nigrostriatal dopamine depletion due to death of dopaminergic (DA) neurons of the substantia nigra pars compacta (SNpc) in the midbrain. The cause for PD onset is largely unknown; therefore, it is imperative to discover the mechanisms that underlie the development of the disease. Neuroinflammation may be involved in the progression and/or onset of PD. Indeed the GTPase-Activating Protein (GAP) activity of Regulator of G-protein signaling (RGS)-10 can protect SNpc DA neurons against inflammatory stimuli; however, it is unknown whether GAP activity of RGS10 is required for DA neuron survival. It is also unknown whether post-translational modifications of RGS10, such as palmitoylation, may promote the neuroprotective functions of the protein. Interestingly, palmitoylation of RGS10 may potentiate its

GAP activity. In the studies herein, we are investigating whether GAP activity or palmitoylation of RGS10 affect its ability to act in a neuroprotective manner. Studies were conducted in mouse mesencephalic MN9D neuroblastoma cells or MN9D cells stably expressing human RGS10 to determine the effects of RGS10 on cell viability. MN9D cells were vulnerable to TNF toxicity while WT RGS10 protein was able to rescue cells from TNF insult. However, palmitoylation deficient RGS10 and RGS10 lacking GAP activity were unable to protect; therefore, it is concluded that palmitoylation and GAP activity of RGS10 may both be required for the protein to act in a protective capacity in neuronal cells.

Electron microscopic localization of GluR1 – ionotropic AMPA receptor subunit in the subthalamic nucleus of normal and parkinsonian monkeys

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Dysfunctions of the basal ganglia, a set of forebrain nuclei, are involved in various movement disorders such as Parkinson's disease. The basal ganglia network comprises various brain structures including the striatum, the internal and external globus pallidus (GPi, GPe), the substantia nigra pars compacta (SNc), the substantia nigra pars reticulata (SNr), and the subthalamic nucleus (STN). The neurons in the STN, the only nucleus of the basal ganglia which uses the excitatory neurotransmitter glutamate, become abnormally hyperactive in Parkinson's disease, which is responsible for some of the main symptoms of Parkinson's disease. Although the exact source of this increased activity remains unknown, it may be due to a dysregulation of neurotransmission at glutamatergic synapses onto STN neurons. The STN receives significant excitatory glutamatergic inputs from the cerebral cortex, thalamus and brainstem. Previous studies in our laboratory have shown that both the cortical and sub-cortical (thalamus and brainstem) glutamatergic inputs to the STN degenerate in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated parkinsonian monkeys. Thus, we hypothesize that this degeneration of glutamatergic inputs to the STN may alter the cellular and subcellular localization of glutamate receptors in STN neurons. To address this issue, we undertook an electron microscopic study to compare the subcellular localization of the GluR1 subunit of the fast acting ionotropic AMPA glutamate receptor (AMPA-GluR1) between the STN of normal and parkinsonian monkeys. Using an antibody raised against the AMPA-GluR1 subunit, we performed standard light and electron microscopy immunohistochemical procedures on normal and parkinsonian monkey STN tissue. In the normal monkey STN (n=2), the AMPA-GluR1 subunit was mainly localized in dendrites (95.5%) and rarely in terminals (4.5%). There was no significant change in the subcellular localization of the AMPA-GluR1 subunit in the parkinsonian monkey STN (n=1), where 97% and 3% of the immunoreactive elements were dendrites and terminals, respectively. Thus, these preliminary data suggest that the reduction in glutamatergic inputs to the STN is not accompanied by a significant change in the subcellular localization of the AMPA-GluR1 receptor subunit in parkinsonian monkeys.

58. Preliminary Study of the Grey Matter Morphology of the Insula: Implications for the Emergence of Self Agency

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The long term goal of this project is to examine the association between social cognition, notably self-recognition abilities, and variation in the volume and asymmetry of the grey matter cortex within the insula. The insula is a small portion of the medial frontal cortex that is buried between the frontal and temporal lobes. Located in the insular cortex are Von Economo neurons, also called spindle cells. Previous research on spindle cells has shown that, among primates, they are only found in humans and great apes but not in monkeys. More recent studies have shown that they are also present in dolphins and elephants, leading some to suggest that spindle cells play an important function in social cognition because they are present in species living in complex social systems. In this study, we conducted preliminary quantifications of the insula from magnetic resonance images (MRI) in a sample of chimpanzees. For each subject, the raw MRI scans were re-aligned in the coronal planes using previously employed methods. Grey matter belonging to the anterior and posterior insula was manually traced in the coronal plane for each hemisphere. The analysis of this preliminary study revealed no significant sex differences in the volume or asymmetry of the insula; however, the chimpanzees showed a significant leftward asymmetry $F(1, 27)=8.84, p < .002$. Further analysis indicated that the leftward asymmetry was particularly prevalent for the anterior portion of the insula. The evidence of leftward asymmetries in the anterior insular cortex is consistent with a previous study in this laboratory with an independent sample of MRI scans. Thus, asymmetries in the insula appear to be repeatable. The functional significance of this result is unclear, but in the future we will assess self-recognition in chimpanzees and correlate their behavioral performance with the measures of the insula.

New Activity of Progranulin in Frontotemporal Lobar Degeneration

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Progranulin (PGRN) is a secreted glycoprotein that contains 7.5 repeats of a 12-cysteine motif. Mutations in PGRN have been identified to cause a form of dementia called Frontotemporal Lobar Degeneration with ubiquitin-positive inclusions (FTLD-U). PGRN is known to act as a growth factor and is involved in inflammation and wound repair in the periphery. PGRN's role in the central nervous system is less clear. Neurons in FTLD-U patients with PGRN mutations have abnormal aggregates of a protein called TAR DNA-Binding Protein 43 (TDP-43). It is unknown how decreased levels of PGRN, a secreted protein, leads to abnormal metabolism and cleavage of TDP-43, which is normally found in the nucleus. We hypothesized that PGRN might shuttle into the nucleus where it could have more direct interaction with TDP-43. Using cellular fractionation we detected a fragment, not full length, PGRN in the nucleus. Experiments with protease inhibitors suggest elastase or cathepsins may be involved in formation of this fragment of PGRN.

59. Psychophysical and Electrophysiological Brain Responses to Speech Sounds Across Development: Native Language Experience Shapes Perception

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Native-language neural commitment theory poses that neural networks become more efficient at processing native language patterns, interfering with the learning of foreign languages. The present study investigated the role of language experience in shaping sensitivity to native and non-native speech sounds by examining psychophysical and electrophysiological measures in a Chinese-

English cross-language design. Adult native English speakers and native Chinese speakers were asked to discriminate native and non-native phonetic contrasts on an English 10-level continuum and a Chinese 11-level continuum. Native English speakers (n=19) reliably discriminated English contrasts ($p < 0.01$), but performed at chance when asked to discriminate Chinese contrasts. Conversely, Chinese speakers were able to reliably discriminate Chinese contrasts. Given their validity to measure perceptual sensitivity at the behavioral level, the same phonetic contrasts were used in a mismatch negativity (MMN) paradigm examining the pre-attentive event-related potential (ERP) response to deviant auditory stimuli that has been used as an index of expertise in speech perception. Preliminary analyses of the topography of the MMN show the predicted strong left-lateralized response to native phonetic contrasts for both English and Chinese speakers, but not to non-native contrasts, indicating that native contrasts activate the brain hemisphere specialized for language processing.

60. Role of glutamate receptor expression on methamphetamine-induced memory deficits: Reversal by modafinil

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Chronic methamphetamine (meth) frequently results in persisting cognitive deficits in animals and humans. We demonstrate here that contingent meth impairs memory on an object-in-place task, which measures the ability to identify an object relative to its location and surrounding objects. We also evaluated whether modafinil reversed this cognitive impairment. Rats self-administered i.v. meth (0.02 mg/infusion) on and FR1 schedule of reinforcement (7 days for 1 hr/day, followed by 14 days for 6 hr/day), or received yoked saline infusions. After one week of withdrawal, rats were tested for object-in-place recognition memory. In brief, rats explored four objects for five minutes in a closed test chamber. Ninety minutes later, the location of two objects was changed in order to assess memory for object location and the total time spent at each object was recorded. Half the rats received either vehicle or modafinil (100 mg/kg) immediately after familiarization. Our results revealed that saline-treated rats spent more time interacting with the objects in changed locations, while meth-treated rats distributed their time relatively equally among all objects, regardless of location. Meth-treated rats that received modafinil showed a reversal in the deficit; that is, they spent more time exploring the objects in the new locations. Our results demonstrate both meth-induced cognitive deficits on an object-in-place task and the subsequent reversal of these deficits by modafinil. Comparisons of glutamate NMDA receptor levels in brain areas involved in memory tasks (e.g. prefrontal cortex, perirhinal cortex, and hippocampus) will be presented. Characterization of meth-induced impairments of glutamate NMDA receptors (e.g. NR1, NR2A, and NR2B) in frontal and temporal cortical areas and their subsequent alteration by modafinil may identify neurobiological substrates that are the basis for the behavioral effectiveness of modafinil and its potential use as a treatment in meth addiction.

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61. Chronic Ethanol Effects on Social Behavior in *Procambarus clarkii*

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In the United States, alcohol consumption leads to more than 100,000 deaths each year. Some of these incidents result from aggressive behavior, but it is unclear whether alcohol increases

aggressive behavior or whether individuals who are more aggressive choose to drink more alcohol. Our study investigates the effects of chronic ethanol (EtOH) exposure on social behavior, using an animal model with a well-characterized agonistic behavioral repertoire, *Procambarus clarkii* (red swamp crayfish). We hypothesized simply that EtOH exposure would increase aggressive behavior in crayfish. Thus, crayfish were exposed to a 400 mM EtOH bath solution one hour per day for 14 consecutive days. On alternating days after the EtOH bath, crayfish were placed in an observation tank and their social behaviors were measured using an ethogram to record frequency of attack, approach, retreat, and escape. Following EtOH exposure, hemolymph was extracted to assess circulating alcohol concentrations. Finally, crayfish nerve cords were collected to analyze 5-HT receptor protein expression, given the known role of serotonin in crayfish aggression. We predicted the following outcomes: 1) EtOH exposure would increase aggressive behavior in crayfish; 2) Hemolymph alcohol content would be detectable after EtOH exposure; and 3) heightened 5-HT receptor protein levels would correlated positively with aggressive behaviors. Although we did not observe increased aggression in EtOH-exposed animals, they were overall more socially active than controls. In addition, we were able to detect EtOH in EtOH-exposed animals. The results from our 5-HT receptor expression analysis remain inconclusive to date. Future studies will further investigate whether 5-HT receptor activity is necessary for the observed behavioral effects of EtOH in crayfish and will identify an EtOH dose-response relationship in this useful animal species.

Social plasticity: the role of urine release in fight dynamics among *Procambarus clarkii*

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Although formation of social hierarchies has been explored in various species, little is known about the underlying neurobiology of the process. In the case of red swamp crayfish (*Procambarus clarkii*), aggressive behaviors are altered in the presence of a conspecific, often lead to 'fights', and eventually result in the formation of hierarchical structures that ultimately facilitate survival in social living environments. Usually physical superiority plays the key role in determining dominance over subordinate conspecifics, but more than physical size may be required to secure a dominant position. Indeed crayfish expel urine as a form of chemical communication that reveals social standing. Dominant crayfish utilize urine as a necessity for grounding and maintaining status. Thus, if the ability to urinate is blocked in a dominant crayfish, the animal too becomes subordinate in the presence of a previously encountered crayfish. This study of chemical communication in fighting crayfish employed a method of visualization using the dye Fluorescein. Our primary aim is to determine if the use of urine-associated pheromones in conjunction with agonistic behaviors is essential for maintenance of a dominance hierarchy. Thus, this study examines the establishment of a dominance hierarchy by pairs of crayfish, maintenance of the hierarchy in new dyadic interactions, and whether blocking urine release influences this maintenance of the hierarchy. We hypothesize that if urine conveys critical information about dominance status, then inhibition of urine release should facilitate role reversal within the dominance hierarchy. Future studies will further address the effects of a familiar and unfamiliar opponent on the maintenance of a dominance hierarchy, as well as identification of the chemical signals that appear critical in determining the result of a dyadic interaction.

62. Cocaine in Crayfish: Testing a Role for Dopamine

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Although extensive evidence suggests that cocaine increases synaptic levels of dopamine and exerts behavioral effects through increased dopamine receptor activation in vertebrates, research on cocaine's neurochemical mechanisms in *Procambarus clarkii* and other crustaceans is limited. Given high potential of the crayfish model system to provide insight about evolution of rewarded and reinforced behaviors using drugs of abuse, such as cocaine, the present experiments were conducted to determine whether cocaine's effects on crayfish are mediated by increased activity at dopamine D1-like receptors. In this experiment, we observed social and locomotor behaviors in adult male crayfish injected with saline (controls), cocaine, and cocaine after pretreatment with a D1-like receptor antagonist (SCH23390), with each injection trial separated by a four-day isolation period. Results indicated that crayfish pretreated with the dopamine receptor antagonist before cocaine did not resemble recorded baseline behavior or that of controls. The present results lead to the conclusion that cocaine's activity may not involve dopamine D1-like receptors. Future experiments will also include a full dose-effect function with SCH23390, as well as experiments to consider the possibility that dopamine (or octopamine) receptors in crayfish are not blocked by the same antagonists as mammalian receptors, and the likelihood that additional neurotransmitter systems are involved in cocaine's behavioral effects.

Development of shRNA technology to knockdown oxytocin receptor gene expression in the prairie vole (*Microtus ochrogaster*)

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In the socially monogamous prairie vole, oxytocin receptor (OXTR) expression in the nucleus accumbens (NAcc) is positively correlated with the degree of alloparental (baby-sitting like) behavior. Both juvenile and adult females with a high density of OXTR expression in the NAcc display an elevated tendency to engage in alloparental behavior, such as licking and grooming, carrying, and hovering over novel pups. Previous studies using an adeno-associated (AAV) virus to over-express the OXTR in the NAcc have suggested a developmental role of OXTR in adult alloparental behavior. In this study we develop an shRNA targeting the prairie vole OXTR (shRNAoxtr) and show that this shRNA knocks-down OXTR expression *in vitro* and *in vivo*. We hypothesize that juveniles injected with shRNAoxtr in the NAcc will display less alloparental behaviors towards pups than those individuals injected with a scrambled shRNA (shRNAsc) in the NAcc. Of the animals tested thus far, those injected with the shRNAsc engaged in alloparental behavior for 664.4s while those injected with shRNAoxtr engaged in alloparental behavior for 173.7s. Further studies are being done to explore this difference.

63. Analgesic Effects of Perfluoroalkyl Derivatives of Ibuprofen

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Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), is a common over-the-counter drug used to relieve pain and decrease inflammation. Perfluoroalkyl derivatives of ibuprofen may have an increased lipophilicity, which may allow these compounds to cross the plasma membrane more readily or increased stability, which may provide a longer half-life *in vivo*. NSAIDs act by non-selectively inhibiting COX-1 and COX-2 enzymes, which prevents the production of prostaglandins to decrease pain and inflammation. In order to test the analgesic effects of the perfluoroalkyl derivatives, p-C4F17-ibuprofen and a mixture of ortho, meta, and para isomers of C8F17-ibuprofen, we performed three analgesic tests on mice treated with vehicle, ibuprofen, or perfluoroalkyl derivatives of ibuprofen. The hot-plate and tail-flick tests were conducted as measures of acute, thermal analgesia while the formalin test was conducted as a measure of chronic, inflammatory pain. We hypothesized that p-C4F17-ibuprofen and the mixture of C8F17-ibuprofen isomers would have a greater effect in reducing inflammatory pain in the formalin test, but would be comparable to ibuprofen on the acute pain tests. Our results confirmed our hypothesis that the p-C4F17-ibuprofen and the mixture of C8F17-ibuprofen isomers did not reduce pain in the acute pain tests, but significantly decreased pain sensitivity in the inflammatory phase of the formalin test as compared to ibuprofen.

64. BUILDING RESEARCH ACHIEVEMENT IN NEUROSCIENCE (BRAIN): UNDERGRADUATE NEUROSCIENCE SUMMER RESEARCH EXPERIENCES IN BIOPHYSICS AND PSYCHOLOGY.

Justin Brantley^{1,2} and Isaac del Rio^{1,3}.

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Building Research Achievement in Neuroscience (BRAiN) is a student training program developed in response to the NIH BPENDURE initiative (R25GM097633). BRAiN aspires to bridge the Neuroscience research participation gap by preparing diverse undergraduates in the Rocky Mountain and Southwest Region for successful entry to Neuroscience Ph.D. programs. The program unites preexisting formal research and education programs at three diverse institutions: the Anschutz Medical Campus at the University of Colorado Denver; New Mexico State University (NMSU), a Hispanic serving minority institution; and the University of Colorado Denver downtown campus (UCD-DT). This poster presents the outcomes of the research projects completed by BRAiN Scholars Isaac del Rio (NMSU; mentor Dr. M. Coussons Read) and Justin Brantley (NMSU; mentors Dr. E. Gibson and Dr. D. Restrepo) during an eight week internship at UCD in summer 2011.

MEASUREMENT OF CA²⁺ DYNAMICS AND LOCALIZATION WITHIN OLFACTORY SENSORY NEURON CILIA

Justin Brantley, Baris Ozbay, Emily Gibson, Diego Restrepo.

In the presence of an odorant molecule, sensory transduction is activated in olfactory sensory neurons (OSNs) thus giving way to a surge of Ca²⁺ influx by way of open, nonselective, cyclic nucleotide-gated (CNG) channels. As the odorant is received by the selective receptor protein, the OSN activates a cascade of cAMP signaling through a G-protein coupled mechanism, consequently permitting the influx of Ca²⁺ ions. Recently, much of the phenomenon of olfactory transduction and response to odorous environments has been ascribed to the cilia within the mucus layer of the epithelium. The proposition can be made that each cilium operates as an individual organelle with the necessary equipment to successfully amplify and regulate odor transduction with high

sensitivity. The localization of Ca²⁺ ciliary micro domains, nanoscale regions of high Ca²⁺ concentration, is the hypothesized mechanism by which regulation of odor transduction occurs. The objective is to employ high-resolution microscopy and electrophysiological measurement techniques to confirm the existence of spatially distributed, distinct molecular nexuses within the ciliary membrane. Furthermore, we wish to understand the dynamics and precise spatial distribution of ciliary Ca²⁺ microdomains.

AN IMMUNE SYSTEM WEAKENED: THE ROLE OF C-REACTIVE PROTEIN, CORTISOL, AND SIGA IN CONGENITAL CYTOMEGALOVIRUS Isaac Del Rio and Mary Coussons-Read.

The goal of the study was to determine if stress experienced during pregnancy affects maternal inflammatory and immune status and increases the risk of congenital cytomegalovirus (CMV) infection. We hypothesized that women reporting high stress and low physical activity would have elevated levels of C-Reactive Protein (CRP), lower secretory IgA (sIgA), higher salivary CMV-specific, and flattened diurnal cortisol rhythms. This combination of changes would suggest stress-related alterations in maternal immune and endocrine status which may increase the susceptibility of congenital CMV infection. We collected samples from 35 women enrolled in a larger study of the effects of exercise on pregnancy during their second trimester of pregnancy. All subjects participated in two trials, one early in the second trimester of pregnancy, and one during the third trimester. The women also took two surveys; The Pregnancy Physical Activity Questionnaire (PPAQ) and Cohen's Perceived Stress Scale (PSS). There were 3 saliva collections over the 24-hour period prior to each scheduled appointment. The 1st collection was upon awakening, the 2nd collection was 30 minutes after awakening, and the 3rd assessment was at 4pm to estimate the basal and reactive function of the HPA axis. Concentrations of salivary CRP, IgA, and CMV-specific IgG, and Cortisol concentrations were determined. Samples were run in duplicate, and at an optical density of 450 nm. Women completed surveys of stress, social support, depressive symptoms, self-efficacy, and physical activity. Saliva was collected for assessment of diurnal decline in cortisol and for measurement of salivary CRP, sIgA, and CMV-specific IgG. Results showed that women reporting higher physical activity had higher salivary sIgA, and women reporting more time being sedentary had lower sIgA, suggesting a supportive role for activity on secretory immunity. Elevated CRP was associated with lower sIgA, lower self-efficacy, higher depression scores, and more reported time being sedentary. Lower physical activity was also modestly related to higher cortisol and flatter diurnal rhythms. We were unable to detect IgG against CMV in the saliva samples we tested, but this may be due to concentrations of the antibody being substantially lower in saliva than in serum. Together, these data provide initial support for the original hypothesis, and raise important questions for future work.

65. The role of microglia and astrocytes in the production of leukotrienes after traumatic brain injury

Dayton J. Goodell, Janna Mize-Berge, Sarah Martin, Robert Murphy, and Kim A. Heidenreich

Cysteinyl leukotrienes (cys-LTs), potent inflammatory lipids derived from arachidonic acid (AA), mediate blood-brain barrier disruption, edema, and cell death after traumatic brain injury (TBI). Blocking cys-LTs by targeting the 5-lipoxygenase (5-LO) pathway may have implications for future pharmacological interventions in human TBI. Prior work in our lab has shown that 50% of cys-LT production after fluid percussion injury in the rat occurs through a transcellular mechanism whereby infiltrating neutrophils (which contain 5-LO) contribute an exogenous source of LTA₄ that is taken up by endogenous brain cells and converted to cys-LTs. Due to their myeloid origin, we hypothesize that microglia also have 5-LO and are the endogenous source of LTA₄ in the brain after injury. Primary cultures were obtained from post-natal day one rats, and microglia and astrocytes were cultured separately with >95% homogeneity. Cultures were stimulated with calcium

ionophore (A23187) either separately or mixed, and cys-LT production was measured using reverse phase high-pressure liquid chromatography/tandem mass spectrometry. Microglia and astrocytes cultured separately were unable to produce cys-LTs when stimulated by A23187, (5 μ M) although an increase in AA and prostaglandins was observed in astrocyte cultures, indicating that cPLA2 and cyclooxygenase were activated upon stimulation.

As previously shown, when astrocytes (3x10⁶) were co-cultured with neutrophils (15x10⁶) significant amounts of LTB₄ LTC₄ and LTD₄ were produced upon stimulation. However, in the mixed cultures of microglia (17x10⁶) and astrocytes (3x10⁶), no leukotriene production was observed. There was no 5-LO activity in stimulated cultures of microglia, astrocytes, or microglia + astrocytes, suggesting that microglia do not contribute to a transcellular mechanism of leukotriene production in cells cultured from newborn rats. However, cultured microglia from newborn rats may not mimic activated microglia present in the adult injured brain.

66. Effects of Adolescent Social Defeat on Adult Cognitive Function and Reward Motivation **Leah Miiller, Andrew Novick, Gina Forster, and Michael Watt**

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Adolescent bullying is associated with greater incidence of psychiatric disorders that can persist into adulthood, the majority of which are characterized by a deficit in executive functioning. This is the cognitive process underlying use and maintenance of task-relevant information, which is mediated by medial prefrontal cortex (mPFC) dopamine (DA) activity. We have found that rats exposed to repeated social defeat (a model of human bullying) during adolescence show decreased mPFC DA function as adults. In addition, previously defeated rats exhibit increased conditioned place preference (CPP) for amphetamine. Here, we conducted two separate experiments to investigate effects of adolescent defeat on working memory, a component of executive function, and to establish whether enhanced CPP for amphetamine also generalized to greater CPP for non-drug rewards. Adolescent male rats were exposed daily to social defeat in the home cage of an aggressive adult male from postnatal day (P)35 to 39, while age-matched controls were placed in a novel empty cage for the duration of each defeat trial. All subjects were then allowed to mature undisturbed to early adulthood (P56). Working memory was assessed using a delayed alternating T-maze paradigm, with delay periods of 30, 60 and 90 sec. A separate group of previously defeated rats and controls underwent CPP training for a food reward (sweetened condensed milk [SCM]), with SCM or water presented alternately over 8 sessions. Rats defeated in adolescence made more errors in the alternating working memory task when a 90 sec delay was introduced, but not with delays of 30 or 60 sec. No differences were found in CPP for SCM, although defeated rats consumed less SCM than controls over the entire conditioning procedure. These findings indicate that exposure to repeated social defeat during adolescent development can cause deficits in working memory in adulthood, which is most likely a function of reduced mPFC DA activity. However, increased CPP following adolescent defeat appears to be specific for amphetamine, and does not generalize to food rewards.

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67. Effects of Chronic Social Defeat on Hippocampal-Dependent Fear Conditioning in Adolescent Rats.

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Recent studies from our lab demonstrate that Chronic-Mild-Unpredictable-Stress (CMUS), an animal model of depression, increases hippocampal-dependent fear conditioning. To determine if

this effect generalizes to other forms of stress, we tested the effects of Chronic Social Defeat Stress (CSDS) on fear conditioning in adolescent Sprague-Dawley (intruders) and Long Evans (residents) rats. Surprisingly, we observed that the intruder animals to be more aggressive during the first five days of the seven day CSDS protocol. Twenty-four hours following the last resident-intruder encounter, all the animals underwent trace fear conditioning. During a test of fear memory, both the Sprague-Dawley and Long Evans animals that were involved in the CSDS exhibited significant higher levels of freezing compared to a control (non-stress) group of Sprague- Dawley animals. Work supported by NIH grant R15 MH085280-01 to CGR.

68. The Impact of Enriched Environment and Transplantation of Neuronal and Glial Precursors on Recovery from Controlled Cortical Contusion Injury. Jonathan Gallagher³, Jacob Dunkerson⁴, Sarah Fluharty², David Mudd^{2,3}, and Jeffrey Smith¹
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Transplantation of embryonic stem cells (eSC) into a damaged brain has been shown to improve the behavioral and pathophysiological outcomes in several preclinical models of traumatic brain injury. In addition, enriching the post-injury environment (EE), a non-invasive behavioral treatment, has proven successful in promoting functional recovery. The current research project was designed to determine if the co-application of both therapeutic approaches would have a greater impact on the behavioral and anatomical consequences of brain injury. In the study, four groups of male Long-Evans rats experienced traumatic brain injury. Two groups received a transplant of eSCs and were placed in EE or standard housing, two groups received no eSCs and were placed in EE or standard housing, and two groups of sham animals did not receive injury but experienced the surgical procedures and were then placed into EE or standard housing. Initial analysis of the behavioral data showed that, following injury, animals receiving the combination of eSCs and EE expressed the greatest amount of functional recovery. In an attempt to determine the role these cells played in recovery, we are currently performing a histological examination of this tissue. We predict this analysis will reveal that transplanted eSCs will be more likely to express neural phenotypical characteristics in animals recovering in an EE whereas animals kept in traditional housing will still have evidence of transplanted eSCs surviving, but these cells will be more likely to express glial (or non-neural) phenotypes. Cell morphology and migration patterns are also being analyzed. This information could be used to guide future research projects by providing evidence for the effects of post-injury environments on recovery from traumatic brain injury, how these environments influence the differentiation of transplanted eSCs, and how concurrent treatment with EE and eSCs has the greatest impact on recovery of function.

69. The Effect of Adolescent Social Deprivation on PSD-95 Expression
Cassandra I. Hayter, Sondra T. Bland

The medial prefrontal cortex is a brain region involved in social and emotional development by moderating correct social behavior. Previous work in our lab has examined the expression of the protein product of Arc, an immediate early gene associated with plasticity, in the medial prefrontal cortex of rats that had received adolescent social deprivation (ASD) compared to group housed controls. We demonstrated a decrease in social interaction-induced arc expression in ASD rats. To better understand potential disruptions in synaptic plasticity in this region, we labeled the same brains as those from the Arc study with immunolabel against PSD-95. PSD-95 is a post-synaptic density protein involved in synapse stability and AMPA receptor trafficking. Male and female Sprague-Dawley rats were either group housed or isolated (ASD) for four weeks, starting on postnatal day 21. Rats were then exposed to a novel same-sex conspecific for 15 minutes and

sacrificed 90 min later. Unbiased stereology was used to determine the amount of small, medium and large PSD -95 punctae. In contrast to the blunted response to social exposure by ASD rats with Arc expression, there was a significant increase in PSD 95 expression, in medium and large punctae, that was greater than that seen in group housed rats. There were fewer large punctae in ASD rats with no social exposure as compared to group housed rats with no social exposure. These results suggest that ASD rats may initially have a hypofunction of the medial prefrontal cortex, but are able to recover from this with social interaction. It is also possible that social exposure could be more of a novel event/learning experience to adjust to for an isolated rat, leading to more PSD-95 expression.

70. Localization of circadian clock components in the starlet sea anemone, *Nematostella vectensis*.

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An organism's daily physiological and behavioral patterns are controlled by an endogenous circadian clock, which is synchronized to rhythmic environmental stimuli. Marine species, particularly invertebrates, have been comparatively overlooked in circadian rhythms research, and as a result, our understanding of their circadian system lags significantly behind that of traditional research organisms. Our lab has been studying the circadian rhythms of the marine anthozoan *N. vectensis*, the starlet sea anemone. Previous experiments in our laboratory have established that diurnal rhythmicity persists under constant photoperiodic conditions (constant light or constant dark) indicating the presence of an endogenous circadian rhythm. In order to gain a better understanding of the regulatory pathways controlling rhythmic behavior in the evolutionarily informative species, we have been investigating circadian gene expression in these animals. *Cryptochrome (cry)* and *clock (clk)* are molecular components of the circadian clock that have been conserved throughout evolution. Clk protein acts to promote transcription of canonical clock genes and other clock controlled genes whereas, Cry protein functions as a circadian photoreceptor in plants and insects or as a negative regulator of clock gene transcription and Clk function in mammals. Both proteins are critical for normal function of the circadian system. Based on sequence homology to insect and mammalian genes, these core clock components have recently been identified and shown to undergo a circadian oscillation in the starlet sea anemone, *N. vectensis*. The aim of our study was to describe the localization and expression patterns of these circadian genes in *N. vectensis* which will provide clues to identifying cells important in clock function in this species. Using *in situ* hybridization techniques we have successfully identified regions of *cry1a* and *clk* expression in the young adult. We found that their gene expression is primarily restricted to portions of the oral disk surrounding the mouth and to the tips of the tentacles, sites that naturally receive maximal exposure to sunlight. Further characterization of these candidate clock cells is important in order to advance our understanding of how the circadian system has evolved. Together, these experiments will allow for a greater understanding of how marine invertebrates regulate their circadian behavior, and provide insight into how these genes and their roles in controlling circadian behavior have been modified over the course of evolution.

71. Presence and Role of Protease Activated Receptor-1 in Avian Schwann Cell and Motor Neuron Interactions

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Previous studies have shown that activation of protease activated receptor-1 (PAR-1) in the central

nervous system (CNS) leads to a decrease in motor neuron survival, along with a decrease in oligodendrocyte myelin deposition during development. While myelin deposition in the PNS is performed by Schwann cells and not oligodendrocytes, they produce many of the same myelin proteins. Furthermore, steps leading to apoptosis and myelination all involve changes in the cytoskeletal structure. Since all of these cells have access to thrombin, the naturally occurring PAR-1 ligand, it is reasonable to suggest that both glial cell types express PAR-1 and that PAR-1 activation results in cytoskeletal adaptations. The purpose of this study was two-fold – (1) to investigate the presence and role of PAR-1 on Schwann cells and (2) to investigate the morphological changes associated with the activation of PAR-1 in both motor neurons and Schwann cells. PAR-1 localization in Schwann cells was determined using a PAR-1 specific monoclonal antibody. Morphological changes between PAR-1 activated cells and non-treated controls were determined using immunocytochemistry to detect changes in actin microfilaments. Proteins isolated from Schwann cells confirmed the presence of PAR-1. Furthermore, activation of PAR-1 on Schwann cells and motor neurons resulted in cytoskeletal differences assessed by differences in the focal adhesion points and differences in fluorescence. Interestingly, PAR-1 activation on Schwann cells resulted in a decrease in cytoskeletal organization; whereas, PAR-1 activation on motor neurons resulted in an increase in cytoskeletal organization. This may be the result of differentiation pathways that occur in nervous system development responsible for the specific interactions of these two cell types.

72. Mechanisms underlying disruptions to cortical dopamine activity caused by adolescent social defeat

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Adolescence is a critical period of behavioral and neural development, thus adolescents are vulnerable to effects of negative social experiences such as bullying. We showed that male rats exposed to social defeat in adolescence exhibit decreased medial prefrontal cortex (mPFC) dopamine (DA) activity as adults, which is associated with heightened sensation seeking. Accordingly, rats defeated in adolescence show enhanced novelty responses and increased amphetamine conditioned place preference as adults compared to non-defeated controls. We hypothesize that reduction in adult mPFC DA activity results from overactivation of DA synthesis-controlling DA D2 autoreceptors in the mPFC during the adolescent defeat experience. Therefore, we investigated whether pharmacological blockade of mPFC D2 autoreceptors during adolescent defeat would prevent the decrease in cortical DA activity. Male adolescent rats were defeated daily by a larger aggressive male for 5 days starting at postnatal day (P) 35, and received bilateral infusions of the D2 receptor antagonist amisulpride (50 ng in 0.3 μ l per side) or vehicle (aCSF) into the mPFC 10 min prior to defeat exposure. Non-defeated controls also received either amisulpride or vehicle infusions, but were placed in novel empty cages for the duration of each defeat trial. To confirm our hypothesis, a separate group of adolescent rats received daily bilateral mPFC infusions of the D2 receptor agonist quinpirole (100 ng in 0.3 μ L per side) or vehicle for 5 days, but were not exposed to social defeat. Brains were taken at either adolescence (P40) or early adulthood (P56), then sectioned and tissue microdissected from the mPFC for analysis of DA activity using HPLC with electrochemical detection. No effect of drug treatment or defeat stress was evident at P40, but pharmacological blockade of mPFC D2 autoreceptors during adolescent defeat successfully prevented decreases in adult mPFC DA activity without altering DA activity in non-defeated controls. Similarly, activation of mPFC D2 autoreceptors in non-defeated adolescent rats had no effect on DA activity at P40, but caused reduced mPFC DA activity in adulthood. These findings suggest D2 autoreceptors play a major role in alterations to mPFC DA activity caused by

adolescent stress, and may represent a potential target for treating behavioral disorders associated with adolescent bullying.

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73. Characterization of behavioral rhythms and generation of transgenic *Xenopus laevis* to examine clock function

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The biological clock molecular mechanism has been conserved throughout evolution, but there are differences in the expression of particular clock genes. *period2* (*per2*) is a clock gene that is expressed differently in *Xenopus laevis* and *Xenopus tropicalis*. In *X. tropicalis*, *per2* is clock regulated, but in *X. laevis*, *per2* is light regulated. We are currently investigating the importance of the *per2* gene in *X. laevis*. We have already established a behavioral assay that is used to monitor the behavior of *X. laevis* tadpoles. The behavior of the tadpoles is monitored using the Hitachi CCD camera which takes pictures of the tadpoles in the assay chamber every second for 3 to 6 days. A total of 12 out of 36 animals have displayed a circadian rhythm in behavior with a period length of 23.96. We will next establish the meganuclease transgenesis procedure in our lab using the cry-GFP meganuclease vector. We have successfully generated the cry-GFP transgene and cloned it into the meganuclease vector that will be used to inject the *X.laevis* embryos for transgenesis. Once this procedure has been established, we will generate a transgenic frog that overexpresses *per2* in *X. laevis*, and measure the behavior of these animals. We will then be able to observe what will happen to the behavior when this gene is altered.

Expression of clock genes in the brain of *Xenopus tropicalis*

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The biological clock determines the timing of rhythms in behavior, physiology and biochemistry of organisms ranging from microorganisms to plants and animals. These rhythms are endogenous and occur once every 24 hours. Gene expression that defines the central clock mechanism is additionally influenced by external factors like light and temperature. Clock gene expression can be varied by changes in light that occur when crossing time zones or in shift work. Some of the central clock genes like *period1*, *period2*, *bmal* and neuropeptides like vasoactive intestinal polypeptide (VIP) and arginine vasopressin (AVP) can be used to monitor changes in the circadian clock. In this research, the above-mentioned circadian genes and neuropeptides were tracked in the *Xenopus tropicalis* brain using in situ hybridization. Brain sections were collected every 4 hours for 24 hours. After being probed with radioactively labeled antisense RNA, these sections were exposed to film and analyzed. The results show that AVP was highly expressed in the SCN and to a lesser degree in the hypothalamic preoptic area. VIP was highly expressed in the SCN, ventral thalamus, and ventral hypothalamus of the forebrain sections. *bmal* was found in the dorsal pallium, ventral striatum, ventromedial thalamic nucleus, hypothalamic preoptic area, lateral thalamus, ventral thalamus, nucleus of ventral hypothalamus of the forebrain and in torus semi circularis and nuclei isthmi of midbrain. *period2* was found to be highly expressed in olfactory bulb, lateral pallium, dorsal pallium, ventral striatum, thalamic axis, hypothalamic preoptic area, ventral hypothalamus. *period1* was found mainly in the lateral pallium, hypothalamic preoptic area, SCN, ventral thalamus of forebrain; the torus semi circularis, ventral and dorsal tegment, pituitary and nuclei isthmi of the

midbrain; and in the cuneate nucleus of the hindbrain. Further analyses of these data to evaluate the timing of the expression of these clock genes are in progress.

74. Effects of Neonatal Hypoxia-Ischemia and Inter-Alpha-Inhibitor Treatment on Brain Weight in the Rat

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Reduced oxygenation (Hypoxia) and blood flow (ischemia) to the brain in neonates can result from umbilical cord occlusion, prolonged labor, preterm birth or perinatal trauma. Following HI, a series of inflammatory responses persist exacerbating tissue damage. Inter-Alpha Inhibitor Proteins (IAIPs), have been shown to significantly reduce advancement of inflammation and tissue injury following infection in mice and adult stroke in rats. The current study investigated the effects of systemic IAIP administration on brain weights following induced HI in postnatal day (P) 3 and 7 rat pups. Separate HI and IAIP groups received ligation of the right common carotid artery to induce ischemia followed by 90 min of 8% O₂. Sham surgery was performed on control subjects with 90 min of open room air exposure. Sham and HI rat pups received an intraperitoneal injection of ~0.1 cc NaCl, while IAI pups received 30 mg/kg IAIP treatment prior to hypoxia and 24 hours following HI. Brain samples were extracted and weighed 72 hours following HI induction. Results from a one-way ANOVA revealed a significant difference in brain weight between P7 groups. Post hoc analysis showed that HI pups had significantly lower brain weights as compared to sham animals. No brain weight differences were seen between sham and IAIP treated subjects. Further, no significant effects of brain weight were seen between the P3 groups. Our results suggest that IAI may prevent loss of brain tissue following P7 injury as evidenced by brain weight sparing. Preliminary data also suggest that the severity of HI injury or the effectiveness of IAIP as a treatment for neonatal HI may be differentially regulated across development. Future studies will assess the distribution and number of dying neurons and quantify the extent of injury in order to evaluate the efficacy of IAIP as a neonatal neuroprotectant.

75. Further Behavioral Characterization of Mice Lacking the Adenosine A1 Receptor

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Adenosine is a neuromodulator recognized as an important endogenous molecule present throughout the extracellular fluid of the nervous system. This purine binds to several receptor subtypes, including the inhibitory adenosine A1 receptor (A1R), which is widespread in the nervous system and has a high affinity for adenosine. Using genetic and pharmacological approaches, this receptor has been shown to have some anticonvulsant, analgesic and anxiolytic properties. Here we used A1R knockout mice to further characterize the constitutive loss of this receptor in three mouse behavior protocols. We examined the responses of wildtype mice (C57Bl6) and mice lacking the A1R (knockout) in: 1) a formalin-induced nociception model (to test hyperalgesic properties), 2) electrically-induced seizures (to test anticonvulsant activity), and a social behavior task (to test social interactions). In the formalin-induced pain model, the right hindpaw was injected with 10ul of 4% formalin and the resulting licking and lifting of the injected paw was monitored and quantified. In the seizure model, the susceptibility of mice was tested and

the CC50 quantified using an up-down method with 6 Hz corneal stimulation. In the sociability task, mice were monitored in a three-chambered apparatus and their preference for socializing and social novelty was quantified. We found that behavioral responses of A1R knockout mice were altered significantly in all tests. In the pain test, A1R knockout mice experienced a significantly stronger nociceptive response in the second (but not first) phase of the formalin response, suggesting that spinal A1 receptors normally limit sensitization of pain nociception. In the seizure model, there was a reduced threshold for seizure induction in the knockout mice. In the sociability task, the wild-type mice preferred to spend time with another mouse over being alone and preferred a novel mouse instead of a familiar one. In contrast, knockout mice exhibited neither preference. These results support and expand prior work that endogenous adenosine, acting through adenosine A1 receptors, has positive effects on nociception, seizure susceptibility, and sociability.

76. The Causes of Gender Identity in the Brain with the help of Fore Core Genotype Mice

Evan Friedenberg, Dr. Melissa Coleman, Dr. Karen Parfitt, and Dr. William Grisham

The purpose of this project is to better understand the influences underlying gender differences in the brain using Four Core Genotype mice. Four Core Genotype mice are transgenic mice in which the SRY gene has been translocated from the Y chromosome to another location. This enables separation of the genetic sex and gonadal sex. For example, there are female mice based on sexual organs but their chromosomes are XY. This allows us to determine whether sexual differentiation in the brain is due to genes or hormones. In this project, I looked at a sexually dimorphic area of the brain, the Bed Nucleus of the Stria Terminalis (BNST), which is twice as large in males than in females. I hypothesize that both chromosomes and gonadal hormones play a part in sexually differentiating the brain including the BNST and thus I predict that the size of the BNST will be the same in XX males and XY females. I measured the BNST from five XX female and five XY male four core genotype mouse brains and confirmed that the BNST is larger in males than in females, as it is in normal mice ($p = .057$). Currently I am processing and measuring the size of the BNST in thirteen brains of XX males and XY females to see if the size of the BNST matches the chromosomes or the gonads. I am blind to the identity of the brains until all measurements have been made. Once I have completed processing the brains of the XX males and XY females, I will have a better understanding of the effects of chromosomes and gonadal hormones on sexual differentiation of the brain. Using these data, we can start to understand people in the Transgender community, or those whose gender identity does not match their biological sex assigned at birth.

77. Hematopoietic-derived stem cells as potential neural precursors in adult neurogenesis

Rachel Kery, Jeannie Benton, Julia Gall, Lindsey Migliore, and Barbara Beltz

Adult neurogenesis, the production of new neurons in the adult brain, occurs in the olfactory pathways of many vertebrate and invertebrate species, including decapod crustaceans. In *Procambarus clarkii*, new neurons are integrated into interneuronal cell clusters 9 and 10. The 1st-generation precursor cells reside in a niche, where they divide symmetrically, with both daughter cells migrating along glial strands to clusters 9 and 10, where additional divisions and neuronal differentiation occur. Although divisions of existing niche cells do not replenish the niche, the niche increases in size over an animal's lifetime. Niche precursor cells must, therefore, originate from an outside source. It has been hypothesized that circulating stem cells of possible hematopoietic origin are migrating into the niche from the hemolymph. Previous lines of inquiry in crayfish have suggested that semi-granular cells circulating in the blood are attracted to the niche. Astakine-1, a homolog to vertebrate prokineticins, has been shown to increase release of semi-granular cells from the hematopoietic tissue and, in parallel, to increase the number of cells in the neurogenic

niche. In this study, ablation of hematopoietic tissues were done in an attempt to better define the relationship between the hematopoietic system and adult neurogenesis. Only the top most-part of the tissue was removed, leaving a small a10 days post-surgery, Ablated animals had significantly fewer niche cells relative to sham and control animals ($p < 0.005$, and $p < 0.05$ respectively). There were no significant differences in numbers of dividing (BrdU-labeled) cells in the niche, or in the interneuron clusters 9 and 10. Future directions of this work include attempting to determine to what extent, and on what timescale, the hematopoietic tissue regenerates, as well as whether the decrease shown in the numbers of niche cells can be reversed in ablated animals treated with astakine-1.

78. Investigating Oral Nicotine Consumption and Effects on the Estrous Cycle of Female Sprague-Dawley Rats

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Nicotine has long been considered a psychoaddictive substance mainly acquired through cigarettes. This study examined voluntary intake of a concentrated oral nicotine solution using an established multiple-bottle approach (Biondolillo & Pearce, 2007) and evaluated whether consumption of oral nicotine alters the estrous cycle in female rats. *Methods:* Following 10 days of baseline water delivered in 5 bottles in the home cage, female adolescent Sprague-Dawley rats ($n=10$) were presented with 4 bottles of nicotine (20 $\mu\text{g/ml}$) and 1 bottle of water for 16 days; animals in the control group ($n=10$) continued drinking water. Estrous was monitored for 7 days during baseline and 16 days during the exposure period for all rats. Using Differential Interference Contrast microscopy, one of four phases of estrous was determined each day by the type of cells present in the sample (Hubscher, Brooks, & Johnson, 2005; Long & Evans, 1922). *Results:* There were no initial differences observed in fluid consumption during the baseline period, but significantly less water was consumed by animals introduced to nicotine. Animals in the experimental group had an average nicotine consumption of 26.27 ± 0.61 ml. Estrous cycles between animals in both groups were similar. *Conclusions:* Such findings suggest continuous oral nicotine exposure did not readily alter estrous for this duration and concentration of nicotine.

Effects of Increased Oral Nicotine Concentration on Intake by Male and Female Rats

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Previous research on the oral route of nicotine exposure using a multiple bottle approach has shown a proportionality of intake dictated by availability (Biondolillo & Pearce, 2007). Further, when two distinct concentrations of nicotine solution were presented in a multiple configuration preference was given to the lower concentration (Biondolillo, et al., 2009). *Methods:* Experimentally and nicotine naïve adult Sprague-Dawley rats, $N=32$; (16 males; 16 females) served as subjects. A five-bottle method was utilized: one bottle of water, two of 15 g/ml of nicotine solution, and two of 30 g/ml of nicotine solution. During a 2 week baseline period all bottles contained water then oral nicotine was introduced and continuously available to the experimental animals for another 2 weeks. Intake was recorded daily and blood samples were taken 24 hours after initial exposure to nicotine and analyzed for cotinine, the primary metabolite of nicotine, by a competitive Enzyme-Linked Immunosorbent Assay (ELISA). *Results:* Animals in the nicotine group averaged 11.90 ml of daily nicotine intake, which was half of the average daily intake of water. Nicotine intake was further examined by the two solutions, which averaged 5.38 ml of the 15 g/ml and 6.46 ml of the 30

g/ml solution. When converted into mg/kg body weight, two times more nicotine was consumed via the higher concentration. Repeated measures ANOVAs revealed no significant difference between the concentrations measured in ml, but a significant difference in mg/kg. No significant differences in terms of intake between males and females, when controlling for body weight, were found. ELISA results confirmed cotinine in sera of exposed rats. *Conclusions:* Overall, intake for both solutions was far below the levels predicted if availability of the substance was the primary factor for intake, as suggested by previous studies. These concentrations have apparently overridden the influence of availability, yet total consumption for both concentrations was equivalent. Further, ELISA data suggest cotinine was systemically circulated following first-pass hepatic metabolism of nicotine.

79. Ultrasonic Vocalizations as a Behavioral Index of Cocaine-induced Contextual Conditioning for sign-tracking and goal tracking response: Implications for Addiction

Rebeca Kelly

Cues that are associated with drugs can become attractive and elicit consumption by acting as conditional reinforcers. In fact, it has been demonstrated through animal models that in some individuals (sign-trackers, ST), but not others (goal-trackers, GT), reward-associated cues attain incentive motivational properties. It remains to be determined, however, whether variations in the propensity to attribute incentive salience to a discrete localizable cue also predicts the ability of other classes of drug-associated stimuli, such as contextual stimuli, to induce desire for the drug and instigate actions. To address this question, we examined drug-induced ultrasonic vocalizations (USVs) in rats, which are an effective behavioral index for assessing reward-related emotional and motivational states. We asked whether a context previously paired with cocaine administration induces differential production of USVs (conditioned response) in individuals who are more or less sensitive to discrete drug cues (STs versus GTs). Results demonstrated that STs are prone to elicit more positive emotional and motivational responses (Frequency-Modulated 50 kHz USVs) to the drug-paired context than GTs; GTs, in contrast, produced increased aversive responding (22 kHz USVs) to the cocaine-associated environment. Thus, this study provides a foundation for determining which individuals will most likely attribute incentive salience to a drug associated environment and will potentially offer new psychological and neurobiological insight into the underlying mechanisms of addictive disorders.

Keywords: 50 kHz USVs, 22 kHz USVs, drug-paired context, sign-tracker, goal-tracker, addiction

80. Effects of cocaine - associated cues on impulsivity

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Substance abuse is a chronically relapsing disorder. Drug-associated cues are one reliable trigger for relapse. Indeed, presentation of drug-associated cues increases craving in humans and reinstate drug-seeking responses in rodent models. We hypothesize that drug-associated cues contribute to relapse in part because they increase impulsive behavior, or the inability to withhold inappropriate responses. To explore this hypothesis rats were trained on the 5-choice serial reaction time task (5CSRTT) until they attained stable levels of responding. Next, discrete cues (a metronome and a bicycle) were paired with a series of either cocaine (15 mg/kg) or saline (1 ml/kg) treatments using a Pavlovian conditioning paradigm. Following conditioning, performance on the 5CSRTT was restabilized and then the ability of the discrete cues to increase impulsivity was assessed. Contrary to our hypothesis cocaine-treated rats did not exhibit more premature responses (an index of impulsivity) in the presence of the discrete cues compared to in their absence. Further cocaine-treated rats did not exhibit more premature responses compared to saline-treated rats in

the presence of the discrete cues. In order to ensure cocaine cue conditioning was successful, locomotor activity was measured in both the presence and the absence of the discrete cues. Importantly cocaine-treated, but not saline-treated rats, exhibited increased activity in the presence of discrete cues suggesting successful conditioning. Although we demonstrated successful cocaine cue conditioning, we did not demonstrate that drug-associated cues increased impulsive behavior. It is possible that the conditioning was not sufficiently robust to produce an observable increase in impulsive behavior. Unlike the limited number of drug-cue conditioning sessions in the current experiment, human cocaine addicts have innumerable drug-cue pairings prior a drug abstinence period.

Effects of medial PFC lesion on choice behavior in a rodent gambling task

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Cognitive deficits, such as decision-making deficits, are a core feature of schizophrenia. Problematically these deficits can impair the ability of people with schizophrenia to live independently, maintain gainful employment and establish meaningful social relationships. Cognitive deficits are hypothesized to be caused by prefrontal cortex (PFC) dysfunction. Indeed, people with schizophrenia display a similar pattern of choice behavior as people with PFC lesions on the Iowa Gambling Task (IGT). Here, we tested whether PFC lesions would impair performance on an analog of the IGT, the rodent gambling task (rGT). Like the IGT there are 4 response options in the rGT and rats have to make choices based on uncertain outcomes. Each choice option is associated with different reward and punishment outcomes such that two options are relatively advantageous and two options are relatively disadvantageous. Rats were trained on the rGT until performance stabilized and then received an ibotenic acid or sham lesion of the medial PFC. After recovery rats were restabilized on the rGT for 5 days. Because PFC lesions can increase dopaminergic activity in the NAc, choice behavior was assessed following D1 receptor antagonist (SCH23390; 0.0-0.06 mg/kg) or D2 receptor antagonist (haloperidol; 0.0-0.03 mg/kg) administration. During the re-stabilization period there was a trend for lesioned rats to make fewer advantageous choices compared to sham rats; other measures of performance were unaffected. Neither SCH23390 nor haloperidol affected choice behavior in either lesioned or sham rats. Following SCH23390 administration (0.06 mg/kg), lesioned rats omitted more trials and made fewer premature responses than sham rats suggesting these rats were more sensitive to the motor disruptive effects of D1 receptor antagonism. Consistent with our hypothesis, PFC lesions impaired decision-making in the rGT. Neither SCH23390 nor haloperidol reversed this deficit.

81. Investigation of the Effects of Decorin on Neurite Outgrowth by Embryonic Cortical Neurons

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Decorin is a small leucine rich proteoglycan that has been shown to suppress scar formation and promote axon growth at sites of injury to the adult central nervous system (Davies et al 2004). In addition to suppressing scar formation, the Davies lab has also shown that decorin can promote robust increases in neurite growth by adult Dorsal Root Ganglion (DRG) neurons cultured on substrates of axon growth inhibitory chondroitin sulfate proteoglycans (CSPGs) and myelin membranes mixed with laminin (Minor et al., 2008). Laminin and fibronectin are matrix molecules that are both known to be supportive of axon growth, a process which can be dependent on neuronal expression of specific integrin receptors (Tomaselli et al., 1988). Although increased

neurite extension was not observed for decorin treated adult DRG neuron grown for 16 hours on laminin alone (Davies et al., 2004), embryonic DRG neurons but not adult DRG neurons have been shown to be able to increase integrin receptor activity and neurite extension when challenged with mixed CSPG / laminin substrates (Condic et al., 1999). In light of these studies, a question remained therefore as to whether decorin might have a direct effect on embryonic neurons and their ability to extend neurites on laminin and fibronectin substrates. Given the importance of axon growth by cortical neurons in supporting functional recovery after brain and spinal cord injury, the present pilot study will investigate whether decorin treatment can affect specific integrin receptor expression, neurite extension / branching by embryonic E-18 cortical neurons grown on substrates of laminin and fibronectin alone after 24 and 48 hours in culture. Future experiments will also test the effects of decorin on neurite extension and integrin expression by adult cortical neurons grown on laminin and fibronectin substrates.

82. Increased rate of action potential firing may lead to increased neurite length in vitro

Deal A and Lom B

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Neurons are the fundamental cells of the nervous system, and action potentials are the primary mechanism by which neurons propagate information. Communication between neurons occurs across specialized connections called synapses. Well before synapses are formed, developing neurons produce spontaneous action potentials that are critical to the proper development of neurons, as well as axons and dendrites, neuronal projections collectively termed neurites. The purpose of this study was to determine if these spontaneous action potentials play a role in shaping neuronal morphology. Dissociated stage 34 *Xenopus* retinal neurons were cultured for 48 hrs in an environment of increased extracellular K⁺ to depolarize the cells and stimulate an increase in the spontaneous action potential firing rate. After 48 hrs, neurons were fixed and treated with Hoechst to label nuclei and β -tubulin immunostaining to delineate neuronal morphology. Neuronal morphology in control and depolarizing (high K⁺) conditions were analyzed by examining primary neurites, total neurite lengths, and extents of neurite branching from isolated neurons. Preliminary results indicate that an increased rate of firing may lead to an increase in the total length of the neurites without affecting primary neurites or branching. Thus, a neuron's activity may influence how it develops. If an increased firing rate is shown to have a significant effect on neurite development, tetrodotoxin and tetraethylammonium will be used in subsequent experiments to determine how silencing action potentials influences neuronal morphology in vitro. Sigma Xi, NSF, HHMI, and Davidson College provided support for this research.

Flowing culture media slows growth cone extension rates in vitro

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Proper nervous system development requires axons to synapse with targets that are often long distances away from the neuron's soma. Growing axon terminals accomplish this wiring task by extending growth cones to traverse these distances. Growth cones are dynamic structures that extend and rapidly modify their morphology by actively restructuring cytoskeletal proteins in response to molecular guidance cues. Previous work in our lab indicated that fibroblast growth factor-2 (FGF-2), one such guidance cue, does not influence *Xenopus* RGC growth cone extension rates when applied to growth cones extending in stagnant culture media (Healey et al., 2006). Yet, when FGF-2 was applied in flowing media, FGF-2 significantly enhanced growth cone extension rates (McFarlane et al., 1996). Thus, to investigate this discrepancy and determine if hydrodynamic forces influence growth cone extension rates, we directly compared *Xenopus laevis* retinal growth

cone extension rates in stagnant versus flowing conditions using time-lapse microscopy. Growth cones in flowing conditions extended about half as rapidly as growth cones imaged in stagnant conditions ($p < 0.01$). These data indicate that flowing conditions, typically used to allow researchers to deliver and gradually remove soluble factors such as growth factors or pharmacological reagents, slow growth cone extension rates. Thus, hydrodynamic forces may become a potential confounding variable and should be carefully considered in experimental design.

83. Slitrk Expression in the Developing Zebrafish Central Nervous System

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Slitrks are a family of six transmembrane proteins implicated in neurite outgrowth, expressed throughout the central nervous system, and associated with neuropsychiatric diseases (Aruga & Mikoshiba 2003; Beaubien & Cloutier 2009; Pocena et al. 2011). All previous research involving Slitrks has been conducted in mouse models. Zebrafish are an excellent alternative vertebrate model system for examining developmental events such as nervous system wiring because zebrafish embryos are transparent, plentiful, and develop rapidly. In order to understand the roles that Slitrks play in establishing the nervous system, we must first characterize where and when these proteins are expressed in the brain through in situ hybridization, which reveals what cells express a specific mRNA. Thus far we have examined Slitrk2 and Slitrk5 mRNAs on cryostat sections of embryos at 72 hours of development. Although further investigation is necessary, preliminary results reveal differences in the expression patterns of Slitrk2 and Slitrk5 in the midbrain, spinal cord, and eye. Staining in the plexiform layers of the retina suggests Slitrk5 mRNA may be present beyond the nucleus. When all six Slitrk expression patterns are characterized, Slitrk expression will be knocked down to observe how the nervous system develops in the absence of specific Slitrks. We will also investigate the intracellular signaling mechanisms regulated by Slitrks. These future studies will help us to understand how Slitrks influence cell morphology and connectivity. This work is supported by HHMI, Davidson College, and a NSF Research at Undergraduate Institutions Award.

84. The role of oxytocin and vasopressin in the anxiety associated with cocaine withdrawal

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Relapse is a major obstacle in the treatment of cocaine addiction, and a primary trigger of relapse is the anxiety associated with abstinence. The neuroactive nonapeptides, oxytocin and vasopressin, are highly involved in anxiety behavior, and are also influenced by cocaine taking. To investigate the role of these neuropeptides in the anxiety associated with cocaine withdrawal we used an animal model of cocaine addiction, in which rats self-administered cocaine during daily 6 hour sessions. After 14 days of cocaine access and 2 days of withdrawal, anxiety-like behavior was measured using the elevated plus maze. We quantified levels of oxytocin and vasopressin receptors in the extended amygdala of these animals and of saline controls. Our results demonstrate heightened levels of anxiety in our cocaine-exposed animals, and suggest that changes in the receptor levels of these neuropeptides may underlie these behavioral changes.

85. Adolescent circadian changes are caused by estrogen in male rats.

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Human adolescents tend to stay up later and sleep later than adults and children, suggesting that natural increases in sex hormones during puberty result in a change in their daily internal clock (also called the circadian system). Similar changes in circadian rhythms in rest and activity have been observed in numerous species during puberty. Our purpose was to test the hypothesis that sex hormone release during puberty alters circadian rhythms in nocturnal Sprague-Dawley rats. We removed the gonads from male rats (GDX) before puberty to create two testosterone-free groups, one that was later implanted with testosterone and the other implanted with a control cholesterol capsule, the precursor of testosterone, which should not have hormonal effects. Another group received “sham” gonadectomies and then was implanted with cholesterol, acting as the control group. Pubertal development was measured by monitoring secondary-sex characteristics such as preputial opening and body weight, to determine the timing of puberty and when sex hormones are present. We found that circadian rhythms, measured through wheel running activity, showed a phase advance in intact animals and those treated with testosterone supplements, while those without sex hormones (GDX) showed no circadian rhythm changes during the adolescent phase. We then implanted GDX males with testosterone in adulthood and found that the phase advance occurs in animals at any age when testosterone is present. Further, we tested whether testosterone caused the phase advance by binding to the androgen receptor or by being aromatized into estrogen by administering dihydrotestosterone (DHT), a form of testosterone that cannot be aromatized, or estrogen to GDX animals. DHT had no effect on circadian rhythms while estrogen caused the same phase advance as was seen in rats that received testosterone. Therefore, while testosterone drives the phase advance of circadian rhythms in the rat, we believe this is due to its aromatization to estrogen in the brain. To further support our findings, we plan to block aromatization in both male and female rats by injecting an aromatase inhibitor into intact animals. We expect that this treatment will cause the animals to regress to their prepubertal activity patterns.

The Expression of Clock Genes During Puberty in *Octodon degus*

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Across the world, teenagers in all cultures tend to stay up later than children or adults. However, this later timing of sleep may have hormonal underpinnings, correlating with the development of secondary sex characteristics. Pubertal hormones may cause a delay, or later phasing, in the circadian system, also known as the body's internal clock. Previously we found that a diurnal rodent, the *Octodon degus* (degu) also shows a change in circadian phase due to pubertal hormones. The primary goal of this experiment is to discover if clock gene expression in different regions of the brain is altered during puberty. To accomplish this, brains from pubertal and post-pubertal *Octodon degus* (degu) were extracted at different time points across the day and sliced. Radioactive In situ hybridization was utilized to analyze the amount of clock gene expression (Per1 and Per2) at various times of the day using a radioactive probe that binds to the clock gene mRNA in the tissue. The results from the In situ were analyzed using autoradiography, a technique that measures radioactivity using film. The films were analyzed by quantifying the amount of radioactive exposure over the different brain regions such as the suprachiasmatic nucleus, striatum, cingulate cortex, parietal cortex, motor cortex, and piriform cortex. Per1 showed no gene expression rhythms in any of the regions, except the SCN, while Per2 showed rhythms in all regions except the striatum. Interestingly, while Per1 showed no rhythms, the regions analyzed did show higher levels of Per1 gene expression in the cingulate cortex, piriform cortex, and the striatum of pubertal animals than in the post-pubertal animals, except in the SCN. This phenomenon occurred only in the striatum for the Per2 analysis. This suggests that the brain regions that demonstrated a difference in the expression of Per1 may be involved in the phase change that accompanies the onset of puberty, although we did not see a phase change in the clock gene rhythms themselves.

86. AMYGDALAR NMDA RECEPTORS AND DE NOVO PROTEIN SYNTHESIS ARE REQUIRED FOR CONTEXTUAL, BUT NOT TRACE, FEAR CONDITIONING

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Numerous investigations have definitively shown amygdalar involvement in delay cued and contextual fear conditioning. However, much less is known about amygdala contributions to trace cued fear conditioning. A recent report showed that muscimol inactivation of the amygdala had no effect on the acquisition or expression of trace fear memories. Given the surprising nature of this finding, the present experiments further assessed potential contributions of the amygdala to trace fear conditioning using NMDA receptor antagonism and blockade of de novo protein synthesis. Rats were trained using a 10-trial trace or unpaired fear conditioning procedure. Infusion of the NMDA receptor antagonist, APV, prior to conditioning disrupted subsequent contextual fear expression while having no effect on the expression of trace fear memories. In addition, APV infusions made prior to trace fear testing had no effect. In another experiment, infusions of the protein synthesis inhibitor, cyclohexamide, immediately following conditioning attenuated subsequent contextual, but not trace, fear memory expression. These data fully support a role for the amygdala in contextual and delay, but not trace, fear memory and underscore the need for further investigation of the neural circuitry mediating different forms of fear learning.

87. Effects of hippocampal injections of zolpidem on conditioned fear retrieval.

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Benzodiazepines (BZs) enhance the inhibitory effects of gamma-amino butyric acid (GABA) and are renowned for their capacity to induce amnesia. The newer non-BZ agent zolpidem, and other so-called "Z drugs," preferentially target $\alpha 1$ -GABAA receptor subtypes ($\alpha 1$ -GABAARs) and are recognized for their capacity to cause amnesia in both animals and humans. While these past studies have provided important behavioral and pharmacological insights into the role of GABAAR subtypes, little is known about the role of the $\alpha 1$ -GABAAR subtype in regionally defined areas of the central nervous system. Given the prevalent use of zolpidem and other $\alpha 1$ -specific drugs, it is important to understand the function of neural circuits containing $\alpha 1$ -GABAARs. The purpose of this study was to investigate the amnesic effects of zolpidem when injected into a CNS region of the brain which is known to play an important role in memory and contains high levels of $\alpha 1$ -GABAARs: the hippocampus. Preliminary findings suggest that post-training microinjections, of zolpidem into the dorsal and ventral hippocampus of C57/Bl6 mice, have no effect on the subsequent retrieval of conditioned contextual fear; however, fear retrieval was reduced with the non-selective benzodiazepine, chlordiazepoxide. Together these results suggest that activation of $\alpha 1$ -GABAARs into these regions of the hippocampus do not mediate the amnesic effects of zolpidem. The reduction of fear retrieval observed with chlordiazepoxide suggests that other GABAAR subtypes may be involved in the amnesic effects of benzodiazepines.

88. The Role of Oxytocin, Vasopressin, and D-cycloserine in Remediating Social Behavior in Rats with Amygdala Lesions

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Autism is a social disorder that affects social behavior. The causes of this disorder are unknown, genetic factors and neuroendocrine dysfunctions have been proposed. Autism demonstrates a

gender bias and affects males more than females. This gender bias suggests a sexually dimorphic cause for why males are affected more than females. Due to the sexual dimorphism observed in autism, the current study tested the effects of the compounds oxytocin, vasopressin, and D-cycloserine as these drugs have been shown to remediate social behavior. This study observed the administration of using these drugs to facilitate social behavior in animal models of autism. Additionally, oxytocin and vasopressin were selected for their effects on the estrogen and androgen systems, respectively; which will help elucidate potential factors that contribute to the sexual dimorphism observed in autism. On post-natal day (PND) 7, male and female rats received bilateral basolateral amygdala lesions with ibotenic acid. Following weaning, animals received saline, oxytocin, arginine vasopressin, D-cycloserine, or D-cycloserine with oxytocin prior to social testing. Animals were tested for 5 days and the amount of social behavior exhibited by a given rat was recorded. Oxytocin, vasopressin, D-cycloserine, and D-cycloserine combined with oxytocin was shown to facilitate social behavior in both male and female rats. Future areas to investigate would include trials on these compounds as therapeutic agents for social disorders. Additionally, sexually dimorphic treatments should be considered for those with social disorders to increase social behavior.

Clozapine Attenuates Methylphenidate-Induced Conditioned Place Preference

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Methylphenidate, (MPH, Ritalin), is commonly prescribed for the treatment of attention deficit/hyperactivity disorder (ADHD). MPH is similar to cocaine in that it inhibits the dopamine transporter (DAT) to elevate extracellular dopamine levels in the striatum and prefrontal cortex. Further, MPH and cocaine have similar behavioral effects such as acting as reinforcers. As ADHD diagnoses have increased, MPH abuse has increased as well; about 25% of college students abuse MPH. These rewarding properties of MPH increase its potential abuse. There are many similarities between MPH and cocaine and evidence that DA antagonists such as clozapine may be effective in mitigating cocaine abuse. It is hypothesized that clozapine will inhibit the rewarding effects of MPH in a conditioned place preference (CPP) paradigm. CPP testing was used to determine the strength of MPH's rewarding effects with and without clozapine. This was determined by calculating the amount of time spent in the drug-paired compartment, which if over 65% of the time meant there was a conditioned preference for the drug paired environment, suggesting that MPH produces rewarding effects. Analysis of the data showed that the MPH treated group had a significantly stronger conditioned preference compared to saline treated animals. Additionally, it was shown that clozapine inhibited the conditioned preference for the MPH's paired compartment. These results indicate that Clozapine can be used to diminish the rewarding effects of MPH; which could have implications for its use as a treatment for psychostimulant abuse. Future studies analyzing dopamine levels in the striatum and prefrontal cortex would provide evidence of the effect of Clozapine on mesolimbic dopamine systems.

Investigation on Decision Making: Analysis of Clozapine on Rational Choices

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One of the symptoms of schizophrenia is deficits in cognition, such as maladaptive decision making. It has been difficult to find a medication that can treat the cognitive deficits as well as the other symptoms the disorder presents. Clozapine, a common medication for schizophrenia, has been shown to be only marginally effective in treating the cognitive deficits characteristic of the disorder. This is due to antagonist effects on the muscarinic and dopamine receptors which are necessary for

proper cognitive functioning, specifically decision making. This study examined the effectiveness of clozapine in reducing cognitive deficits produced by MK-801 and scopolamine, and thus improve decision making. A pay off probability task examined rats choices between a 4 arm radial maze with arms assigned reward probabilities. The task measured their decision to choose between a higher probability rewarded arm and a lower probability rewarded arm. It was observed that MK-801 and scopolamine produced cognitive deficits, which was observed as the rats choosing the lower probability arm over the higher probability arm. The results also indicated that clozapine didn't influence pharmacologically produced cognitive deficits and caused the rats to choose the low probability arm over the high probability arm more than control condition. Based off these results we can conclude that clozapine's pharmacodynamic properties do not improve decision making or cognition within a pharmacological model of cognitive deficits. Also, other agents that act agonistically to the muscarinic and dopaminergic receptors may be better suited in treating the cognitive deficits exhibited in schizophrenia.

89. Effects of naturally-occurring variation in early-life social environment on neurophysiology and behavior in adulthood

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Lifelong physiological and behavioral differences between genetically similar organisms can result from early-life experience that differentially shapes the course of development. Naturally-occurring variation in levels of early-life maternal care that rat dams direct towards their offspring alters offspring stress-reactivity and may shape a wide range of characteristics in adult offspring. This allows for the study of environment-dependent phenotypic plasticity in the context of normal, undisturbed neurobiological and psychosocial development as it occurs in the laboratory. We bred 40 Long-Evans rats and characterized maternal behavior during postnatal days 1-6 to classify litters as having received high vs. low levels of maternal licking and grooming behavior. For offspring of these "high" and "low" litters we measured anxiety-like behavior, feeding behavior and body weight, social interaction behavior, and ultrasonic vocalizations. Future work will use stored tissue samples to examine neural correlates (oxytocin, vasopressin 1a, and dopamine D1- and D2-like receptors) of early-environment-dependent phenotypic plasticity, and DNA methylation patterns at the glucocorticoid receptor promoter and oxytocin receptor promoter regions.

90. Latent inhibition of a conditioned taste aversion (CTA) in fetal rats is age-dependent

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Conditioned taste aversions (CTAs) may be acquired when an animal consumes a novel taste (Conditioned Stimulus = CS) and then experiences the symptoms of poisoning (Unconditioned Stimulus = US) (Pavlov, 1927; Garcia et al., 1955). When later re-exposed to the CS, the animal will avoid the taste or reduce consummatory oral-facial movements (Grill & Norgren, 1978a,b). In the current studies we sought to determine if a CTA could be diminished by non-reinforced pre-exposure to a CS (i.e., latent inhibition; LI) in fetal rats. We injected E17 or E18 pregnant Sprague-Dawley rats with 100% allicin (pure garlic extract; i.p.) or an equal volume of physiological saline. The taste/smell of garlic has been shown to cross the placental barrier (Gruest et al., 2004) and we were able to measure it (via HPLC) in the amniotic fluid during pilot studies. One day later the pregnant dams received a second injection of the CS, allicin (i.p.) followed by either LiCl (81 mg/kg, i.p.; the US) or a control injection of saline. Forty-eight hours later (either E20 or E21) a spinal block was performed on the dam producing complete abdominal analgesia while pups were removed

(still attached via umbilical cord), and tested in a temperature-controlled isotonic saline bath. Pups received oral lavage with 10 μ l, 0.1% allicin (i.e., similar to the concentration experienced in the amniotic fluid days earlier). Observations of ingestive orofacial motor responses (mouthing and licking) were recorded during the oral lavage of the garlic taste. If allicin had been paired with LiCl *in utero*, E21 fetuses exhibited a conditioned suppression of orofacial movements, indicative of an aversion to this taste (Grill & Norgren, 1978a,b). However, pre-exposure to the garlic taste on E18 produced a latent inhibition of this CTA. Rats one day younger during conditioning (E18) did not exhibit signs of a CTA when they were tested *ex utero* on E20. LI of a CTA is a non-associative form of learning that requires the animal to remember the non-reinforced CS if it is going to be effective in diminishing the CTA acquisition. Thus, our data provide the first demonstration that fetal rats can acquire a LI. Our data also suggest that this ability emerges when pre-exposure to the CS occurs on E18 but not E17.

91. Role of Progesterone Receptors in the Midbrain Dopamine Systems

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The midbrain dopamine systems modulate many essential behavioral functions such as coordination, balance and voluntary movement. Major sites for dopamine production in the midbrain are the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). The SNc, which is a part of the nigrostriatal system, is important for voluntary movement and some cognitive functions. The VTA, together with the nucleus accumbens, is part of the reward circuit. Little is known about hormonal contributions toward the development and function of these areas. Using transgenic male and female mice that lacked functional progesterone receptors (PR knockout mice) and comparing them to wild type (WT) mice, the current project investigated the influence of progesterone and its receptors in the development and/or maintenance of these midbrain dopamine structures. Immunohistochemistry for the rate-limiting dopamine synthetic enzyme, tyrosine hydroxylase (TH), was used to identify dopamine cells in the midbrain. We counted three sections per animal and determined the average number of TH positive cells in the SNc. The mean number of TH positive neurons are greater in knockout (KO) than in WT males ($p < 0.05$). Female KO and WT mice showed no difference in the average of TH positive cells in the SNc. We are currently in the process of conducting cell counts on the VTA as well as a region that is developmentally negative for PR, the zona incerta. The zona incerta has no clear function but is linked to limbic-motor integration. The zona incerta will serve as the control for any global effects of transgenic manipulations we may have in our knockout mouse. We hypothesize that if the zona incerta shows an increase in dopamine cells than progesterone has no factor in the midbrain dopamine systems. The findings from the present study will add to our understanding of how hormones such as progesterone may influence the development and/or maintenance of midbrain dopamine structures.

92. Amyloid precursor protein levels in an estrogen receptor knockout mouse

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Alzheimer's disease (AD) is an irreversible, progressive brain disease that can be caused by several factors, one of which is mutations in the amyloid precursor protein (APP) gene leading to the pathological hallmark of AD, plaques. In other cases, the production or failure in clearance of APP fragments can result in the accumulation that ultimately also causes the formation of the characteristic amyloid plaques. The likelihood of having AD increases substantially after 70 years of age and may affect around 50% of people over the age of 85 years. Interestingly, postmenopausal

women who undergo hormone replacement therapy are less likely to get AD. Furthermore, others have shown that estradiol downregulated APP mRNA levels in both adult and old female mice, indicating that APP is capable of hormonal regulation. Estradiol and other estrogens regulate gene expression through two transcription factor receptors: ER β and ER α . Using immunocytochemistry, the present study examined the levels of APP immunoreactivity in transgenic mice that lack functional ER α compared to their respective wild type (WT) controls. Since the hippocampus and cortex are two brain regions most ravaged by amyloid plaques, we focused our analysis to these regions. Initial observations indicated there were no noticeable differences in APP levels between knockout (KO) and WT mice; however, we are in the process of conducting image analysis to determine if there is a statistically significant difference between the KO and control mice. If estrogen regulates APP protein levels, then we would expect to observe significantly lower levels of APP in WT mice compared to either of the KO mice strains in both the hippocampus and the cortex. Findings from this study can help us better understand how estrogen may affect the production of APP and ultimately contribute toward the prevention of AD.

93. α 2a Adrenergic Receptor Expression in Cultured Cells from the Medulla Oblongata of Neonate Wistar Rats

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The nucleus of the solitary tract (NTS) is one of the main nuclei responsible for orchestrating cardiovascular responses. Cardiovascular regulation are modulated by the neurons and astrocytes found in this region. The α 2a-adrenoceptor (AR) is involved in cardiovascular regulation and is present in both neurons and astrocytes. However, the modulation of astrocytes expressing α 2A-AR remains to be elucidated. In this present study, we analyzed the protein expression of α 2a-AR in 7, 22, and 30 day cultured cells from medulla oblongata by immunoblotting in order to determine if the amount of receptor changes in cell cultures of different ages. Data showed increase of α 2A-AR expression in the older cell cultures. These results suggest the expression of α 2A-AR is optimized with 30-day cell culture. The variation in the amount of the receptor found could be related to several factors, such the maturation of the cells or in the proportion of neurons to astrocytes. Supported by 5T37MD001378-11 (MECF)

94. Psychophysical and Electrophysiological Brain Responses to Speech Sounds Across Development: Native Language Experience Shapes Perception

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Native-language neural commitment theory poses that neural networks become more efficient at processing native language patterns, interfering with the learning of foreign languages. The present study investigated the role of language experience in shaping sensitivity to native and non-native speech sounds by examining psychophysical and electrophysiological measures in a Chinese-English cross-language design. Adult native English speakers and native Chinese speakers were asked to discriminate native and non-native phonetic contrasts on an English 10-level continuum and a Chinese 11-level continuum. Native English speakers (n=19) reliably discriminated English contrasts ($p < 0.01$), but performed at chance when asked to discriminate Chinese contrasts. Conversely, Chinese speakers were able to reliably discriminate Chinese contrasts. Given their validity to measure perceptual sensitivity at the behavioral level, the same phonetic contrasts were used in a mismatch negativity (MMN) paradigm examining the pre-attentive event-related potential (ERP) response to deviant auditory stimuli that has been used as an index of expertise in speech

perception. Preliminary analyses of the topography of the MMN show the predicted strong left-lateralized response to native phonetic contrasts for both English and Chinese speakers, but not to non-native contrasts, indicating that native contrasts activate the brain hemisphere specialized for language processing.

The Role of Reinforcement Learning in Controlled Retrieval

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Dopamine projections to the striatum and frontal cortex play an important role in behavior modulated by reward. Unpredicted rewards trigger the phasic response of dopamine neurons, whereas predicted rewards that fail to arrive inhibit these neurons below baseline rates, and rewards that match the prediction do not affect the firing rate. In this study, we focus on reward maximizing behavior in humans as modeled by Reinforcement Learning (RL). After shallow encoding of concrete nouns, participants (12 18-35 year olds, 6 females) performed an unforewarned computer-based memory test. They were presented with an equal amount of new and previously seen concrete nouns, one at a time. We sought to alter recognition memory discernment by probabilistically giving inaccurate positive feedback for either misses or false alarms, reinforcing 'new' and 'old' decisions, respectively. False positive feedback biased participants' future choices, shifting their decision criteria from neutral toward the reinforced condition. These findings suggest that people can exploit environmental cues to guide decision-making, without being aware of it.

95. Δ 9-THC Reduces Connectivity Between Default Mode Network Regions During Non-Task Periods Within an Emotion Task

Yasmin Zakiniaieiz

Neuroimaging has identified a network of interacting brain regions - PCC, IPL and vmPFC - coactivated at rest. This default mode network (DMN) shows greater activity during rest than during cognitive tasks. Cannabinoids such as marijuana have been shown to modulate neural network function. However, the effects of marijuana on DMN connectivity are unknown. We expected modulation in DMN activation during non-task due to the affective and cognitive effects of Δ 9-tetrahydrocannabinol (Δ 9-THC), which may enhance focus on internal tasks such as memory retrieval and future envisioning. Fifteen healthy right-handed adult mild cannabis users underwent fMRI imaging following administration of Δ 9-THC and placebo while viewing pleasant, unpleasant, and neutral pictures from the IAPS ("task") interspersed with nonemotional pixelated pictures ("non-task"). Activity in PCC and IPL was greater in non-task conditions. There was no main effect of drug. PPI analysis using a PCC seed revealed connectivity between the three regions of the DMN. Greater PCC connectivity with vmPFC was found when subjects were on placebo than Δ 9-THC ($p=0.008$), indicating that Δ 9-THC may reduce connectivity between regions of the DMN. These findings provide further understanding of the effects of THC on emotion processing which may have implications for brain changes in drug addiction.

Tracking the Eyes of the Beholder: Temperament differences in scanning patterns of faces

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While people with uninhibited temperament (UT) are adventurous and outgoing, and tend to respond to novelty with approach behavior, people with inhibited temperament (IT) often respond

to novel people with wariness or avoidance. We used eye tracking to investigate the scanning patterns of novel faces employed by IT and UT participants. We hypothesized that people with IT would demonstrate hypervigilance toward the eye region, which carries emotional salience, while people with UT would process faces holistically. During the familiarization phase, we exposed participants to sets of faces one, three, five, or seven times. During the testing phase, participants were shown the familiarized faces and an equal number of novel faces and were asked to determine whether or not they had previously seen each face. While both groups demonstrated similar recognition accuracy for faces which had been seen once or seven times, people with IT showed impaired recognition of faces which had been seen three or five times. The IT group showed hypervigilance toward the eye region, while the while UT group demonstrated a more inclusive facial scanning pattern. It is therefore possible that hypervigilance towards the eye region, employed by IT people, translates into less effective mechanisms for remembering faces.

96. Pursuit of the Model Mouse: Behavioral Studies of Autism-Associated SERT Ala56 Knock-In Mice

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Autism spectrum disorder (ASD) is a heritable condition characterized by abnormal social behavior, restricted repetitive behavior, and communication deficiencies. We examined a Serotonin Transporter Gene (SERT) Gly56Ala knock-in mouse, the same genetic mutation associated with autism in humans, to better understand the causes and characteristics of these changed behavioral domains. Behavioral assays were performed on 16 mutated and 20 wild type mice to observe differences. The tube test for dominance (in which two mice enter two sides of a tight tube and eventually one backs out, with the mouse left in the tube declared the winner) was used to test for abnormalities in social behavior between the two genotypes. Preliminary data shows a significant amount of wins ($p < .01$) for the wildtype mice compared to the mutant mice, representing abnormal social behavior in the mutant mice. Future studies will extend to other measures of social, communication, and repetitive behavior, as well as compare behavior in male and female mice. Further, we hope to identify changes in brain regions that underlie the observed behaviors. We hope that this genetic mouse model will allow us to better understand the causes of ASD and to potentially develop novel treatments.

Behavioral study of fear and its implications on skin conductance recordings

Daanish Chawala

We conducted a study using a within-subjects design, coupling a standard Pavlovian fear extinction paradigm and simultaneous skin conductance response (SCR) recording in 10 healthy adult volunteers and tested extinction retention 24 hours after extinction learning. During fear acquisition subjects were presented with three different colored squares (conditioned stimulus, CS) and two of the squares (CS+s) were paired with an aversive noise burst (unconditioned stimulus, US), while the third square (CS-) was never paired with the US. Subjects showed an increase in SCR to the CS+s and maintained low SCR levels to the CS-. Twenty-four hours after fear conditioning, one CS+ was extinguished (CS+E) while the other CS+ was not (CS+U). At the beginning of the extinction session subjects showed high SCR, indicative of successful fear conditioning from the previous day, but over the course of the extinction session SCR levels gradually decreased to the CS+E. Twenty-four hours after fear extinction, subjects repeatedly presented with the CS+E and CS+U in the absence of the US to assess success of extinction recall on SCR. Subjects showed lower

SCR to the CS+E than compared to the CS+U, suggesting that successful within-session extinction was successfully maintained 24 hours after extinction learning.

97. Development of functional measures in a guinea pig model of spinal cord injury

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Researchers using the guinea pig model of spinal cord injury (SCI) have previously used rudimentary functional measures such as the placing and toespread responses and the *cutaneus trunci* muscle reflex (Blight et al., 1990; Blight, 1994; Blight et al., 1995; Yates et al., 2007). The limitations of these measures include a ceiling effect and insufficient sensitivity that may hide functional improvements and treatment differences. Several measures that have previously been used in rat spinal cord injury studies were tested in the guinea pig model including air righting behavior (Pellis et al., 1996; Wayner et al., 2000) contact righting behavior (Bouet et al., 2004), open field activity and the incline plane apparatus. Preliminary results show injury severity-dependent changes in function for air and contact righting but not open field activity. Inter-rater reliability is also high in the air and contact righting measures. Testing of the incline plane apparatus (Fehlings & Tator, 1995) is ongoing, Testing includes the ability of animals to perform the behavior as well as whether the measure is able to distinguish injury severity and recovery progress.

98. A magnetoencephalographic study of depth perception

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Monocular depth perception relies on a number of visual cues, some of which are based on motion. We were interested in whether depth information generated from moving and non-moving stimuli are processed differently in the brain. Specifically, we hypothesized that depth information derived from motion would be generated in a bottom-up manner (with brain activity associated with depth in this case appearing first earlier in the visual hierarchy), whereas depth information derived from static pictorial cues would be processed first later in the visual hierarchy, i.e. top down. To test this hypothesis, we presented subjects with displays that specified three levels of depth (no depth, medium depth, high depth), using one of five different visual cues: three pictorial (static) depth cues and two motion-based depth cues. We recorded the subjects' brain activity using a 248-channel axial gradiometer MEG system while they passively viewed these stimuli. To determine the time course of depth information embedded in neural activity, we first divided the MEG sensors into groups. A simple method of dividing the sensors is separate them into two groups: anterior and posterior. This grouping puts sensors over early visual areas (occipital and early parietal) in the posterior group, and sensors over later visual areas (anterior temporal and frontal) in the anterior group. (Other grouping schemes were also used, with little change to the results.) We then used linear discriminant analysis to decode the depth status of each of the stimulus presentations, in 100 ms bins, moving every 10 ms through the trial. We noted the time at which this analysis could successfully classify depth status of a trial's stimulus at levels above chance, and compared the time of first significance across sensor groups. We found that, in both motion- and non-motion- based cues, depth information was first seen in earlier visual areas than later visual areas. This suggests that in pictorial cues, depth information is processed in parallel with object identity information.

99. Anxiogenic Effects of Cocaine Withdrawal in Rats

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Drug addiction is a chronic relapsing disorder associated with compulsive drug taking behavior and the subsequent impairment of social and occupational functioning. In individuals with a compulsive substance abuse disorder, drug relapse is hypothesized to be motivated by an aversive affective state that increases the probability that an addict will seek out substances of abuse in order to temporarily remove unpleasant feelings associated with withdrawal. In this study, the transition to compulsive cocaine abuse was modeled using rats on extended access, cocaine self-administration. Subjects exhibited an escalation in drug taking behavior as the trials progressed. In particular, an escalation in the amount of cocaine infusions was found in the first hour of self-administration trials. Following acute withdrawal, anxiety-like behavior was measured in the subjects using the elevated plus maze. Behavioral measures indicate a statistically significant increase in anxiety-like behavior among subjects undergoing withdrawal from cocaine compared to control subjects.

100. Site-directed metabolic biotinylation of AMPA receptors may perturb protein-protein interactions with TARPs

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AMPA receptors are glutamate-gated ion channels that mediate fast excitatory synaptic responses. AMPA receptor expression is regulated by stargazin, a transmembrane AMPA receptor regulatory protein (TARP). The goal of the present study is to probe the quaternary structure of AMPA receptor-TARP complexes at the plasma membrane. We hypothesized that biotin acceptor domains (BADs), expressed as cassettes of 32 amino acids that include the 17 amino acid BAD motif and a flexible glycine/alanine linker, could be inserted at putative sites of interaction in rat GluA2, and that subsequent biotinylation of these sites might sterically block functional interactions between GluA2 and stargazin (γ -2) protein. The sites at which BADs were inserted (GluA2-BAD mutants) include parts of the receptor that lie directly above, below and within the transmembrane helices. GluA2-BAD mutants were transiently transfected into HEK 293 cells with and without stargazin and viewed using confocal fluorescence microscopy. We found that GluA2-BAD mutants were efficiently expressed in HEK 293 cells, suggesting that the insertions alone did not significantly impair receptor trafficking or function. Specifically, expression of GluA2-BAD MKV (an insertion below the M4 transmembrane domain) led to predominantly intracellular localization of the protein, similar to the wild type receptor, and co-expression of GluA2-BAD MKV with stargazin resulted in efficient trafficking of the mutant receptor to the plasma membrane, similar to wild type receptor. Our results demonstrate that insertion of the biotin acceptor domain itself at this site is not enough to prevent association with stargazin. Ongoing experiments will include a functional analysis of GluA2-BAD MKV using patch clamp electrophysiology, as well as the testing of other GluA2-BAD mutants that we have constructed. These experiments will lead to a better understanding of how the activity-dependent association of GluA2 with auxiliary proteins impact AMPA receptor synaptic physiology. This research is supported by NIH R01MH06674.

101. Determining the Fate of Dorsal Root Ganglion Cells in the Absence of Functional Neurogenin 1

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The cells of the dorsal root ganglia (DRG) are generated during embryogenesis from neural crest cells, which migrate, condense, and differentiate into different types of neurons and glia. This process begins with neural fate determination, during which neural crest progenitor cells develop into either glial or neural progenitors. After this has occurred, neural progenitor cells undergo neural subtype specification to give rise to distinct neuronal subtypes. Prior research has shown that the basic helix-loop-helix transcription factor neurogenin1 (*ngn1*) is required for the development of one subtype of neuron, the *trkA*-expressing pain-sensing neurons, in the DRG (Ma et al., 1999, *Genes Dev.* 13:1717-1728). It is not clear, however, whether *ngn1* function is required for neural fate determination or for neural subtype specification in this tissue. *Mash1*, another basic helix-loop-helix transcription factor that is homologous to *ngn1*, has been shown to be involved in neural fate determination in the olfactory epithelium (Murray et al., 2003, *J. Neurosci.* 23:1769-1780) so we hypothesize that *ngn1* is involved in neural fate determination in the DRG. To test this hypothesis, we are examining the fate of progenitor cells in the DRG in the absence of functional *ngn1*. If *ngn1* is involved in neural fate determination, we would expect to see an increase in the proportion of glial or progenitor cells combined with a decrease in neural cells in *ngn1* knockout embryos. We have examined the expression of the neural markers *trkA*, *trkB* and *trkC* and have confirmed a specific loss of *trkA*-expressing neurons in the absence of *ngn1*. We have seen an increase in the expression of the glial progenitor marker *P0* and in the expression of *Sox9*, a gene expressed in neural crest progenitors as well as in glial cells. We did not detect a change in the expression of the neural crest progenitor cell markers *nCAD* or *ITGA-4*. Our data suggest that there may be a decrease in the number of *trkA*-expressing neurons, an increase in the number of glial cells, and no change in the number of progenitor cells in the DRG of *ngn1* knockout embryos which is consistent with our hypothesis that *ngn1* is involved in neural fate determination in the DRG. Supported by NIH Grant # P20 RR-16460 from the IDeA Networks of Biomedical Research Excellence (INBRE) Program of the National Center for Research Resources.

102. A Conditional Lineage Tracing Approach to Identify the Role of Neurogenin1 in Dorsal Root Ganglia Neurogenesis

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The neurons of the dorsal root ganglia (DRG), that are responsible for sensory input to the nervous system, arise from neural crest progenitor cells that migrate from the dorsal aspect of the neural tube during embryonic development. When neural crest cells reach the DRG, they divide and give rise to the different types of sensory neurons as well as the glial cells that make up this tissue. It is thought that the development of these cells involves two decisions; first the cells decide whether to become neurons or glia (neural fate determination), then those that have committed to become neurons decide what type of neuron to become (neural subtype specification). We know that the neurogenin1 gene is involved in this decision making process because mouse embryos lacking the neurogenin1 gene are missing one subtype of neuron in the DRG; the pain-sensing nociceptive neurons (Ma et al., 1999, *Genes Dev.* 13:1717-1728). While the loss of one specific subtype of neuron in the DRG of neurogenin1 knockout mice seems to imply a role for this gene in neural subtype specification, it is also possible that neurogenin1 is involved in neural fate determination of one type of progenitor cell that specifically gives rise to this subtype of neuron. Based on its homology to *Mash1*, a gene involved in neural fate determination in the olfactory epithelium (Murray et al., 2003, *J. Neurosci.* 23: 1769-1780), we hypothesize that neurogenin1 is involved in neural fate determination in the DRG. To test this hypothesis, we have used a conditional lineage tracing approach to label embryonic cells expressing neurogenin1 so that we can identify the progeny of these cells later in development. If neurogenin1 is involved in neural fate determination

instead of neural subtype specification, we might expect to find glial cells that are derived from neurogenin1 expressing progenitor cells. To conditionally label neurogenin1 expressing cells we have bred transgenic mice expressing a Cre-ER recombinase under the control of neurogenin1 regulatory elements to reporter mice that can be induced to express the betagalactosidase reporter gene upon induction of the Cre-ER recombinase. Induction of the Cre-ER recombinase is determined by the injection of a hormone at a particular developmental time and results in the genetic labeling of neurogenin1 expressing cells and all of their progeny. We have been able to detect expression of the reporter gene in the progeny of neurogenin1 expressing progenitors and are currently performing double-labeling techniques to determine the identity of these cells.

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103. Tracking intracellular Htt inclusion formation using FIAsh labeling

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disease. It derives from a CAG repeat expansion in the huntingtin (Htt) gene that causes an elongated polyglutamine tract in the Htt protein. HD patients exhibit progressive personality changes, a characteristic movement disorder, and dementia that generally progress over about 20 years. Much evidence suggests that the polyglutamine expansion in Htt causes the protein to misfold, aggregate, and become neurotoxic. It has been difficult to quantify Htt aggregation in cells and in vitro. The biarsenical reagent FIAsh-EDT2 fluoresces when bound to recombinant proteins containing a short tetracysteine motif, and is otherwise not fluorescent. We constructed Htt proteins with a Cys-Cys-Gly-Gly motif attached to the N- or C-termini to test whether Htt aggregates would reconstitute the tetracysteine motif, coordinate FIAsh-EDT2, and produce fluorescence. We found that it was possible to track intracellular Htt inclusion formation using FIAsh labeling. Wild-type Htt protein, which does not aggregate, did not produce fluorescent signal. This method could be very useful to quantify Htt aggregation in cells and in vitro.

104. Changes in synaptic efficiency in the guinea pig intrinsic cardiac plexus: Effects of acute myocardial infarction and neuromodulators.

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Chronic heart disease has been shown to induce both phenotypic and functional remodeling of neurons within the intrinsic cardiac plexus of the guinea pig. The current study examined the time scale of this remodeling process, looking specifically at changes in synaptic efficiency at different time points following surgically-induced heart disease. Heart disease can be surgically-induced in the guinea pig to model myocardial infarction (MI) by ligation of the coronary artery and dorsal vein on the heart leaving an ischemic area on the surface of the ventricle. Fifteen male Hartley guinea pigs (Charles River) weighing between 300 and 500 grams were given myocardial infarctions and allowed to recover for either 4, 7, or 14 days. Nine animals, with no surgery, were used as controls. Animals were euthanized via CO₂ inhalation and exsanguination. The heart and lungs were removed and the heart was dissected to expose the intrinsic cardiac plexus as a whole mount preparation for intracellular voltage recordings. An extracellular focal electrode was placed on nerve bundles connecting to the individual neuron used for recording. Fibers were stimulated with suprathreshold stimuli for 2 seconds at a frequency of 10, 20, or 30Hz and the number of

action potentials produced by the postsynaptic cells was determined. Previous studies found that animals with chronic MI (6 week recovery) show no difference in frequency output compared to control animals. Conversely, in the acute MI studies, the 7 day recovery animals showed a significant increase in frequency output ($p < 0.002$ at 30Hz) that was not seen at either 4 or 14 days post MI. Previous studies also demonstrated that several neuromodulators, such as norepinephrine (NE), PACAP27 (P27), and substance P (SP), increase neuronal excitability in these cells. Therefore the ability of these substances to increase frequency output with fiber tract stimulation (FTS) was tested. NE (Sigma, 10-3M), P27 (American Peptide, 10-5M), and SP (American Peptide, 10-4M) were applied by local pressure ejection to individual neurons. FTS (20Hz) was tested in with and without the application of either NE, P27, or SP. In both control and all three acute recovery time points, there was no significant differences in output frequency with neuromodulator application. This suggests that the increased excitability seen with disease at 7 days post MI is not due to enhanced adrenergic or neuropeptide release, but rather to an as yet, undetermined mechanism. Supported by NIH HL098589 to JCH.

105. The role of neuropeptides in cocaine withdrawal associated anxiety

Sonam Bhimbra, Catherine Claro, Ronald See, R Parrish Waters

Cocaine addiction prompts a variety of adverse effects on to the human body and brain and the resumption of cocaine use often alleviates these symptoms. In particular, anxiety levels tend to be a significant issue that develops with cocaine addiction. Multiple neuropeptides, such as neuropeptide Y (NPY), vasopressin (AVP) and oxytocin (OT) act in brain regions associated with mood disorders and stress response to influence levels of anxiety. The goal of this study is to investigate the role of NPY, AVP, and OT in changes that occur in the brain during withdrawal from cocaine use. We investigated this relationship using an animal model of cocaine self-administration. Animals self-administered cocaine in 6 hour sessions for 14 days. Following 2 days of abstinence we measured anxiety using the elevated plus-maze, and measured levels of NPY, AVP and OT in the extended amygdala a commercially available ELISA kit. Preliminary evidence suggests that acute cocaine withdrawal increases anxiety levels, and that changes in levels of these neuropeptides may influence this behavioral effect.

Cocaine Self-Administration Modulates Vasopressin Receptors in the Extended Amygdala

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Relapse is a major obstacle in the treatment of cocaine addiction, and a major contributor to relapse is the anxiety associated with abstinence from cocaine. Vasopressin is a neurotransmitter that is highly involved in anxiety, and evidence suggests that it could play a central role in the anxiety associated with cocaine withdrawal through activation of stress related brain centers. To investigate this possibility we used rats trained to self administer cocaine to study behavioral and physiological changes during cocaine addiction and withdrawal. We analyzed levels of vasopressin and vasopressin receptors in the brains of the animals using the immunohistochemical method of protein detection. These levels were compared to those of control animals that self administered saline. Data collection is ongoing, and we have detected increased anxiety levels in animals that self administered cocaine. Preliminary evidence suggests a modulation of vasopressin receptors in the brain regions that mediate anxiety, such as the amygdala, BNST, and nucleus accumbens.

106. **Anti-Epileptic Drugs and Seizure Severity in *bss¹* and *sda* *Drosophila***

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FACES; Facts, Advocacy, and Control of Epileptic Seizures began as a non-profit organization dedicated to epilepsy outreach with the goal of erasing any negative misconceptions and providing direct assistance to people of all ages living with epilepsy. FACES also has a lab component entirely run by undergraduate students. Through the use of bang sensitive (*Bss¹*) and slamdance (*sda*) *Drosophila*, the FACES lab is investigating the neural mechanisms of commonly prescribed anti-epileptic drugs with a special focus on Lamictal (Lamotrigine) and Keppra XR (Levetiracetam). Each drug is administered to *Drosophila* at different dosages beginning at 0.015 mg/ml and increasing at ten fold increments until a maximum dosage of 1.0 mg/ml is reached. *Drosophila* are exposed to the anti-epileptic drugs for five days, during which they are tested for once for seizure sensitivity through vortex at intervals of ten seconds. Flies are then allowed to reproduce and grow from the larval stage on the same medication medium. The F2 generation is then tested for seizure susceptibility in the exact same manner. Susceptibility to seizures, severity, and duration of paralysis and seizure activity were measured at 15-second intervals until each fly had recovered. Complete recovery was described as resuming negative geotaxis behavior. Type of seizure behavior was also recorded, which primarily included isolated leg shaking and helicopter behavior. In the F1 generation, both *bss¹* and *sda* *Drosophila* displayed a significant reduction in each parameter of seizure behavior measured after three days on Keppra XR. Both *bss¹* and *sda* flies also showed greatest improvement on the third day of exposure to Lamictal, although not to the same extent. With each drug, the best dosage for treatment was found to be 0.15 mg/ml across each day of the study. In the F2 generation, both *bss¹* and *sda* flies responded better to Keppra than Lamictal. For each day and on each medication, seizure behavior was reduced across all parameters to a significantly greater extent than the F1 generation. Both *bss¹* and *sda* flies respond positively to the human AEDs Keppra and Lamictal. Future tests will include administration of alternate anti-epileptic drugs.

107. **The cell signaling response to ER stress in oligodendrocytes.**

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The elevated rates of lipid and protein synthesis required for the establishment of a functional myelin sheath make oligodendrocytes particularly sensitive to disruptions in the endoplasmic reticulum (ER). Myelin pathologies display accumulation of unfolded proteins that may arise, in part, from failure to adapt to ER stress, but the cellular signaling mechanisms that mediate the adaptive response to ER stress in oligodendrocytes are not fully characterized. mTOR, a serine/threonine protein kinase that is part of the PI3K/AKT signaling pathway, controls rates of protein translation and cytoskeletal dynamics in response to growth factors and to amino acid and energy levels. We recently demonstrated that disruption of the PI3K/Akt/mTOR signaling with rapamycin (an mTOR inhibitor), does not interfere with terminal differentiation of oligodendrocytes but impedes their morphological and biochemical maturation. Here we investigate the activity of Akt and mTOR signaling in response to the ER stressors thapsigargin (TG, 100 nM), tunicamycin (TU, 2 ug/mL) and dithiotreitol (DTT, 200 uM) in oligodendrocyte progenitors (OLPs) and mature oligodendrocytes (MOLs). We found that the cellular viability of OLPs, but not MOLs, is decreased by TG, TU and DTT in a dose-dependent manner. In OLPs, pre-

treatment with FGF2 prevents this loss in cell viability. We analyzed the phosphorylation state of AKT and mTOR in protein lysates from OLP cultures after a 3 hour exposure to TG, TU and DTT. We found an elevation in levels of pAKT(T308) in response to ER stressors TG and TU. This suggests that the PI3K/Akt/mTOR signaling system is part of the cellular response to ER stress that regulates the function of the ER in pre-myelinating oligodendrocytes.

108. Are rats able to solve shape discriminations on a spatial vs. non-spatial touch screen task?

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In this study, we explored what mechanisms control our ability to learn sequentially and how that directs the behaviors that follow. For this experiment, we used 8 male Long-Evans hooded rats (*Rattus norvegicus*). With these subjects, we observed if rats were capable of retaining an 8-item sequence based off of shape or if they retain the order of a sequence based off of spatial learning alone. Previous studies showed that it was hard to tell if a rat was simply learning a pattern of movements or abstractly solving a problem in real-time. Half of our rats experienced only spatial (fixed) cues and the other half received non-spatial (randomized) cues, all set on a touch screen. Our preliminary results indicate that there was an initial significant difference in acquisition of the pattern between our rat groups, though this difference was not apparent after the first five blocks of data. Therefore, our results suggest that it does not matter if rats are presented the same pattern in a fixed spatial or more randomized non-spatial pattern in their ability to perform this task. Further implications and planned follow-up studies will be discussed.

109. Evaluating student learning gains from illustration of course concepts in 2D and 3D online collaborative environments

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Explaining complex cellular phenomena in lecture format is a challenge for neuroscience educators. Students are also challenged to express their understanding of course concepts, and receive feedback, primarily through text-based assessments. In an undergraduate neuroscience course, we are evaluating how learning is affected when groups of students construct visual explanations of course concepts in two-dimensional (2D) and three-dimensional (3D) online collaborative environments. Working in teams of four, students spend 45 minutes constructing a summary figure that visually communicates the principal findings of a given research article. Using either Google Documents Drawing (2D) or Open Cobalt (3D), members of each team simultaneously edit the same summary figure and are then given 5 minutes to use that figure to present the research findings to the rest of the class. Each of these presentations is immediately followed by an objective assessment of concept understanding and a subjective Student Assessment of Learning Gains survey (Seymour 2000). The objective assessment is a short answer question requiring higher-order application of course concepts. The subjective assessment asks students to report on their progress towards achieving both lower-order (*knowledge, comprehension*) and higher-order (*analyzing, hypothesizing and designing experiments*) learning objectives. Exercises are administered at the conclusion of the instructional week with each program being used for 3 consecutive exercises. At the outset of the study, students also completed an Index of Learning Styles survey (Felder and Soloman 1991) to assess learning preference along four dimensions (active / reflective; sensing / intuitive; visual / verbal; and global / sequential). All surveys are administered on a computer and coded to protect student identity. We expect the results of this

study to provide quantification of how collaborative illustration of course concepts in both 2D and 3D formats affects students learning. Additionally, this study allows for analysis of how learning preference may interact with the format of instructional media. Additional study content and resources for classroom implementation are available at: <http://dibs.duke.edu/education/innovation>

Reproducibility of Functional Connectivity in Normal and Diseased Populations

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Alzheimer's disease is a degenerative disease that affects neuronal networks and cognitive processes. Understanding the complex dynamics of these brain systems and how those are affected by disease may provide new insights into mechanisms and help develop new diagnostic tests. Functional connectivity MRI (fcMRI) provides a tool to study functionally connected brain networks. In this pilot study, we calculated whole brain connectivity for 66 subjects using fMRI data taken during an active encoding performance task. Subjects were divided into four groups, Alzheimer's disease (AD), MCI-convertors (MCI-c), MCI-stable (MCI-s), and healthy cognitive status (ONS) After preprocessing of fMRI data, whole brain connectivity was defined by correlation and covariance data matrices for each of the three runs in every subject. One of the focuses of this study was to ascertain reproducibility of functional connectivity from run to run in an ONS individual and between subjects. With alpha level at 0.05, intra-subject comparisons in the ONS group produced more reproducible results as apposed to inter-subject, as expected. Another goal was to determine the reliability of two different methods of functional connectivity measurement: correlation and covariance. In both intra and inter-subject comparisons, correlation results were significantly different than covariance. In inter-subject, correlation was the more reproducible statistic while for intra-subject, covariance was. The last focus was on the affects of disease on a brain's inherent networks. All categories exhibited the disruptive effect of disease; patients with AD looked less like each other, and even themselves from run to run, in terms of whole brain connectivity as compared to people with no disease symptoms. The most significant downward trend occurred in inter-subject comparisons of connectivity defined by correlation. Our results provide some insight into the extent of variability of whole-brain connectivity measures in relation to presence or absence of neuronal disease. Because prior studies have shown that people with incipient AD have greater intra-subject test-retest variability in their cognitive scores, the extent of intra-subject fcMRI variability might also prove to be a surrogate marker of neural disconnection. Clearly this is a pilot study. Our data also suggests that further improvements in fcMRI techniques might be warranted to reduce variability within normal subjects so that the test can be better used to study brain disease.

110. Evaluating Social Judgments in Capuchin Monkeys

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The ability to distinguish between helpful and unhelpful individuals is an essential skill for all social animals. Individuals living in complex social groups have to frequently and quickly make social judgments about others; however, it is unclear how these social evaluation skills develop and whether or not they are unique to humans. Studies have shown that human infants as young as 6 months prefer helpful individuals over hindering individuals, possibly showing the presence of innate social preferences in humans. We are investigating whether these social skills are exclusive

to humans or whether they are also found in other primates. Brown capuchins (*Cebus apella*) are New World monkeys that live in complex social groups, suggesting that social skills are essential for survival in this species. We hypothesize that capuchin monkeys, similarly to human infants, are able to socially evaluate the actions of others and will preferentially distinguish helping individuals from hindering individuals. Using eyetracking technology, we will examine the looking times of both humans (young adults and infants) and capuchins while they observe videos of social scenarios. We will use looking time as an indicator of preference. To date we have collected preliminary data from the young adults and human infants and are training the capuchins to fixate on the eye-tracking monitor. If humans look preferentially at the helping individual, it would further support the assertion that humans have social preferences. Additionally, if capuchins reveal a preference for the helping individual, this would indicate that the ability to socially evaluate individuals is not exclusive to humans.

Estrogen Regulated Secretion of Neuroprotective Factors in Astrocytes

Claire Gerall, James Roberts, PhD

The symptoms of Parkinson's disease are caused by a lack of dopamine resulting from neurodegeneration of dopaminergic neurons in the midbrain. It has been proven that estrogen provides neuroprotection for these dopaminergic neurons, mediated in part through the astroglia which surround all neurons. Preliminary studies from our lab suggested that the estrogen causes astrocytes to release a neuroprotective factor. This study has biochemically characterized the factor(s) in the 3000 to 30,000 Dalton range produced and secreted from the astroglia in control and in response to 100nM 17 β estradiol treatment. Comparison of the secretory pattern of young and old astrocytes has also been investigated. The astroglia used were prepared from midbrains dissected from day 4 neonates and 12 month old rats, and are grown in tissue culture. Mass Spec analysis of the secreted proteins done in conjunction with our collaborators at Rosalind Franklin University in North Chicago has identified novel growth factors in the secreted proteins as well as antioxidant enzymes. (supported by Trinity University HHMI Summer Research Program)

111. Studies of Non Human Primate Behavioral Biology

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Histology of the Corpus Callosum in Non Human Primates

We are examining the histological organization of the corpus callosum from post-mortem tissue in several nonhuman primate species (including pigtail monkeys, squirrel monkeys, chimpanzees and capuchin monkeys). In humans, analysis of post-mortem brain tissue indicates that small-diameter (< 2 μ m), lightly myelinated fibers are found mainly in the genu and splenium and connect higher-association areas, whereas large-diameter fibers (> 2 μ m) are predominant in the body of the CC and isthmus and connect primarily motor and somatosensory areas. Postmortem samples were imaged using transmission electron microscopy (TEM). TEM was used to map out the axons of the CC, specifically within the 5 subregions of the CC: genu, anterior midbody, medial midbody, posterior midbody and splenium. Axon diameter of the images of post-mortem CC samples were analyzed using NIH Image J. Analysis of the pigtail CC is currently underway and analysis on other nonhuman postmortem tissue samples will continue. We will determine the proportion of small and large diameter axon fibers in each subregion of the CC and possibly be able to see a similarity to the organization seen in humans.

Resting-state Networks in Brown Capuchins

Recent functional magnetic resonance imaging (fMRI) studies have isolated multiple Resting-state

Networks (RSNs). RSNs are reliably identifiable networks of spontaneous brain activity that have been observed in humans as well as nonhuman primates such as macaques. The current study is the first to characterize RSNs in a New World primate species, brown capuchins (*Cebus apella*). Resting-state fMRI data were collected from 7 anesthetized subjects whose ages ranged from birth to adulthood. Each subject contributed multiple thirty-minute fMRI sessions at various age-points, which were spaced no less than two months apart. Scans were preprocessed to remove skull and non-brain components and correct for inhomogeneity of the bias field. Probabilistic Independent Components Analysis (PICA) was then performed using MELODIC to decompose the 4D fMRI data into spatial and temporal components. Output provided a spatial map thresholded and overlaid on the standard capuchin brain along with the relevant timecourse of the ICA decomposition. These spatial maps were matched to known RSNs in humans. The observed activation in auditory, visual, sensorimotor, executive control, default mode, and attention networks compared favorably to activation in humans and macaques. Continuing work aims to define relevant similarities between the RSNs of capuchins and chimpanzees, as well as describe the development of RSNs in brown capuchins.

Life Without Stress: Effects of Visual Barriers on Brain Development in Rhesus Macaques

Prolonged stress in primates leads to an increased production of glucocorticoids, which are known to affect various brain regions. In an attempt to reduce the level of stress and production of the glucocorticoid cortisol in rhesus monkeys, *Macaca mulatta*, the present study inserted visual barriers into the breeding colonies to allow subordinate animals to get out of visual eye-sight of dominant animals. We predict that the visual barriers would increase both hippocampal volume and corpus callosum area as a result of a decrease in cortisol production. Eight control and eight visual-barrier breeding colonies were established at the M.D. Anderson Cancer Center in Bastrop, Texas. At 8 months of age, structural MRIs were acquired; hippocampal volume and corpus callosum area were measured from these scans. Additionally, hair samples were collected for cortisol analysis prior to and 3-months after visual barrier insertion from preliminary experimental and control groups. A significant interaction between the housing conditions and the times of hair collection was found; cortisol was significantly reduced in subjects after the visual barrier was inserted. Furthermore, statistical analyses revealed a non-significant difference in hippocampal volumes and corpus callosum areas between the visual barrier and control conditions. The potential for this study to reduce stress could have important implications for the standard set-up of rhesus macaque breeding colonies throughout the U.S.

112. Development of Neuroscience Lab Exercises Utilizing the SpikerBox and Biopac Data Acquisition System.

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Effective demonstrations and laboratory investigations of physiological principles are valuable tools for students at different educational levels. We wish to expand the applications of the cockroach leg preparation for use in both secondary and undergraduate programs. To this end we employed both the SpikerBox system (Backyard Brains), which has been used in science outreach programs in secondary schools and the Biopac data acquisition system, which is commonly used in undergraduate physiology labs. The SpikerBox unit allows the easy demonstration of the neural responses generated by movement of tarsal joints and tibial spines of the cockroach leg. Simple pin electrodes fix the leg to a cork substrate and detect extracellular action potentials generated by sensory nerves in response to tactile stimulation. The unit amplifies the signals and converts them to an audio output. We connected the output of the SpikerBox to a Biopac MP36 system allowing the recording and measurement of the sensory responses. The low voltage stimulator of the Biopac

MP36 was used to deliver stimuli of various durations (0.1 -1.5 ms) and the threshold voltage for each stimulus duration was determined by finding the lowest voltage that caused a visible twitch of the tarsus. Stimuli were delivered via needle electrodes or by attaching clip leads to the recording pins (allowing sensory and motor testing in the same preparation). This exercise readily produced a classic strength-duration curve. While the cockroach leg is not considered to be a preparation that is amenable to pharmacological experiments, we tested the effects of volatile anesthetics on both sensory and motor responses. Diethyl ether, chloroform, and FLYNap® severely depressed sensory and motor activity. The effects of chloroform and FLYNap® were not reversible; however, the effect of ether was readily reversible. The sensory and motor responses recovered at similar rates. The effect of ether on the motor response was assessed by generating strength-duration curves during and after exposure. Ether shifted the strength-duration curve to the right (rheobase and chronaxie were increased) indicating a loss of neural excitability. The SpikerBox can serve as a bridge between classroom demonstrations and experimentation. It could also be a useful addition to undergraduate physiology and neuroscience labs.

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113. The Effects of Aerobic Exercise on Cocaine Self-Administration: Importance of Temporal Relationship between Physical Activity and Initial Drug Exposure

Maryam A. Witte and Mark A. Smith

Previous studies have reported that aerobic exercise decreases cocaine self-administration in laboratory rats with long-term access (9+ weeks) to activity wheels. In most previous studies, rats had access to activity wheels for extended periods of time both before and after initial drug exposure. The purpose of the present study was to determine whether exercise retains its efficacy to reduce cocaine self-administration if access to activity wheels is confined only to the period time (1) before or (2) after initial drug exposure. To this end, female rats were obtained at weaning and divided into four groups: (1) EXE→SED rats were housed in exercise cages (with activity wheel) for six weeks and then transferred to sedentary cages (no activity wheel) after the first day of cocaine exposure; (2) SED→EXE rats were housed in sedentary cages for six weeks and then transferred to exercise cages after the first day of cocaine exposure; (3) SED→SED rats remained in sedentary cages for the duration of the study; and (4) EXE→EXE rats remained in exercise cages for the duration of the study. Cocaine self-administration differed significantly across conditions, and the four groups were rank ordered on the basis of cocaine intake: EXE→SED > SED→SED >> EXE→EXE > SED→EXE. Thus, exercise reduced cocaine self-administration if activity wheels were available only after initial drug exposure, but did not reduce cocaine self-administration if activity wheels were available only before drug exposure.

The Effects of Aerobic Exercise on Cocaine Self-Administration: Importance of Exercise Output

Justin C. Strickland, Maryam A. Witte, Elizabeth G. Pitts, and Mark A. Smith

Previous studies have reported that voluntary wheel running decreases cocaine self-administration in laboratory rats; however, it is less clear whether greater degrees of running are associated with greater reductions in cocaine self-administration. The purpose of the present study was to determine whether greater amounts of running in a forced exercise procedure is associated with greater reductions in cocaine self-administration. To this end, male rats were obtained at weaning and trained to run on a treadmill for 0 min/day (sedentary), 30 min/day (low output), or 60 min/day (high output) at 13.4 m/min (0.5 mph). After 6 weeks, rats were implanted with

intravenous catheters and trained to self-administer cocaine under positive reinforcement contingencies. Cocaine self-administration did not differ between rats in the sedentary and low output conditions; however, cocaine self-administration was markedly reduced in rats in the high output condition. These data suggest that a large amount of exercise (i.e., > 30 min/day) may be required to produce protective effects on measures of drug self-administration.

114. Damage to the medial amygdaloid nucleus disrupts olfactory fear-potentiated startle and conditioned freezing behavior

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The acquisition and expression of phasic conditioned fear is supported by a distributed network that prominently includes lateral and central amygdaloid nuclei. A possible role for corticomedial nuclei, including the medial nucleus (MeA), is less clear. Although damage to the MeA has been shown to spare auditory conditioned freezing behavior, blockade of MeA glutamate receptors has been shown to disrupt expression of olfactory fear-potentiated startle (FPS). The present findings show that pre-training excitotoxic lesions directed at the MeA disrupted both FPS and conditioned freezing behavior elicited by re-exposure to a discrete olfactory conditional stimulus, suggesting that MeA involvement in olfactory conditioned fear is not limited by form of behavioral expression. Further, MeA lesions had mixed effects on fear elicited by diffuse cues, as light-enhanced startle was disrupted but context-elicited FPS was not. These findings confirm that the MeA contributes to either the acquisition or expression of phasic olfactory conditioned fear and may play some role in forms of sustained fear.

Nicotine withdrawal potentiates light-enhanced startle in rats.

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Anxiety is a common symptom of drug withdrawal in humans. Previous studies have shown that drug withdrawal potentiates the acoustic startle response in rats, and this phenomenon is thought to reflect an elevation in fearful or anxious state precipitated by drug cessation. In order to evaluate the possibility that withdrawal may enhance the anxiogenic effects of stressors, the present study evaluated the impact of withdrawal from daily exposure to nicotine, morphine, or caffeine on light-enhanced startle (LES) assessed 8-9days and 17-18days after onset of a daily ip drug exposure regimen. Withdrawal from daily exposure to nicotine had no impact on baseline startle reactivity at the 17-18day time point but potentiated LES in a dose-dependent fashion. At the doses tested, withdrawal from daily exposure to caffeine or morphine potentiated LES but to a lesser extent than nicotine. These findings are discussed in relation to data collected on ultrasonic vocalizations and spontaneous motor activity in a subset of subjects and within the broader context of our efforts to develop procedures for the assessment of withdrawal potentiation of LES across several classes of addictive drugs.

115. Functional Consequences of Chronic Electrical Stimulation on Cultured Neural Networks

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Chronic electrical stimulation is a technique that is thought to emulate a repeated external stimulus in the brain, such as a repetitious thought or practicing of a skill. We examine the functional consequences of chronic stimulation on neural networks at the single-cell level. Hippocampal E18 neurons are grown on 60-electrode multi-electrode arrays, allowing delivery of a user-defined electrical stimulus to individual electrodes. Probe sequences are implemented followed by hour-

long chronic stimulation of an electrically active channel. We are currently investigating strength, latency, and jitter across experimental time within cultures, both pre- and post-stimulation. Additionally, we are comparing these parameters between stimulated and control cultures. We hypothesize that chronic stimulation will result in neural networks refining their number of functional synapses, simultaneously strengthening certain connections while weakening others, and improving their efficiency, as represented by smaller latencies post-stimulus.

A Cell-Type Specific Transcriptional Profiling Method in *Xenopus laevis*.

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Adult lower vertebrates such as amphibians, reptiles, and fish do not lose their ability to regenerate their optic nerve following injury whereas adult higher vertebrates such as mammals do lose this potential. The overall aim is to study the visual system of the frog to identify molecular signaling pathway differences in axon growth, protection, and optic nerve recovery following injury. As a means of identifying important molecules involved in the optic nerve injury model, we have modified the bacTRAP method developed for translational profiling of different cell types in the brain of mice for use in distinguishing distinct cell types such as RGCs, Müller cells, and rod photoreceptors in the eye of *Xenopus laevis*. Using sperm-mediated transgenesis, we created several lines of *Xenopus laevis* animals expressing an EGFP reporter gene fused to a ribosomal protein expressed in the large ribosomal subunit. Immunostaining using an antibody to green fluorescent protein shows the characterization of F1 progeny from three cell-type specific lines of *Xenopus laevis*. Using quantitative RT-PCR, we show preliminary evidence indicating we are able to extract cell type specific mRNAs and that these expression levels reflect those found by *in situ* hybridization. These preliminary data provide evidence that the transcriptional profiling TRAP method can be used in *Xenopus laevis*.

116. Contributions of Neural Circuits in Vocal Communication

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In studying vocal communication, songbirds are an effective model system. Auditory information is required for both the production of learned song in males and mate choice in females. We are studying the role of oscillations in producing synchrony within the song system of the male zebra finch brain and the effect of dopamine on female song preference. An important function attributed to neural synchrony is sensorimotor integration. In the production of birdsong, sensorimotor integration is crucial, as auditory feedback is necessary for the maintenance of the song. A cortical-thalamic-cortical feedback loop is thought to play a role in the integration of auditory and motor information for the purpose of producing song. Synchronous activity has been observed between two nuclei in this feedback loop, MMAN and HVC. Since low frequency field potential oscillations have been shown to play a role in the synchronization of nuclei within the brain, we hypothesize that this may be the case in the zebra finch song system. In order to investigate whether oscillatory activity is a mechanism behind the synchronous activity observed between HVC and MMAN, we performed dual extracellular recordings of neural activity within the zebra finch song system. Preliminary results show that correlated spiking and correlated oscillations seem to go hand in hand in this system. Further study may reveal possible roles that this synchrony plays in the production of song. Auditory information is also critical for mate choice. In order to better

understand the neural basis of mate choice, we are looking at the effects of dopamine reward pathways on mate preference of female zebra finch. Previous research in our lab focusing on the neural circuitry involved in mate preference has shown that the midbrain dopamine nucleus, VTA, projects to the auditory area NCM. Because dopamine is known to be involved in motivation, reward, and decision making, we hypothesize that dopaminergic input to NCM contributes to song preference. This study focused on the specific effects of DA-1 like agonist on song preference and neural activity. We hypothesize that the D1 receptor agonist will enhance behavioral preference by increasing neural activity in NCM.

117. The enhancement of the neuroprotective properties of silymarin and silibinin by addition of phosphatidylcholine and various bioantioxidants against neurotoxic insult-inducing Parkinson's disease in neuroblastoma cells in vitro

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Parkinson's disease (PD) may be characterized, to some degree, by increases in oxidative stress and the subsequent loss of affected neurons. *Silybum marianum*, commonly known as milk thistle, consists primarily of silymarin, a polyphenolic flavonoid, and its major active compound silibinin, which have been shown to be strong antioxidants, and are considered hepatoprotective by modulating the insulin-like growth factor (IGF) system. Milk thistle extracts, when used *in vitro*, have prolonged neuronal survival and protected hippocampal neurons against neurotoxic-induced stress. Silymarin may alter cell membranes to prevent the entry of toxic substances. The neuroprotective behavior of silibinin may be through the amelioration of oxidative stress on memory impairment and cognitive deficits. One of the drawbacks of silymarin is its bioavailability; its poor absorption is due to the low level of hydrophobicity and its multiple-ringed structure, which impedes diffusion. To increase the bioavailability of silymarin, phytosomes can be formed, complexed with soy-derived phosphatidylcholine. Cotreatments with bioavailable lipophilic antioxidants, such as the Vitamin E species, may also aid silymarin in cell membrane stabilization. Vitamin E tocotrienols may be more protective against glutamate toxicity-induced stress in neuronal cells than the tocopherols. To test this, B35 and SK-N-SH neuroblastoma cells were pretreated in 96-well plates with each of the silymarin or bioantioxidant constituents for 24 hours before a potent dose of a neurotoxic insult, either MPP+ or 6-OHDA, a PD *in vitro* model. Cotreatments with each agent and the neurotoxic insults were performed to elucidate possible preconditioning or gene activation versus actual mechanisms of action. Posttreatment studies were exposed to the insult first, followed by each potential neuroprotective agent, for 24 hours. The MTT or Neutral Red Assay determined the cell proliferation of triplicate data sets ($p < 0.05$). Standard dose-response curves determined effective doses for silibinin at 10⁻⁷g/ml, for silymarin at 10⁻⁷ to 10⁻⁹g/ml and for silymarin with phosphatidylcholine at 10⁻⁹g/ml. Previous wound-healing studies with WS-1 human skin fibroblasts have shown that the phytosome complex was most effective at wound closure than either silymarin or silibinin. Delta tocotrienol significantly outperformed the other isomers under posttreatment conditions. These results may indicate that silymarin, with phosphatidylcholine or delta tocotrienol, has neuroprotective effects in PD models *in vitro*, and therefore may be useful in prevention or treatment of PD and other neurodegenerative diseases.

118. Escape and avoidance learning in the earthworm?

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The earthworm can serve as an inexpensive preparation for behavioral neuroscience research. For investigators interested in learning, the earthworm is capable of Pavlovian conditioning (CS: light, vibration, or "odor;" US: light, touch, "odor;" UR: contraction or locomotor change). Instrumental learning is less well documented: early demonstrations of T-maze learning were confounded by pheromone secretion in response to electric shock. We present data bearing on escape/avoidance learning in the earthworm. Earthworms in the Learning group were exposed to a vibratory CS that preceded an aversive light/thermal US. Locomotion by the earthworm during the US caused US offset; locomotion during the CS prevented the subsequent US. Yoked controls experienced the same number and duration of CS and US presentations in an unpaired manner. Experiments were conducted in Duplo open fields in a dimly lighted room. Learning worms made escape and avoidance responses twice as often as the Yoked controls made comparable responses; for the Yoked worms there was no contingency between the response and the aversive US. We demonstrated that the worms' behavior is subject to instrumental learning. Implications for future learning and neuroscience studies are discussed.

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119. Neural Correlates of Implicit Sexual Identity Bias as a Function of Religiosity

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As the Zeitgeist of western culture progresses, egalitarian efforts to study the roots of sexual identity bias are gaining momentum. The link between religiosity and enhanced outgroup bias has become harder to dismiss as empirical data attesting to their relationship continues to accumulate. This experiment explored the priming effects of specifically themed scripture and religiosity on Implicit Association Test (IAT) measures of reaction time. It was also an attempt to identify specific neural correlates of implicit bias via event-related potentials (ERPs). Forty-five participants completed a version of the IAT in which images of heterosexual and homosexual couples were paired with positive and negative adjectives. Prior to each set of trials, participants were primed with four verses of either benevolently themed scripture (e.g. "Give thanks to the God of gods. His love endures forever.") or persecutory scripture (e.g. "Thou shalt not lie with mankind, as with womankind: it is abomination."). All participants were exposed to both scripture conditions in counterbalanced orders. Additionally, electroencephalographic (EEG) measurements were recorded during the experiment. Three post-experiment questionnaires were used to obtain personality correlates of religious fundamentalism, quest, and explicit attitude towards homosexuality. The results revealed a statistically significant positive correlation ($r = 0.41$) between fundamentalism and enhanced implicit bias, as well as a significant negative correlation ($r = -0.42$) between enhanced bias and the quest measure. As expected, there were significant differences between the compatible and incompatible conditions for both benevolent ($t = -6.27(44)$, $p = .001$) and persecutory ($t = -8.06(44)$, $p = .001$) verses. ERPs elicited by pictures and adjectives are currently being extracted from the EEG data to determine whether both N400 and Late Positivity were present during incompatible conditions, as shown in a recent experiment (Williams and Themanon, 2010). Such results would lend support to a semantic rather than a familiarity explanation of IAT results. The possibility that the semantic explanation is partly religious in nature is being investigated through correlations between these ERP components and our measures of religious fundamentalism.

120. Serotonin, SIDS, and the maturation of cardiorespiratory control: the effects of prenatal nicotine exposure on postnatal survival in the serotonin-deficient *Pet-1* knockout mouse

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Sudden Infant Death Syndrome (SIDS) is the leading cause of post-neonatal infant mortality in the United States. Accumulating evidence suggests that infants who die from SIDS suffer an abnormality in serotonin (5HT) neuron development that is linked to a deficiency in brainstem 5HT levels, resulting in compromised cardiorespiratory control. It has been postulated that sudden death in SIDS may be due to failed autoresuscitation, a cardiorespiratory protective mechanism characterized by a series of gasps that re-oxygenate brainstem tissues leading to resumption of rhythmic breathing after prolonged apnea. In addition, several factors including prenatal exposure to nicotine through maternal smoking have been postulated to increase the risk for SIDS. Recently, knockout of the *Pet-1* gene in mice was shown to produce a 70% loss of brainstem 5HT neurons that was associated with depressed breathing and increased mortality during the early postnatal period. *Pet-1* knockout mice can autoresuscitate from a single episode of experimentally induced apnea, but their autoresuscitation response is delayed compared to wild-type littermates. Given the potential link between brainstem 5HT deficiency, prenatal nicotine exposure, compromised respiratory function, and sudden postnatal mortality, we assessed the effects of prenatal nicotine exposure on survival and autoresuscitation capability in normal (wild-type) and 5HT-deficient *Pet-1* knockout neonates. We hypothesized that prenatal exposure to nicotine would exacerbate the already compromised autoresuscitation response in 5HT-deficient *Pet-1* knockout mice. We used osmotic mini-pumps implanted in pregnant dams to deliver either nicotine (60 mg/kg/day) or saline to developing pups via the placental circulation during embryonic and fetal development, then measured autoresuscitation responses to experimentally induced apnea during the early postnatal period using body plethysmography. Contrary to our original hypothesis, we found that the abnormal autoresuscitation response that we had previously characterized in the *Pet-1* knockouts was in large part normalized by prenatal exposure to nicotine. Nevertheless, nicotine exposure further increased neonatal mortality in the knockouts following successful autoresuscitation. We speculate that despite improved respiratory function, this increased mortality may be due to an impaired ability of the knockout to re-establish a stable heart rate following the autoresuscitation challenge.

121. Understanding the Second Messenger Pathway Associated with the Protease- Activated Receptor (PAR-1) on Developing Spinal Motor Neurons in *Gallus gallus*

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The G-protein linked, protease-activated receptor-1 (PAR-1) located on the plasma membrane of spinal motor neurons in developing *Gallus gallus* embryos has been linked to apoptosis necessary for proper development of the central nervous system and to apoptosis associated with neurodegeneration. However, the mechanism by which PAR-1 activates the necessary apoptotic proteins is unknown. The purpose of this study was to identify which of the G-protein pathways is triggered following PAR-1 activation. Previous work has shown that cAMP is uninvolved, but that Ca²⁺ levels following activation are significantly increased. It was established using RT-PCR that the apoptotic marker gene *bid* was up-regulated 12-24 hours after PAR-1 activation. It was further shown that cells treated with both ryanodine (SER Ca²⁺ channel blocker) and SFLLRNP (PAR-1 activator) showed levels of *bid* not significantly different from those of control cells. These data show a causal link between Ca²⁺ and *bid* up-regulation. The initial increases in Ca²⁺ concentration are likely a result of inositol 1,4,5-triphosphate (IP3) activity opening the SER Ca²⁺ channels, and serve to act as the second messenger that up-regulates the *bid* gene. Mapping the specific G-protein

second messenger pathway associated with PAR-1 linked apoptosis is an important step toward the understanding of developmental phenomena that may ultimately lead to the prevention of neurodegenerative conditions.

122. The effects of two neuromodulators on the cardiac central pattern generator in *Homarus americanus*

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Behavioral modulation is vital for an organism's survival. Central pattern generators (CPGs), which can be modulated, are responsible for generating patterned behavior; they spontaneously produce patterned rhythmic bursting without rhythmic input. The cardiac ganglion (CG) of the American lobster, *Homarus americanus*, is a simple CPG, consisting of nine neurons: 5 motor neurons that synapse on heart muscle tissue, and 4 pacemaker cells that are electrically and chemically coupled to the motor neurons. The CG innervates the lobster neurogenic heart and determines heartbeat frequency and amplitude. We have begun to examine the effects of two peptides, both of which we have shown to modulate the whole heart, on the isolated lobster cardiac ganglion. Applying physiologically relevant concentrations of the intrinsic neuromodulator *Homarus americanus*-specific calcitonin-like diuretic hormone (Homam CLDH) to the lobster whole heart caused an increase in contraction frequency and amplitude. Furthermore, when CLDH was perfused across the isolated CG, burst frequency increased. Electrophysiological recordings were used in an attempt to identify the specific location at which Homam CLDH acts within the CG. Application of Homam CLDH to the pacemaker cells caused an increase in burst frequency similar to that provoked by CLDH application to the entire CG. When the pacemaker cells were silenced with tetrodotoxin, CLDH evoked an increase in burst frequency and a decrease in variability of the patterned CG output. More recordings and an immunohistochemical analysis will be used to determine specifically where CLDH is acting. The second peptide we have been examining, SGRNFLRFamide (SGRN), is not found in the CG itself, but is presumably delivered hormonally, having been detected (Ma et al, 2008) in neuroendocrine organs. Interestingly, some of the effects of SGRN differ dramatically when it is perfused through the whole heart and when it is applied to the isolated cardiac ganglion. While

SGRN applied to the whole heart causes an increase in contraction amplitude and cycle frequency, application of physiologically relevant concentrations to the isolated CG generally result in a decrease in cycle frequency. At the same time, however, burst duration increases dramatically. Experiments to determine both the mechanisms that underlie these changes and the mechanisms responsible for the differences in the response to SGRN by the whole heart and the isolated ganglion are ongoing.

123. Mechanisms for producing different chewing patterns in the crab: G-SIFamide as a *Coneurotransmitter of the Modulatory Commissural Neuron 5 (MCN 5)*

LINNA GAO, BOWDOIN COLLEGE
Professor Dickinson and Professor Stemmler

Like most decapod crustaceans, crabs are highly opportunistic feeders and depend on their ability to eat and digest a wide range of food in order to survive. The stomatogastric nervous system (STNS) is the part of the crustacean nervous system that controls the foregut, in which chewing and the initial processing of food takes place. Most of the neurons in the stomatogastric ganglion are attributed to the pyloric filter, which divides food particles by size, and the gastric mill, which controls the grinding of the three teeth in the crab stomach. Both of these rhythmic networks are

considered to be Central Pattern Generators (CPGs), which are fixed networks of nerves that generate the neuronal outputs that drive rhythmic movements. Modulation of these networks, mostly by peptides and amines, allows for flexibility in the patterns that these networks generate (Dickinson, 2008). Many studies have ascribed this flexibility to the actions of both circulating neurohormones and locally released peptides. In the crab *Cancer borealis*, a major source of locally released modulators is a group of projection neurons in the STNS, including the Modulatory Commissural Neuron 5 (MCN5). Mass spectrometric and immunohistochemical evidence has indicated that GYRKPPFNGSIFamide (G-SIFamide) is broadly distributed within the STNS of *Cancer* crabs, including extensive neuropile in the stomatogastric ganglion and somata in the Commissural Ganglia. Morphological data further suggests that MCN5 contains G-SIFamide, which thus far has been the only identified transmitter in the neuron. We have tested the hypothesis that many of the previously described effects of MCN5 in (Norris et al, 2006) are mediated by this peptide. Physiological data have shown that G-SIFamide evokes effects comparable to MCN5 activation in activating and exciting the pyloric pattern as previously observed (Norris et al, 2006). Additionally, we have found that G-SIFamide application activates or enhances the gastric pattern. Studies in the Nusbaum lab have found that MCN5 likewise exerts excitatory effects on the gastric motor pattern (personal communication). Taken together, these data suggest that G-SIFamide is a major co-neurotransmitter of MCN5, and that many of the effects of MCN5 may be mediated by G-SIFamide.

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124. Modulation of Melanopsin Signaling by Beta-Arrestins

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Rods and cones are two photoreceptors that reside in the vertebrate retina and play a key role in image-forming vision. In the past decade, scientists have discovered a third class of photoreceptors called melanopsin retinal ganglion cells (mRGCs). Unlike rods and cones, these photoreceptors play a role in nonvisual functions, like regulation of circadian rhythms by light and pupil constriction in response to light. Melanopsin, the photopigment that makes these cells light sensitive, is a G-protein coupled receptor. The melanopsin phototransduction cascade is similar to the cascade of invertebrate photoreceptors such as those from fruit flies. In fruit flies, photoreceptor signaling is modulated by a class of proteins called arrestins. These arrestins are expressed in the mRGCs of vertebrates. To test whether arrestins are involved in mRGC light responses, we recorded from mouse retinas genetically engineered to lack arrestin. We found that arrestin did affect mRGC light responses, but in an unexpected way.

Delayed Functional Recovery of Crawling After CNS Injury in the Leech

Gina Collings, Kevin Crisp. St. Olaf College

Although much research has explored anatomical repair (e.g., growth of damaged axons, etc) in damaged central nervous system (CNS), functional recovery has received less attention. Similar to their vertebrate counterparts, the medicinal leeches, *Hirudo verbena/medicinalis*, can respond to CNS injuries through regenerative processes, (e.g. microglial chemotaxis and laminin secretion). Leech nervous systems regenerate much better than those in humans, therefore research in the field of regeneration in impaired leech nervous tissue can lead to the advancements of knowledge in human CNS injuries, such as Parkinson's disease or hydrocephaly, simply due to a better model in the repaired leech CNS. To investigate functional recovery after CNS injury in the leech, rhythmic crawling behavior was observed in juvenile leeches before and multiple times after the CNS injury. Analysis of crawling kinematics was obtained through pre-and post-lesion videos that were recorded and converted to individual frames. The recorded data was represented through phase

portrait plots, the change in movement over time. Similar crawling kinematics with minute variation were observed between pre- and post-lesion. Although there was no definite re-connection in the nervous system, the data may suggest that functional recovery may depend on re-wiring of preserved tissue elements rather than regeneration of the pre-lesion anatomy.

125. Effect of Caffeine on Ethanol Place Conditioning in Adolescent Mice

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With the rising prevalence of caffeinated alcoholic beverages it is important to investigate whether caffeine interacts with different properties of alcohol. Consumption of alcohol is presumed to be driven at least in part by its motivational properties. Place conditioning has been used to study both the positive and negative motivational properties of alcohol in mice. Previous research in mice has shown aversion to cues experienced immediately prior to injection of 2 g/kg ethanol and preference for cues experienced immediately after. This study used 80 DBA/2J mice to examine how caffeine affects conditioned place aversion with ethanol. Mice were randomly assigned to three drug groups (CE, SE, CS) and underwent two cycles of two conditioning trials followed by one test day. Mice received an i.p. injection of 20 mg/kg caffeine or saline (C or S) ten minutes prior to exposure to the floor stimulus in the conditioning chamber. After a five minute conditioning trial mice received an injection of 2 g/kg ethanol or saline (E or S) and were returned to the home cage. After two conditioning trials, CE mice showed a degree of place aversion equivalent to that of the SE mice. However, after two additional trials, CE mice continued to show a strong place aversion while aversion in SE mice was reduced. As seen previously, alcohol-induced place aversion in adolescent mice was weaker after four conditioning trials, possibly indicating a tolerance to this effect. Interestingly, caffeine pre-exposure may slow the development of tolerance. The effects of caffeine on ethanol induced conditioned place preference will also be presented.

126. Sex Differences in Diet-Induced Cognitive Impairment

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The diet of Western civilized societies is dominated by sugar and saturated fat. Although most people are aware of the physiological consequences (e.g. obesity, diabetes, cardiovascular disease) of consuming a Western-style diet, the neurological implications of this dietary regime are relatively unknown. Recent epidemiological studies suggest that obesity and diabetes increase the risk of developing dementias like Alzheimer's disease. Animal research has shown a relationship between high-fat/high-glucose diets and impaired memory; however, these studies have only utilized male animals. Therefore, the purpose of this study was to explore possible sex differences in vulnerability to the Western-style diet. Male and female Sprague-Dawley rats were fed control chow or high-fat/high-glucose chow for 10 weeks. All female rats were ovariectomized, and then half of the females were implanted with slow-release estrogen pellets to restore sex hormones. At the end of the feeding period, the memory and learning capabilities of all animals were examined with the Morris Water Maze and the Novel Object Recognition tasks. Preliminary results indicate that Western-style diet has a negative effect on memory functioning in male rats, but not female rats. The findings of this study will have important implications for future medical research and for public health policy.

127. Determination of Anxiety Differences between C57BL/6 N and J Mice Using the Elevated-Plus Maze and Light/Dark Transition Paradigms to Investigate Fear Extinction Learning Disparity

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We are interested in studying the cellular and molecular neurobiological bases for individual differences related to anxiety disorders, in particular Post Traumatic Stress Disorder (PTSD). PTSD has been singled out as a health disparity issue among Hispanic American minorities by the Surgeon General. We use two C57BL/6 mouse substrains, J versus N, as animal models to approach the study of individual mental health disparities related to PTSD. In the Pavlovian fear conditioning paradigm, J mice are able to extinguish previously acquired fears more efficiently than N mice; i.e., N mice are poor fear extinguishers, compared to J mice. Such impairment constitutes a form of emotional perseveration, or continued execution of fear related behaviors, similar to what can be displayed in PTSD. However, it is not known whether these two C57BL/6 substrains differ in terms of innate anxiety, which have been proposed as a possible indicator of PTSD susceptibility in humans. To address potential differences in innate behavioral anxiety between N (poor fear extinguishers) and J (good fear extinguishers) mice, we ran experiments using the Elevated Plus Maze (EPM) and Light/Dark Transition (LDT) paradigms. We hypothesized that if innate anxiety is significantly higher in N mice in relation to J mice, they will explore less and spend more time in the closed EPM arms and the dark enclosed LDT chamber. EPM trials showed that N mice spend significantly more time in the open arms and have a greater number of open arms entries compared to J mice. J mice spend significantly more time in the hub (center), had a greater number of entries and explorations to the closed arms and grooming behavior compared to N mice (n=16). In the LDT tests, we found no significant differences of the time spend in the light or dark chambers, the total number of entries or explorations and the number of explorations to the light between N and J mice. Although, our LDT experiments showed that J mice explored significantly more times the dark enclosed side of the LDT paradigm than N animals. Therefore, N impairment to extinguish previously learned fear is not related to higher levels of pre-existing anxiety in relation to J mice. Our EPM data suggest that N mice seems to be willing to engaged in more risky behaviors, and spend more time in the maze's open spaces, compared to J mice. In addition, J mice held a precautious behavior, by remaining and exploring the closed arms while in the EPM's hub and likewise, by exploring the dark enclosed LDT side more, which could be parallel to the animal's burrow, compared to N mice. Supported by: NIMH 1SC1MH086072, MHDBSRN-NIH IP20MD003355, and URGREAT-MBRS-RISE 2R25GM066250-05A

128. Role of Learning in Hue Detection

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These authors contributed equally to the project

Since Krauskopf et al. (1982), numerous psychophysical experiments have investigated chromatic mechanisms in humans by measuring changes in hue detection thresholds due to various types of chromatic adaptation. Similarly, physiological studies have explored color processing in monkeys with the notion that we may link these physiological studies in monkeys with psychophysical

results in humans due to the similarity between color detection in humans and monkeys. We evaluated baseline hue detection thresholds for humans and monkeys in order to assess the similarity in hue detection. In addition, we compared the changes in detection thresholds over time to quantify the role of learning in the hue detection task. In a four-alternative forced choice task, each of 16 hues generated in Derrington-Krauskopf-Lennie (DKL) space was presented at varying saturation levels against a neutral gray background until the detection threshold (the point at which the hue was barely detectable) was determined for each color. Preliminary results show that humans and monkeys have different baseline detection thresholds for certain hues. In general, humans were found to have higher hue detection thresholds than monkeys, indicating that monkeys are better able to detect color than are humans. Humans, on the other hand, were able to reach plateau performance after fewer trials than monkeys. Currently, we are collecting additional data to address whether certain hues exhibit different rates of learning in both monkeys and humans.

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129. Estrogen receptors and the rapid effects of estradiol on visually guided sexual behavior and retinal responses to light stimuli in male *Carassius auratus*

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Social stimuli, specifically sexual stimuli, can stimulate the synthesis and release of sex hormones in vertebrate animals. Increased levels of sex hormones lead to changes in social behavior, such as sexual behavior. Sex hormones, classically known to act through genomic mechanisms, are more recently understood to also rapidly mediate cellular and behavioral responses through nongenomic mechanisms. Studies have shown estradiol (E2) rapidly increases social approach responses of male goldfish towards females, even when the only behavioral cue from the female is visual. There are high levels of aromatase, the enzyme that converts testosterone to estradiol, and estrogen receptors localized in the goldfish retina, suggesting that testosterone and estradiol play a role in modulating the sensitivity of the male goldfish to female visual cues. However, the receptor by which E2 mediates this rapid effect is unknown. Membrane embedded receptors ER α , ER β , and G protein-coupled receptor 30 (GPR30) could possibly work individually or in collaboration to mediate this rapid behavioral response. Intraperitoneal injections of two agonists, G-1 and diethylstilbestrol (DES), targeting estrogen receptors GPR30 and ER α /ER β respectively, were used to determine the estrogen receptor responsible for the rapid influence on the approach response of the male goldfish given only a visual cue of the female stimulus. Time spent in proximity to the female visual stimulus 30-45 minutes after injection revealed no effect of G-1 on the approach response. Although it was not significant, DES tended to increase social approach. Future studies will further examine the potential role of membrane versions of ER α and ER β in mediating rapid effects of estradiol on this behavior. Using an electroretinogram (ERG), the rapid effects of estradiol were further investigated by measuring the effects of estradiol on retinal responses to light stimuli in male goldfish. The effect was quantified by measuring the b-wave amplitude, the ON response to the light stimulus, from each ERG. Initial results suggest a trend that estradiol increases the b-wave amplitude ($p=0.08$). We are currently increasing our sample sizes to see if estradiol does rapidly increase visual sensitivity, which may play a role in estradiol's ability to stimulate behavioral response towards the visual stimuli of males in this species.

130. Altered disgust responses to visual stimuli in anorexia nervosa

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Individuals with anorexia nervosa typically consume fewer than 500 calories a day and exhibit an obsessive fear of weight gain. These symptoms may arise due to a conditioned disgust response to food. In the current study, we use electromyography (EMG) to measure the disgust response in participants with and without a history of anorexia nervosa. Activity in the levator labii muscle, located under the nose, is the evolutionary adaptation of distaste exhibited by many mammals as a means to reject or expel potentially harmful stimuli. Disgust, a higher order manifestation of distaste, is a universal emotion amongst humans, and previous imaging studies have mapped the experience of disgust onto the insular cortex. Moreover, previous studies have shown the insula to be disordered in subjects who have experienced anorexia nervosa. In the present study, participants attend an experimental session during which EMG electrodes are placed on the levator labii while anorexic subjects and control subjects are exposed to various categories of visual stimuli, including social images and images of contamination. Additionally, each participant explicitly reports subjective ratings of disgust, valence, and attractiveness in response to each image. We hypothesize that participants with a history of anorexia nervosa will have significantly different disgust response to food stimuli and body stimuli than control subjects. With this behavioral study, we expect to further implicate the insular cortex as a source of neural dysfunction in anorexia nervosa.

Mapping the Intrinsic Structure of Cognitive Neuroscience

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Cognitive neuroscience, as a discipline, links the biological systems studied by neuroscience to the processing constructs studied by psychology. To understand its intrinsic structure, we applied network test analysis to an exhaustive corpus of abstracts published over a 30-month period in five major neuroscience journals, including all studies that used fMRI to investigate psychological processes. Semantic links were derived from the co-occurrence of Anatomy and Concepts terms, generating three networks: *Anatomical* (Anatomy x Anatomy), *Conceptual* (Concepts x Concepts), and *Functional* (Anatomy x Anatomy). Our analyses of the network visualizations identify the hubs of cognitive neuroscience, as well as regions that are understudied relative to their importance in the network. Comparing the position of each node to its frequency in the text, we revealed outliers of disproportionately high centrality that represent important targets for future research. Collectively, these results provide prescriptive recommendations for topics whose further study will most efficiently build new links between structure and function.