31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#117 Abstract Title:	**Selective intra-arterial administration of Verapamil is neuroprotective in acute ischemic stroke.**
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Abstract: Despite the urgent need for better stroke therapies, experimental stroke treatments have largely failed to translate to stroke patients. In an effort to bridge this translational gap, we have concentrated our efforts on drugs that are FDA approved and associated with treating stroke-associated pathophysiology, such as cerebral artery vasospasm, with the goal of repurposing them to protect brain tissue from ischemic injury. Verapamil, a calcium channel blocker, is one such drug that is often infused intra-arterially by neurosurgeons treating vasospasm that results in ischemia. In demonstrating a reliable and reproducible stroke model (mouse transient middle cerebral artery occlusion, MCAo) with the addition of a retro-engineered IA drug delivery model mimicking the human condition, we were able to optimize the injection volume and flow rate for pharmacotherapy administration of verapamil. Through this direct route of administration we have shown a significant decrease in infarct volume and trending towards significance an increase in behavioral outcome when comparing treated animals versus control. Perfusion studies did not show significant differences in perfusion to account for vasomotor changes as the likely mechanism for ischemia reduction. To further explore this, after 1 hour MCAo in three month old C57/Bl6 mice, we examined the potential neuroprotective effects of verapamil on post stroke day 3. Whole brains were harvested and flash frozen for cryostat sectioning and cellular staining to compare apoptosis, appearance of mature neurons and astrocyte activation. Results suggest that IA administration of verapamil, more specifically than reducing infarct volume, is directly neuroprotective on brain parenchymal tissue at risk.

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#118 Abstract Title:	**A custom antibody detects calcineurin proteolysis in astrocytes and small vessels in human AD brain specimens**
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Abstract: The Ca2+ dependent protein phosphatase calcineurin (CN) has been implicated in multiple neuropathologic features of Alzheimer's disease (AD) including synapse dysfunction, neuroinflammation, and amyloidosis. CN dysregulation during AD arises, in part, from the removal of the CN autoinhibitory domain near the C terminus of the CN catalytic subunit. Using Western blots, commercial antibodies to the N terminus of the CN catalytic subunit reveal the presence of an approximately 48 kDa fragment in human mild cognitive impairment (MCI) brain tissue and in experimental models of neurodegeneration, but do not reveal in which cell types proteolysis occurs. Knowing where proteolysis occurs in nervous tissue is critical to understanding the mechanistic basis of its actions, because CN is found at high levels in both neurons and glial cells where it has different cellular functions. To better our understanding of CN regulation, we generated custom rabbit polyclonal antibodies to CN based on previously identified calpain (CP)-dependent cleavage sites. One of these antibodies (ΔCN48) selectively detects a 48 kDa fragment in Western blots. The ΔCN48 antibody was then used for IHC/IF labeling of human brain sections with AD and mixed AD/vascular pathologies. The ΔCN48 antibody labeled astrocyte clusters in human AD brains and astrocytes and small vessel elements in the human vascular dementia brains. The results suggest that astrocytes, and possibly small vessels, are a primary site for CP-dependent CN proteolysis in injured or diseased nervous tissue. This work may provide new mechanistic insights into the impact of Ca2+ dysregulation on neurodegenerative diseases.

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#119 Abstract Title:	**Cotinine, the Primary Metabolite of Nicotine, Alters Trafficking and Assembly of Nicotinic Acetylcholine Receptors**
Author(s):	A. M. Fox, Dept of Chemistry, U of Kentucky F. H. Moonschi, Dept of Chemistry, U of Kentucky C. I. Richards, Dept of Chemistry, U of Kentucky

Abstract: Nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated ion channels containing alpha (α2-α10) and beta (β2-β4) subunits. Correct assembly is necessary to ensure proper function and subcellular localization of receptors. Exposure to nicotine has been shown to alter the trafficking and assembly of nAChRs, resulting in their upregulation on the plasma membrane. Although the complete mechanism is not understood, these changes are believed to contribute to nicotine addiction. We have found that cotinine, the primary metabolite of nicotine, also alters the trafficking, expression, and assembly of nAChRs. We use a pH sensitive fluorophore, super ecliptic pHluorin (SEP), to differentiate between intracellular and inserted nAChRs. SEP studies determine the relative number of receptors on the plasma membrane, as well as distribution of these receptors within the cell. Similar to nicotine, exposure to cotinine increases the number of α4β2 receptors on the plasma membrane and causes a redistribution of intracellular receptors. Conversely, the number of α6β2β3 receptors on the plasma membrane decreases in the presence of cotinine. We also use single molecule photobleaching of green fluorescent protein (GFP) to determine the stoichiometry of individual nAChRs by spatially isolating receptors in a cell membrane derived vesicle. The number of bleaching steps corresponds to the number of GFP labeled subunits, and therefore the stoichiometry. Cotinine and nicotine both alter the assembly of α4β2 receptors to favor the high sensitivity (α4)2(β2)3 stoichiometry. These results, in combination with its long pharmacological half-life, give cotinine a potential role in the mechanism of nicotine addiction.

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#120 Abstract Title: Mechanisms of insulin actions on hippocampal neurons

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Abstract: Recent work from our lab identified that intranasal insulin improves cognition in the aged F344 rats (Maimaiti et al., 2015). It is well documented that neurons in the brain are insulin sensitive. It has also been shown that this brain insulin sensitivity may be reduced in aging and/ or Alzheimer's disease (AD). Further, clinical trials have repeatedly shown that intranasal insulin can significantly improves symptoms of memory not only in AD patients, but also in younger healthy individuals. However, the mechanism whereby insulin can alter neuronal function is not clear. While prior work has highlighted changes in AMPA and NMDA receptors, very little work has focused on voltage-gated Calcium channels/ currents (VGCCs) as a target of insulin action in the brain. Earlier studies from our lab have looked at intracellular Ca2+ as a key neuronal molecular regulator of hippocampal-dependent memory. Elevated intracellular Ca2+ levels have been shown in aged animals with poor spatial memory. Recently, we have shown that insulin reduces the Ca2+-dependent afterhyperpolarization (AHP) in hippocampal neurons in both young and aged animals (Maimaiti et al., 2015). However, the underlying mechanism that underlies this reduction has not been studied in depth. The goal of the present work is to test the hypothesis that insulin reduces Ca2+ current through VGCCs. We used whole cell voltage-clamp techniques to measured Ca2+ currents from 13-17 DIV hippocampal neurons in vitro. Inactive (boiled) or active (10 nM) glulisine insulin Apidra® (rapid-acting, zinc-free form of insulin) was tested acutely for effects on VGCCs. The study results show 10 nM Apidra® reduced Ca2+ current significantly. This indicates the mechanism of insulin-mediated memory improvement could be due to reduced calcium flow through VGCC and a reduction in the AHP.

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#121 Abstract Title:	**Reward Omission as a Mild Form of Stress: Individual Differences in Amphetamine Self-Administration, Extinction, and Reinstatement**
Author(s):	V. G. Weiss, Dept of Psychology, U of Kentucky Y. R. Yates, Dept of Psychology, Northern Kentucky U M. T. Bardo, Dept of Psychology, U of Kentucky

Abstract: Clinical evidence indicates that omission of an expected reward is a frustrating or stressful event that can lead to impulsive behavior. The present study determined if individual differences in response to reward omission predict acquisition, extinction, and/or reinstatement of amphetamine self-administration in rats. The reward omission task consisted of two components: (1) a Pavlovian component where a light signaled non-contingent food delivery; and (2) an operant component where food was earned on a DRL 5" schedule. On test sessions, the expected reward was omitted on some trials in the Pavlovian component and an efficiency ratio was measured in the subsequent operant component. Rats were divided into either "High" or "Low" groups, with High rats showing a greater decrease in efficiency ratio than Low rats. Rats were then assessed for amphetamine self-administration (0.03 mg/kg/infusion), extinction and reinstatement induced by a natural stressor (30 min restraint), pharmacological stressor (1.25 mg/kg yohimbine) or cue (light). During an initial autoshaping procedure where a cue light signaled drug availability, rats in the High group earned significantly more infusions than the Low group. However, as the schedule was incremented from FR1 to FR5, group differences dissipated. Furthermore, rats in the High group showed significantly more perseverance of responding during extinction (no cue or drug). While neither restraint stress or yohimbne did not reinstate responding, reintroduction of the cue reinstated responding in the Low group, but not in the High group. Thus, rats that showed the greatest reactivity to unexpected reward omission, a mild stressor, showed the greatest amphetamine self-administration at a low unit dose and greater perseverance in responding during extinction, suggesting that individual differences in reactivity to reward omission may be a useful predictor of amphetamine abuse.

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#122 Abstract Title:	**Ethanol Activates Hippocampal mGluR1-and-5-containing Receptors to Promote Loss of Neuron Specific Nuclear Protein during Chronic, Intermittent Ethanol**
Author(s):	A.R. Reynolds, Dept of Psychology, U of Kentucky M.A. Prendergast. Dept of Psychology and Spinal Cord and Brain Injury Research Center, U of Kentucky

Abstract: The Gαq-linked group 1 metabotrophic glutamate receptors (mGluRs) consist of mGluR1 and mGluR5 and likely influence ethanol voluntary intake in preclinical models. However, the functional influence of group 1 mGluRs in promoting development of ethanol dependence is not fully understood. The present studies sought to examine the functional relationship between ethanol-induced activation of group 1 mGluRs and hippocampal cytoxicity using an in vitro model of chronic, intermittent ethanol (CIE). Rat hippocampal explants were exposed to three cycles of CIE (five days of 50 mM ethanol exposure, followed by one day of withdrawal, repeated three times), with or without the addition of the noncompetitive mGluR1 antagonist (hydroxyimino)cyclopropa[b]chromen-1a-carboxylate ethyl ester (CPCCOEt; 0.5, 1, and 3 μM), or the noncompetitive mGluR5 antagonist (E)-2-methyl-6-styryl-pyridine (SIB-1893; 20, 100, 200 and μM). Sparing of ethanol-induced loss of neuron specific nuclear protein (NeuN; Fox-3) by antagonists was assessed using immunohistochemical labeling of NeuN in CA1, CA3, and dentate gyrus (DG) hippocampal subregions. Binge-like ethanol exposure (50 mM) and multiple withdrawals produced significant loss of NeuN (Fox-3) immunoreactivity in all primary cell layers of the hippocampal formation of 20-35%. These effects were attenuated by co-exposure to the mGluR1 antagonist CPCCOEt (3 μM) with ethanol in the CA3 and DG, but not the CA1. By contrast, these effects were blocked with the mGluR5 antagonist SIB-1893 (20 μM) in each primary cell layer of the hippocampal formation. These data demonstrate that ethanol acutely activates group 1 mGluRs to promote the development of ethanol dependence, as well as subsequent withdrawal-associated loss of NeuN immunoflourescence. These findings suggest that group 1 mGluRs, in particular mGluR5, may be a therapeutic target for treatment of alcohol use disorders.

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#123 Abstract Title:	DMXB-A REDUCES CELL DAMAGE FOLLOWING DEVELOPMENTAL ETOH EXPOSURE IN A RODENT HIPPOCAMPAL SLICE MODEL
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Abstract: Prenatal alcohol exposure has life-long consequences for the developing offspring. One way that alcohol damages the developing brain is excitotoxicity caused by ethanol (ETOH) withdrawal (EWD). In rodent models, targeting this excitotoxicity has been shown to be a promising approach for improving outcome following developmental ETOH exposure. Activation of nicotinic acetylcholine receptors (nAChR), in the central nervous system can be protective against various excitotoxic challenges, including ETOH withdrawal. In this study, we examined whether the administration of DMXB-A, a α7 nAChR agonist, could reduce neurotoxicity caused by EWD in the hippocampus. To test this, an organotypic hippocampal slice culture was used. Hippocampal slices were either exposed to ETOH (100mM) or control medium. After 10 days of ETOH exposure, the slices treated with DMXB-A (1, 3, or 10uM) during EWD. Uptake of propidium iodide (PI; a non-specific marker of cell damage) was measured to examine cell damage in the CA1, CA3, and dentate gyrus of the hippocampus. The combination of EWD and NMDA produced increased toxicity compared to controls in the CA1 region, however 10uM DMXB-A attenuated this effect, suggesting that DMXB-A was protective against EWD induced neurotoxicity in vitro. These findings are exciting because this drug is currently being tested in clinical trials for a variety of CNS conditions and so has significant translational potential. Further research is necessary to better understand the extent of its neuroprotective properties and to determine the ability of DMXB-A to reduce behavioral deficits following prenatal ethanol exposure.

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#124 Abstract Title:	**Tracking the fate of her4 expressing cells in the regenerating retina using the photoconvertable Kaede reporter**
Author(s):	S. G. Wilson, Dept of Biology, U of Kentucky W. Wen, Dept of Biology, U of Kentucky L. Pillai-Kastoori, Dept of Biology, U of Kentucky A. C. Morris, Dept of Biology, U of kentucky

Abstract: Purpose: Retinal neurogenesis results from complex interactions of regulatory networks and spatiotemporally controlled gene expression events. Hairy-related 4 (her4) is a BHLH-O transcription factor expressed during both initial embryonic neurogenesis and regeneration of the zebrafish retina. Here, we investigated the role of her4 during regeneration and traced the lineage of her4 expressing cells in chronic as well as acute photoreceptor damage models. Methods: Expression patterns of her4 were characterized using in situ hybridization (ISH) in adult rod-specific degeneration/regeneration background in conjunction with BrdU pulse-chase experiments to assess proliferation. The her4:Kaede transgenic line was generated using Tol2 transpose mediated transgenesis and expression of the reporter was compared to that of endogenous her4 by ISH. Lineage tracing analysis was conducted on a time-course of photoconverted rod degeneration retinas as well as retinas that experienced acute light damage. Results: Her4 was expressed in proliferative zones of the peripheral retina, and in a background of rod degeneration was found to be expressed in proliferating cells in the inner nuclear layer (INL) of the central retina. 2-color ISH showed that expression of the Kaede reporter recapitulates endogenous her4 expression. Lineage tracing experiments revealed that cells that retained the Kaede reporter co-locolized with markers for the rod lineage. Following acute light damage, her4 was highly upregulated in proliferating cells of the INL. Conclusions: Our results show that her4 is expressed in slowly proliferating subsets of Müller cells in the INL and the number of these cells increases in proportion to the extent of damage to the retina. Lineage tracing using the her4:Kaede transgenic line showed that her4 expressing cells contribute to the rod lineage, and that the cycle of her4 expression to rod genesis was completed as quickly as 3 days.

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#125 Abstract Title: Altered Emotional Enhancement Effects in Persons with Mild Cognitive Impairment

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Abstract: Emotional enhancement effects (EEEs) encompass the tendency of emotional arousal or non-neutral hedonic valence to be associated with memory retention. Competing models of the status of EEEs in Alzheimer's disease (AD) and its predecessor state, mild cognitive impairment (MCI), propose that they are spared or disrupted. We hypothesize that this disconnect arises in part from the influence of parallel memory systems on the manifestation of EEEs. We examined the interrelation of such memory systems in the context of clinical MCI using an affective repetition paradigm. 16 participants – 8 with mild cognitive impairment, 8 with normal cognitive status – participated in an affective repetition task while electrophysiological data (EEG) were collected. Images from the International Affective Picture System (IAPS) image set were shown to participants, and participants indicated whether low arousal positive (LAP) and high arousal negative (HAN) images included human body parts. Temporospatial principal components analysis was applied to the epoched EEG data to differentiate independent components. The three primary components of the event-related potentials (ERPs) showed group differences in the classical P300 window such that repeated stimuli, WWJt/c (1.0, 13.0) = 5.57, $p = 0.039$, and HAN stimuli, WWJt/c (1.0, 13.6) = 12.17, $p = 0.006$, were associated with higher-amplitude electrophysiological activity. There was also a main of HAN valence in the later part of the P300 time-window, WWJt/c (1.0, 13.0) = 18.59, $p = 0.0020$. Behaviorally, LAP stimuli and repeated stimuli were associated with faster RT and improved accuracy ($ps < 0.05$); no group differences were observed. We found that adults with MCI showed enhanced brain responses to repeated HAN stimuli, suggesting that such stimuli may be more deeply encoded in individuals with MCI.

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#126 Abstract Title:	**Cocaine-Induced Behavioral Sensitization and Conditioned Place Preference in Female Japanese Quail**
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Abstract: Studies suggest that men and women differ in their subjective experience and biological response to cocaine. Men and women are equally likely to use cocaine if given the opportunity, but women are more likely to reach dependence criteria compared to men. This “telescoping” effect has been largely attributed to ovarian hormones. Estrogen, in particular, has been shown to increase behavioral responding to cocaine and enhance drug reward in female rats relative to male rats. Japanese quail are a promising alternative model to examine the interaction between hormones and drug effects. Quail have color vision and high visual acuity unlike rodents. Additionally, circulating hormones may be non-surgically altered using photoperiodism in quail. The current studies explored cocaine-induced activity and reward in female quail, and investigated the role of estradiol and dopamine in these effects. In Experiment 1, levels of estradiol did not correlate with cocaine-induced activity. In Experiment 2, photostimulated quail demonstrated cocaine-induced CPP and therefore, estradiol enhanced the rewarding properties of cocaine. Ecologically, female quail have reduced activity during their breeding months when estradiol is high. Since Experiment 2 revealed that cocaine is rewarding to female quail, we speculated that estradiol may suppress activity to a degree that is insurmountable to cocaine. Experiment 3 explored this possibility using a D2 antagonist to facilitate the effects of cocaine. The antagonist enhanced acute cocaine-induced activity in female quail. Collectively, our studies suggest that estradiol may differentially mediate the behavioral response to cocaine, and that this mediation may be dependent on dopaminergic mechanisms.

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#127 Abstract Title: **Transcranial Direct Current Stimulation Combined with Peripheral Nerve Stimulation to Aid in Upper Extremity Motor Recovery after Stroke: Preliminary Findings from an Ongoing Study**

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Abstract: Both peripheral nerve stimulation (PNS) and transcranial direct current stimulation (tDCS) are non-invasive neuromodulation techniques that can upregulate neuroplasticity and enhance motor performance. Only 1 small-scale study in stroke survivors with mild hemiparesis has investigated whether these techniques have adjuvant effects. Our ongoing, double-blind, randomized, controlled study is the first to evaluate PNS combined with tDCS and upper extremity motor training for subjects with severe post-stroke hemiparesis. Each subject receives 1 of 4 conditions: 1) active PNS/active tDCS; 2) sham PNS/active tDCS; 3) active PNS/sham tDCS; or 4) sham PNS/sham tDCS. All subjects participate in 2 hours of upper extremity motor training immediately following each session of neuromodulation (10 sessions total). Our central hypothesis is that the group receiving active PNS paired with active tDCS will show significantly greater cortical neuroplastic change and significantly more improved motor function than the other 3 groups. Outcome measures include the upper extremity motor score of Fugl-Meyer Assessment (FMA), Stroke Impact Scale (SIS), and cortical reorganization (measured with transcranial magnetic stimulation). For the 36 subjects who have completed intervention to date (target n=40), ANOVA analysis of changes in FMA indicate least benefit for sham PNS/sham tDCS and most benefit for sham PNS/active tDCS. Active PNS/active tDCS led to less improvement on SIS than all other conditions. Thus, while combined PNS/tDCS may enhance outcomes of motor training after stroke, the combination of PNS with tDCS may be suboptimal in cases of severe hemiparesis. We expect final analyses to substantiate these findings and show neurophysiological correlations.

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#128 Abstract Title: Selenium deficiency is detrimental following traumatic brain injury

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Abstract: Traumatic brain injury continues to be a substantial clinical problem with few available treatment strategies. Individuals who are at a greater risk for sustaining a brain injury, such as professional athletes and military personnel, may benefit from a prophylactic supplement that would intervene in the neurodegenerative pathways immediately following injury. Different dietary levels of selenium, a cofactor for antioxidant enzymes, were supplemented in the diets of male Sprague-Dawley rats. Included in this study were diets deficient in selenium, equivalent levels to normal rat chow, and two levels of enriched selenium. Animals received diets for 4 weeks prior to receiving a severe (2.2mm) controlled cortical impact brain injury or sham craniotomy. Twenty-four hours following impact, the injury epicenter was isolated for mitochondrial respiration assays. Respiration was measured using oxygen consumption rates (Seahorse Bioscience©) in response to mitochondrial substrates, mimicking various stages of the electron transport chain. These studies showed that selenium deficiency is detrimental to mitochondrial respiration and exacerbated the observed injury effect. Additionally, animals on the selenium deficient diet had a decrease in glutathione peroxidase activation following injury. Animals given diets enriched in selenium did not show significant improvements over animals given control diets, suggesting a possible ceiling effect with selenium supplementation. The increased injury effect of selenium deficiency suggests that there are critical levels of dietary selenium for maintenance of mitochondrial function following injury. Supplementation on top of normal levels, however, may not specifically increase protection of mitochondria after TBI.

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#129 Abstract Title:	**Sox4 Regulates Choroid Fissure Closure by Limiting Hedgehog Signaling during Ocular Morphogenesis**
Author(s):	W. Wen, Dept of Biology, U of Kentucky L. Pillai-Kastoori, Dept of Biology, U of Kentucky S. G. Wilson, Dept of Biology, U of Kentucky A. Krishna, Dept of Biology, U of Kentucky A. C. Morris, Dept of Biology, U of Kentucky

Abstract: Purpose Sox4 is a member of the group C SRY-box containing transcription factors. It promotes differentiation of multiple cell lineages during development. Zebrafish have two co-orthologs of the mammalian sox4 gene: sox4a and sox4b. Their functions during zebrafish ocular development are not clear. The purpose of this project was to study the role of sox4 during eye development in zebrafish. Methods Gene expression was analyzed by fluorescent in-situ hybridization (FISH) and quantitative reverse transcript PCR (qPCR). Retinal neurogenesis was analyzed by immunohistochemistry and fluorescent reporter transgenic lines. A combination of morpholino mediated gene knockdown, mRNA overexpression, reporter gene expression, pharmacological inhibition of Hh signaling, and CRISPR/Cas9 system were used to study the function of Sox4 in ocular development. Results Sox4a/b was expressed in the brain and periocular tissues during early development. Knockdown of Sox4 caused ocular coloboma (choroid fissure fails to close). The coloboma phenotype was reduced by inhibition of Hh signaling. Consistently, the expression of pax2a in the optic stalk, which is induced by midline Hh signaling, was expanded in sox4-deficient zebrafish embryos. We found that Sox4 negatively regulates the expression of Hh ligand ihhb. Overexpression of sox4 resulted in increased expression of ihhb, caused cyclopia. The coloboma phenotype was validated by using the CRISPR/Cas9 system. It was observed in a significant number of sox4 sgRNA/Cas9 injected founder embryos. Conclusion Sox4 is required for proper choroid fissure closure by negatively regulating ihhb expression.

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#130 Abstract Title:	**Discovery of M5 Muscarinic Acetylcholine Receptor Antagonists: 1-Methyl-4-Phenylpiperidine Analogs**
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Abstract: Ventral tegmental area (VTA) dopamine (DA) neurons project to nucleus accumbens (NAc) and are believed to mediate the rewarding effects of abused drugs. Stimulation of M5 muscarinic acetylcholine receptors (mAChRs) activates VTA DA neurons (Omelchenko N et al., 2006). M5 knockout mice exhibit reduced cocaine and morphine self-administration (Fink-Jensen et al., 2003; Basile et al., 2002). Microinfusion of scopolamine (M1-M5 mAChRs antagonist) into VTA attenuates cocaine self-administration (Solecki et al., 2013). Thus, M5 mAChR antagonists may be novel treatments for drug abuse. We evaluated a series of 1-methyl-4-phenylpiperidine containing analogs as antagonists at M5 mAChRs. Affinity for 12 analogs at the [3H]N-methylscopolamine binding site was determined using Chinese hamster ovary cell membranes expressing human M1, M3 or M5 mAChRs. XZ-11341a exhibited the highest affinity at M1, M3 and M5 mAChRs (Ki = 0.67 ± 0.08, 0.37 ± 0.04, 0.38 ± 0.011 μM, respectively). Generally, replacing the ester in with an amide reduced affinity at all subtypes. For example, XZ-11343b (amide) had no affinity compared with XZ-11343a (ester, moderate affinity) at M3 mAChRs. Replacing the carbamate moiety with a carbamide also attenuated affinity at all subtypes. Current insights regarding the SAR will direct future synthetic approaches towards identifying potent selective M5 mAChR antagonists (Supported by DA030667).

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#131 Abstract Title:	**Brain arteriolosclerosis: Elucidating Clinical Risk Factors and Cognitive Consequences in Aged Individuals Using a Longitudinal Human Dataset**
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Abstract: Small blood vessel disease is a nearly universal dementia-associated pathology seen in aged brains. We focused on brain arteriolosclerosis (B-ASC), a small blood vessel pathology characterized by degenerative thickening of arteriolar walls. Here, we report evidence of clinical risk factors and cognitive consequences of B-ASC using the National Alzheimer's Coordinating Center (NACC) dataset. NACC is responsible for maintaining a database on research subject information collected from over 34 past and present NIH funded Alzheimer's Disease Centers in the US. The present analyses included clinical and autopsy information on 2,390 cases, 75.27% of which had B-ASC pathology. Inferential statistics showed that age of death ($p<0.0001$), gender ($p=0.001$), and hypertension ($p<0.0001$) were associated with B-ASC. Logistic regression analyses showed that a one-year increase in age of death significantly increased the adjusted odds of B-ASC for mild-B-ASC (1.03: C.I. 1.01 – 1.04, $p=0.002$), moderate B-ASC (1.05: 1.04 – 1.07, $p<0.0001$), and severe B-ASC (1.06: C.I. 1.03 – 1.08, $p<0.0001$) compared to no B-ASC pathology while controlling for the significant clinical covariates listed previously. Intriguingly, among the "oldest-old," the association appeared weaker (relative to younger individuals) between vascular risk factors and B-ASC. With respect to cognitive consequences of B-ASC, linear regression analyses showed that severe B-ASC pathology was associated with worse scores on the Mini Mental State Exam and Clinical Dementia Rating Scale indicative of lower global cognitive function. With this study, we are beginning to reveal the frequency, risk factors, and cognitive consequences of B-ASC -- an extremely common age-associated cerebrovascular pathology.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#132 Abstract Title: **Analysis Of Sleep Traits In Knockout Mice From The Large-scale KOMP2 Population Using A Non-invasive, High-throughput Piezoelectric System**

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Abstract: Our current study employs a non-invasive, high throughput piezoelectric system that characterizes sleep-wake phenotypes in a large population of control and single-gene knockout mice; recorded as part of the Knockout Mouse Phenotype Program (KOMP2) at JAX, which in turn is part of the IMPC (International Mouse Phenotyping Consortium). A piezoelectric sensor pad placed at the bottom of the mouse cage records gross body movements. The pressure signals thus generated are classified by an automated classifier into sleep and wake. The system characterizes traits including sleep time over 24 hours, as well as during the light and dark phase, and distribution of sleep bout lengths. The system has been well validated over many years, and matches approximately 95% with EEG and 90-95% with human observation. Quality control is ensured by a data confidence metric, automating the rejection of any poor quality data. Newer algorithms also allow sleep to be differentiated into REM vs. non-REM sleep. To date, over 150 knockout and 1000 control mice have been recorded in addition to many inbred mouse strains for more than 200 physiological and behavioral phenotypes that allow both known and unknown correlations to be assessed across the KOMP2 and the entire IMPC. The goal of this project, which aims to eventually characterize over 20,000 single gene knockout mouse lines, is to aid the scientific community to functionally annotate these genes and elucidate gene networks. We present the results of the sleep phenotyping performed thus far in this project for a variety of single-gene knockout and control mice. A number of potential genes influencing various sleep traits have been identified in these mice, and these data will also be compared and correlated with non-sleep traits as well.

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31st Annual BGSFN Spring Neuroscience Day
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#133 Abstract Title: **Intranasal Delivery of DNSP-11 in Rodent and Non-Human Primate Models of Parkinson's Disease**

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Abstract: A major issue in treating neurodegenerative disorders, including Parkinson's disease (PD), has been challenges associated with delivery of large biotherapeutics to the brain. Due to its small size and bioactivity, we hypothesized that the synthetic peptide, Dopamine neuron stimulating peptide-11 (DNSP-11), would be a candidate for non-invasive delivery to the brain using intranasal administration. Repeated intranasal administration of DNSP-11 in normal Fischer (F344) rats , under light isoflurane anesthesia, increased DA turnover at 300 µg in both the striatum and substantia nigra (*$p<0.05$) as measured by HPLC-EC. Furthermore, a one-time 125I labeled DNSP-11 intranasal dose indicated rapid uptake into the CNS, CSF and blood as measured by gamma counting and autoradiography. To determine DNSP-11's effects in a PD model, F344 rats were treated with DNSP-11 intranasally 7 days a week prior to 6-OHDA striatal injection, and 5 weeks thereafter. Here we show that repeated intranasal administration decreased d-amphetamine induced-rotation at 2 weeks (*$p<0.05$) and DA turnover in the lesioned striatum at 5 weeks as measured by HPLC-EC (*$p<0.05$) compared to vehicle. Currently, we are investigating intranasal administration of DNSP-11 in non-anesthetized, chair trained, MPTP hemiparkinsonian rhesus macaques. After 10 weeks of escalating DNSP-11 doses we observed a decrease in DA turnover in the lesioned striatum (****$p<0.05$) as measured by HPLC-EC, and rapid distribution of a one-time 125I-labeled DNSP-11 intranasal dose in the CNS, CSF and blood as measured by gamma counting and autoradiography. Cumulatively, these studies indicated DNSP-11's rapid and diffuse uptake into the CNS and neurochemical protection of the nigrostriatal system.

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#134 Abstract Title: A 'NEET' target to improve outcomes following TBI: Pioglitazone and mitoNEET

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Abstract: A major focus has developed for the discovery of neuroprotective therapeutics to help the estimated 1.7 million Americans who receive a traumatic brain injury (TBI) annually. The most promising of these therapeutics target neuroinflammation, ROS production and mitochondrial dysfunction. Pioglitazone, a known PPAR agonist, has shown promise in altering neuroinflammation and decreasing ROS production. Work from our lab also found that pioglitazone can increase mitochondrial bioenergetics, cortical sparing and functional recovery following TBI. However, these effects seem to be independent of interactions with PPAR and may be attributed to its ability to bind a novel mitochondrial protein called mitoNEET. Therefore, we hypothesize that pioglitazone's neuroprotective mechanism is dependent on interactions with mitoNEET. To test this we used mitoNEET null mice and a novel mitoNEET ligand called NL-1. Ex vivo dose response studies show that pioglitazone can increase mitochondrial bioenergetics in isolated mitochondria with and without Ca2+ insult, which is an effect lost in the mitoNEET null mice. Next, wild-type and mitoNEET null mice (pioglitazone and NL-1 study) and Sprague Dawley rats (NL-1 study) were subjected to sham or severe controlled cortical impact (CCI) TBI surgery. In these animals, pioglitazone lost the ability to increase mitochondrial respiration and provide neuroprotection in mitoNEET null mice. Lastly, the mitoNEET specific ligand, NL-1, increased cortical sparing and motor recovery following TBI. These results support pioglitazone as a novel mitochondrial targeting drug which alters mitochondria bioenergetics following TBI through interactions with mitoNEET.

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31st Annual BGSFN Spring Neuroscience Day
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#135 Abstract Title:	**The role of acetylcholine in neural circuit modulation, behavior and development in Drosophila melanogaster.**
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Abstract: Acetylcholine is the excitatory transmitter in sensory neurons as well as among neurons in the CNS of Drosophila melanogaster larvae. Activity of neurons and communicating with target neurons is important in sculpting the developing neural circuitry as well as maintaining establish connections. We are interested in investigating the role of specific cholinergic receptor subtypes in regulating sensory-motor circuits at the level of interneurons. We will report on the effect of acetylcholine and defined agonistic/antagonistic on a sensory-CNS-motor circuit. Genomic screens have confirmed the presence of ten nicotinic acetylcholine receptor subunits in Drosophila and two muscarinic subunits. A pharmacological approach will be taken in order to test the modulation of neural circuits in an open preparation. Isolating the CNS in this preparation allows for examination of modulation of motor activity without the influence of confounding variables. Genetic modified lines are being used to enhance and suppress the cholinergic system during various larval stages to examine the impact on behavior and the associated neural circuits. Knowledge regarding the expression of specific receptor subunits within the larval CNS is limited. This research will aid in identifying specific receptor subtypes that modulate sensory-motor circuits and will help increase understanding of crucial subunits that may be integral in guiding formation and maintenance of relevant neural circuits.

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#136 Abstract Title: Neuromuscular physiology in chronic and acute cold exposed crayfish

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Abstract: The crayfish, Procambarus clarkii, is an invasive species widely spread from Gulf of Mexico to great lakes. This project is to investigate how P.clarkii copes with acclimated acute and chronic cold temperature in terms of their physiology responses at neuromuscular junction. Two groups of crayfish were tested in this study: (group A) from room temperature (20°C) to acute cold temperature (10°C), and (group B) from chronic cold (10°C) to room temperature (20°C) to mimic the winter and spring scenarios. Group A crayfish were dissected and recorded their EPSPs in opener muscle in room temperature saline and then rerecorded in 10°C saline. Group B were dissected and recorded their EPSP in opener muscle in 10°C saline and then rerecorded in 20°C saline. Results: EPSP amplitudes are larger in cold temperature as compared to room temperature. Facilitation rates are increased as well. EPSPs in chronic cold muscles are larger than when they are recorded in warm saline. The EPSPs are also larger than in acute cold muscles. Muscle input membrane resistance is larger in cold temperature as compared to room temperature. This suggest a compensation in synaptic transmission in cold acclimation.

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Poster Presentation Abstracts

#137 Abstract Title: Application of Cell-Derived Vesicles in Single-Molecule Studies

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Abstract: Single molecule studies are primarily limited to proteins that can be purified and solubilized outside of the cellular environment. For membrane receptors this is usually achieved by employing surface acting agents. However, these techniques are not applicable to many types membrane receptors. These complex proteins often consist of multiple subunits and require the presence of a lipid bilayer to maintain function and structural integrity. Both are lost in a detergent environment. We isolated transmembrane proteins such as the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), nicotinic receptors, and epidermal growth factor receptors into cell derived vesicles for single molecule studies. Isolating receptors in vesicles keeps the protein intact in a native cellular membrane. Receptors contained in vesicles were isolated on the surface of a glass substrate to determine their stoichiometry. We found that α3β4 was predominately present with a (α3)2 (β4)3 stoichiometry. The stoichiometry of α3β4 was validated employing a dual-color single molecule experiment within the same vesicle. We also showed that single molecule studies of vesicles can be extended to solution based applications. Binding of epidermal growth factor (EGF) to vesicles containing epidermal growth factor receptors (EGFRs) was observed using fluorescence correlation spectroscopy (FCS). We believe these methods will extend single molecule studies to previously inaccessible transmembrane proteins.

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31st Annual BGSFN Spring Neuroscience Day
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#138 Abstract Title: **A comparative study of circadian rhythms and sleep between the house mouse (Mus musculus) and African spiny mouse (Acomys cahirinus)**

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Abstract: The study of circadian and sleep behavior in different organisms can provide valuable insight for understanding behavioral, physiological and environmental influences on these processes. Interestingly, two species of African spiny mice, Acomys russatus (Golden spiny mouse) and Acomys cahirinus (Cairo spiny mouse) have been reported to exhibit different circadian rhythm patterns in locations where the two species overlap. Both species are primarily nocturnal when not in direct competition, but in areas of overlap A. cahirinus exhibit nocturnal behavior, while A. russatus become more diurnal. However, very few studies on the circadian activity of these species are available and nothing is known of their sleep behavior, which can be the dominant force in driving other diurnal variables. Therefore, we have begun to study one of these species (A. cahirinus) in greater detail alongside the well-studied house mouse (Mus musculus) using a well validated, non-invasive, piezoelectric system, that picks up all movements during wake, and the breathing rhythms during sleep. In these studies, we found A. cahirinus and M. musculus to be primarily nocturnal, but with clearly distinct behavioral patterns. Specifically, the activity of A. cahirinus sharply increases right at dark onset, which is common in nocturnal species, but surprisingly, decreases sharply just one hour later. These differences may be related to foraging differences between these species, or may be related to the socialized behavior of A. cahirinus and its poorer adaptation to isolation as compared to Mus musculus. We have sequenced and assembled a low coverage genome for A. cahirinus and explored genes known to influence sleep and circadian rhythms in A. cahirinus and M. musculus. We are currently investigating these and other variables that might explain A. cahirinus sleep behavior including a comparison of genomic sequences between these species.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#139 Abstract Title: Chronic Effects of Repeated Mild Traumatic Brain Injuries in a Mouse

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Abstract: The majority of traumatic brain injuries (TBI) that occur every year are classified as “mild”. Many individuals, such as military personnel and athletes, are at an increased risk for sustaining multiple head injuries. It is widely presumed that if the brain is not allowed an adequate amount of time to recover, a subsequent head injury will result in more severe pathological and behavioral consequences. However, the amount of time required for recovery is not well understood. A pneumatically controlled device with a silicone tip was used to deliver a diffuse, midline impact directly onto the mouse skull which was repeated five times at either a 24h (n=8) or a 48h (n=9) inter-injury interval. In our previous studies, we found that extending the inter-injury interval from 24h to 48h significantly reduced the extent of acute inflammation and cell death in the entorhinal cortex. In this study, mice were examined periodically across 10wks for motor and cognitive deficits following repeated mild TBI. Both inter-injury intervals resulted in persistent motor and cognitive deficits for the duration of the study compared to the repeated sham group (n=10). However, neither the severity nor the duration of motor and cognitive dysfunction was significantly influenced by the inter-injury interval. Based upon histological analyses, repeated mild TBI caused persistent neurodegeneration in the optic tract, but did not appear to be associated with chronic neuroinflammation in the hippocampus or entorhinal cortex. Together this data suggests that, in mice, the longer, 48h inter-injury interval protects against an acute exacerbation of cellular pathology, but does not protect against chronic behavioral dysfunction.

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31st Annual BGSFN Spring Neuroscience Day
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#140 Abstract Title: Mtor inhibition after traumatic brain injury alters hilar interneuron excitability

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Abstract: Traumatic brain injury (TBI) is among the most common causes of acquired temporal lobe epilepsy (TLE). The latent period after injury and prior to expression of seizures includes plasticity events that support epileptogenesis, including cell loss and synaptic reorganization in the dentate gyrus. A murine model of TBI using controlled cortical impact (CCI) injury was used to examine the effect of rapamycin treatment on granule cell neurogenesis, GABAergic hilar interneuron survival, and excitability of surviving GABA neurons in mice that express GFP in a subset of inhibitory neurons (FVB-Tg(GadGFP)4570Swn/J; i.e., GIN mice). Cell counts were made in sham-operated controls, CCI-injured, and CCI-injured + rapamycin treatment (3 mg/kg) 48-72 hours after surgery. Rapamycin did not affect injury-induced hilar somatostatin inhibitory interneuron loss, but suppressed injury-induced granule cell proliferation. Whole cell patch-clamp and on-cell recordings in vitro were used to examine spontaneous EPSC frequency and action potential firing rates of surviving GFP-positive hilar interneurons in GIN mice that were treated with rapamycin for 8-12 weeks after CCI injury. Results suggest an increase in spontaneous EPSC frequency and action potential firing rate of GFP-positive hilar interneurons ipsilateral to CCI injury relative to cells contralateral to the injury. Preliminarily, rapamycin treatment resulted in a reduction in the injury-induced increase in sEPSC frequency and spontaneous firing rate of GFP hilar interneurons and reduced mossy fiber sprouting ipsilateral to the injury. Rapamycin treatment reduces the enhanced synaptic excitation of hilar interneurons after CCI in a manner consistent with a suppressing effect on granule cell reactive plasticity.

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#141 Abstract Title:	INSULIN-LIKE GROWTH FACTOR-1 OVEREXPRESSION PROMOTES SURVIVAL OF ADULT-BORN NEURONS AFTER TRAUMATIC BRAIN INJURY
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Abstract: The pathology associated with traumatic brain injury (TBI) manifests in motor and cognitive dysfunction following injury. Immature neurons residing in the neurogenic niche of the dentate gyrus (DG) in the hippocampus, a brain structure required for learning and memory, are particularly vulnerable to TBI. The inability to restore this population of hippocampal immature neurons following TBI has been causally linked to cognitive impairment. Insulin-like growth factor-1 (IGF-1) is a potent neurotrophic factor capable of mediating neuroprotective and neuroreparative processes. We have shown that elevating brain levels of IGF1 stimulates hippocampal neurogenesis, enhancing the recovery of immature neuron numbers after severe TBI in mice. However, little is known about the effectiveness of IGF1 to promote long-term survival of neurons born after injury. To this end, astrocyte-specific IGF1 conditionally overexpressing mice (IGF1-TG) and wild-type (WT) mice received controlled cortical impact (n=9/genotype) or sham (n= 2/genotype) injury and 50 mg/kg BrdU (i.p.) twice daily for 7 days following TBI. At six weeks following injury, total numbers of proliferated cells (BrdU+) and the subset expressing a mature neuronal marker (NeuN+/BrdU+) were counted at the injury epicenter (3 sections/animal). IGF1 significantly increased NeuN+/BrdU+ cell density at 6 weeks post-injury ($p<0.05$, compared to WT injured mice). These data suggest that IGF1 stimulates the formation of new hippocampal neurons acutely after brain injury and that these new neurons survive to maturity. Future studies will examine the electrophysiological function of these newborn neurons.

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#142 Abstract Title:	**Mitochondrial Supplementation after Spinal Cord Injury Maintains Cellular Bioenergetics**
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Abstract: Traumatic spinal cord injury (SCI) begins with a primary mechanical insult that develops into secondary pathophysiological cascades responsible for increasing the spread of injured tissue. Therefore, experiments are being designed to assess whether supplementing the injured spinal cord with exogenous mitochondria can potentially provide a multi-mechanistic neuroprotective approach to target critical upstream effectors of the secondary injury cascade, possibly salvaging at-risk tissue that would otherwise be compromised. Specifically, using a rat model of severe contusion SCI we are testing the hypothesis that intraspinal transplantation of exogenous mitochondria after SCI increases overall cellular bioenergetics to preserve damaged tissue and provide neuroprotection, to be further correlated with improved hindlimb function. Preliminary data indicate that transplantation of allogeneic transgenically-labeled (tGFP) mitochondria increases overall mitochondrial bioenergetics of the injured cord, acutely. Specifically, oxygen consumption rates of tissues that received 100ug mitochondria microinjected around the injury site show a trend for increased mitochondrial respiration compared to contusion injury alone after 24 hr. Ongoing studies are using confocal microscopy to evaluate host cell phenotypes which incorporate these exogenous organelles. Preliminary observations with antibodies that label the outer or inner mitochondrial membranes appear to show differential co-localization with grafted tGFP-labeled mitochondria in both naïve and injured rat spinal cords. Whether this may be attributed to damaged mitochondria, thus exposing differential membrane epitopes or their degradation by host macrophages is currently being evaluated.

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#143 Abstract Title:	**Using microarray data for an improved sleep related gene ontology and identifying candidate genes for sleep QTL**
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Abstract: Humans spend approximately one third of their lives sleeping, but compared with other biological processes, most of the molecular and genetic aspects of sleep have not been elucidated. A nearly random gene ontology and lack of a dedicated database containing a comprehensive list of sleep related genes and their function presents a hurdle for sleep researchers. Using a two-pronged approach to solve this problem, publicly available microarray data from NCBI GEO (National Center for Biotechnology Information - Gene Expression Omnibus) database was used to develop a list of sleep related genes for traits of interest. The data was analyzed using R Bioconductor and custom Perl scripts. The genes from this list were then matched with the genes in QTL (Quantitative Trait Loci) for the trait. The genes within the QTL chromosomal region matching any in the list of sleep-related genes were considered as potential candidates for causing variations in the Quantitative trait. Here we present the results from our preliminary study conducted for sleep deprivation (SD) using this approach. Three microarray datasets belonging to two superseries in GEO database were analyzed. The datasets were selected on the basis of similarity of experimental design. 227 candidate sleep related genes were identified by comparing data from control and sleep deprived mice. We were able to identify 4 candidate genes in Dps1 QTL, 2 in Dps2, and 9 genes in Dps3. These Dps loci are the QTL associated with delta power in slow wave sleep. The list contains Homer1 that has already been established as a molecular correlate of sleep loss, with alleles that appear responsible for Dps1. A second highlighted gene, Asrb, has also been previously reported as a candidate gene. Analysis of additional datasets from mice and Drosophila is underway. The advantage of this approach is that it provides more information and cross support than a simple list of sleep related candidate genes. Experimental validation of candidate genes identified using this approach will help in establishing the validity of this method. The use of microarrays and other data for improved lists of sleep related genes is not perfect, but should represent a substantial improvement over the existing list of genes returned using the query “sleep” or other similar terms in gene ontology database, and should be useful for many sleep researchers.

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31st Annual BGSFN Spring Neuroscience Day
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#144 Abstract Title: Methylglyoxal produces pain in type 2 diabetes via TRPA1 and AC1

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Abstract: Type 2 diabetic pain remains difficult to treat, in part because the mechanisms that lead to painful diabetic neuropathy (PDN) are poorly understood. Metabolic dysregulation produces an increase in the glucose metabolite methylglyoxal (MG) [1]. MG activates TRPA1 in peripheral sensory neurons to produce pronociceptive neurotransmitter release, conduction deficits (i.e. neuropathy) [2], and pain-like behavior [3]. Indeed, blood levels of MG correlate with PDN in patients [1]. Spahn et al suggest that activation of TRPA1 may alter heat sensitivity via a TRPA1-AC1-PKA-TRPV1 sensitization pathway [4]. The current data led to our hypothesis that elevated MG in diabetes contributes to heat hyperalgesia in PDN by sensitizing spinal nociceptive neurons via activation of TRPA1-AC1. We confirmed that methylglyoxal is increased in rat (Zucker Diabetic Fatty) and mouse (db/db) models of type 2 PDN. Intraplantar injection of MG produced multiple types of pain-like behaviors. MG also triggered spinal nociceptive transmission, as it evoked expression of pERK and increased intracellular calcium in superficial dorsal horn neurons. Disruption of TRPA1 attenuated pERK and pain-like behavioral responses to intraplantar MG. Knockout of AC1 abolished MG-induced hyperalgesia. Finally, the antagonists HC030031 (TRPA1), NB001 (AC1), and the novel MG scavenging peptide GERP10 attenuated hyperalgesia in db/db mice. We conclude that elevated MG in type 2 diabetes contributes to PDN through a TRPA1-AC1 dependent pathway.

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#145 Abstract Title:	NPY Y1 Receptor Signaling Masks Spinal Transmission of Chronic Pain by Inhibiting TRPV1 and TRPA1 Channels and Adenylyl Cyclase 1
Author(s):	W. Fu, Depts of Physiology, U of Kentucky B. K. Taylor, Depts of Physiology, U of Kentucky

Abstract: We previously reported that spinal neuropeptide Y (NPY) acts at the Y1 receptor . We found that when allowed to resolve for several weeks, behavioral hypersensitivity could be reinstated with intrathecal administration of Y1 receptor antagonist BIBO3304 in a dose-dependent manner. What's more, adenylyl cyclase type 1 (AC1) is negatively regulated by Gαi, which is downstream of NPY Y1 receptor, a G-protein coupled receptor. We found that AC1 germline knockout inhibited the reinstatement of hypersensitivity induced by BIBO3304. In addition, AC1 is activated by Ca2+/calmodulin following NMDA receptor activation, contributing to inflammatory and neuropathic pain. We found that the reinstatement of hypersensitivity by BIBO3304 could be reversed with intrathecal administration of NMDA receptor antagonist MK801. Taken together, NPY Y1 receptors appear to be part of an endogenous braking mechanism whereby mammals naturally recover from the NMDA receptor mediated hyperalgesia associated with inflammation and nerve injury, in an AC1 dependent manner. On the other hand, we found that the reinstatement of hypersensitivity induced by intrathecal BIBO3304 could also be reversed by intrathecal TRPA1/V1 antagonist, HC030031 and AMG9810 respectively; indicating spinal TRPA1/V1 channels are also downstream targets of spinal Y1 inhibitory signaling.

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31st Annual BGSFN Spring Neuroscience Day
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#146 Abstract Title:	**Hemorrhagic hypotension-induced hypersensitivity of vagal pulmonary C-fibers to chemical stimulation and lung inflation in anesthetized rats**
Author(s):	R.-L. Lin, Dept of Physiology, University of Kentucky Medical Center Y.-J. Lin, Dept of Physiology, University of Kentucky Medical Center F. Xu, Lovelace Respiratory Research Institute L.-Y. Lee, Dept of Physiology, U of Kentucky Medical Center

Abstract: This study was carried out to investigate whether hemorrhagic hypotension (HH) altered the sensitivity of vagal pulmonary C-fibers. The fiber activity (FA) of single vagal pulmonary C-fiber was continuously recorded in anesthetized rats before, during, and after HH was induced by bleeding from the femoral arterial catheter into a blood reservoir and lowering the mean systemic arterial blood pressure (MSAP) to ~40 mmHg for 20 min. Our results showed: 1) After MSAP reached a steady state of HH, the peak FA response to intravenous injection of capsaicin was elevated by ~5 folds. The enhanced C-fiber sensitivity continued to increase during HH and sustained even after MSAP returned to baseline during the recovery, but slowly returned to control ~20 min later. 2) Responses of FA to intravenous injections of other chemical stimulants of pulmonary C-fibers (phenylbiguanide, lactic acid and adenosine) and a constant-pressure lung hyperinflation were all significantly potentiated by HH. 3) Infusion of sodium bicarbonate alleviated the systemic acidosis during HH, and it also attenuated, but did not completely prevent the HH-induced C-fiber hypersensitivity. In conclusion, the pulmonary C-fiber sensitivity was elevated during HH, probably caused by the endogenous release of chemical substances (e.g., lactic acid) that were produced by tissue ischemia during HH. This enhanced C-fiber sensitivity may heighten the pulmonary protective reflexes mediated through these afferents (e.g., cough, J reflex) during hemorrhage when the body is more susceptible to other hazardous insults and pathophysiological stresses.

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31st Annual BGSFN Spring Neuroscience Day
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#147 Abstract Title: NFAT 4 Is Upregulated in Astrocytes in Traumatic Brain Injury Model

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Abstract: Our lab focuses on the role of the inflammatory response within brain that happens in Alzheimer's disease, traumatic brain injury, etc. One brain region that plays a vital role in learning and memory and is affected early on in these disease processes is the hippocampus. Within the hippocampus, we focus on astrocytes, which play important support roles for neurons, protecting them physically, providing nourishment, and eliminating wastes. In the face of injury or disease, these astrocytes become "activated", demonstrating hypertrophic appearance and greater expression of GFAP. Chronically activated astrocytes may lose protective functions and/or promote actions that negatively impact neuronal function and viability. The protein phosphatase calcineurin is thought to regulate astrocyte activation, in part, through de-phosphorylation of NFAT transcription factors which move into the nucleus and drive the expression of numerous genes involved in neuroinflammatory signaling. There are four calcineurin-dependent NFAT isoforms, each of which may be beneficial and/or detrimental to neural function. The question we want to answer is: which NFAT isoform is present in astrocytes and is responsible for injuring neurons. This poster focuses on expression of NFAT 1 and 4 in traumatic brain injury (TBI). Coronal brain sections were stained with antibodies to NFAT 1 and 4 and imaged using confocal microscopy. For NFAT4, there was a clear increase in expression on the injured side. NFAT 4 was expressed at high levels in astrocytes, while NFAT 1 was expressed more in other cell types. These results suggest that NFAT4 is involved in deleterious astrocyte-neuron interactions.

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#148 Abstract Title: Characterization of an Insm1 mutant in the zebrafish

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Abstract: Insm1a, the zebrafish ortholog of mammalian INSM1, is a known regulator of pancreatic beta cell differentiation, sympatho-adrenal development, and is upregulated in many cancers. Using morpholino-mediated knockdown, our lab has shown a requirement for insm1a in rod and cone photoreceptor differentiation. However, because the knockdown only persists for 4 days, we have an incomplete picture of the effect of insm1a after 4 days post fertilization (dpf). To examine the function of insm1a later in development and in the adult retina requires an insm1a mutant. Here, we present a characterization of a zebrafish line carrying a putative null mutation in insm1a (K141X). Using immunohistochemistry and cell counting, we observed that there was not a significant decrease in rod photoreceptor cells amongst homozygous mutants, indicating that the K141X mutant does not phenocopy the photoreceptor cell phenotype of the insm1a morphant during the first 4 days of embryonic development. We hypothesize that the K141X mutant protein may retain some functionality. To test whether the mutant allele is sufficient for normal photoreceptor development, we are using both wild type and K141X mutant mRNA to attempt to rescue the photoreceptor specific phenotype of the insm1a morphants.

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#149 Abstract Title:	**Modulation of Habituation in Autonomic Control of Heart Rate and Tail Flips in Crayfish**
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Abstract: Habituation is an evolutionary adaptation where an organism learns to ignore a repeated stimulus that provides no new information. It is considered to be the simplest form of learning, and therefore key to understanding the more complex forms of mental association. This project investigates several possible modulators for the process of habituation: nicotine, serotonin (5-HT), and low ambient temperatures. All three of these modulators were predicted to decrease the rate of habituation. These effectors were tested by repeatedly stimulating the crayfish in two ways to observe habituation in tail flips and heart rate (HR). The first was by tapping the crayfish on their tails with a glass stirring rod, then recording whether or not the crayfish tail flipped. The second method was exposing the crayfish to constant light for four hours, then cutting the lights for one second. Both procedures also employed impedance detectors to record the crayfish HRs during the experiment, and monitoring the length of the pause in heart rate in response to the stimulus. Any change in HR in response to the trials was calculated. The first treatment had the following groups of subjects: control, low dose of nicotine, and high dose of nicotine. The second used control, saline injected, serotonin injected, and reduced temperature crayfish. The trials in this project are still underway, and therefore no conclusions can be drawn yet. However, preliminary evidence suggests that 5-HT and nicotine are slowing down the rate of habituation or, in other words, prolonging the time to habituate. This study hopes to shed light onto mechanisms regulating habituation in defined neural circuits.

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31st Annual BGSFN Spring Neuroscience Day
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#150 Abstract Title: **Role of calcium ions in the positive interaction between TRPA1 and TRPV1 channels in bronchopulmonary sensory neurons**

Author(s): C. C. Hsu, Dept of Physiology, School of Medicine, U of Kentucky
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Abstract: Both transient receptor potential ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1) receptors are abundantly expressed in bronchopulmonary C-fiber sensory nerves, and can be activated by a number of endogenous inflammatory mediators. A recent study has reported a synergistic effect of simultaneous TRPA1 and TRPV1 activations in vagal pulmonary C-fiber afferents in anesthetized rats, but its underlying mechanism was not known. This study aimed to characterize a possible interaction between these two TRP channels and to investigate the potential role of Ca2+ as a mediator of this interaction in isolated rat vagal pulmonary sensory neurons. Using the perforated patch-clamp recording technique, our study demonstrated a distinct positive interaction occurring abruptly between TRPA1 and TRPV1 when they were activated simultaneously by their respective agonists, capsaicin (Cap) and allyl isothiocyanate (AITC), at near-threshold concentrations in these neurons. AITC at this low concentration evoked only minimal or undetectable responses, but it markedly amplified the Cap-evoked current in the same neurons. This potentiating effect was eliminated when either AITC or Cap was replaced by non-TRPA1 and non-TRPV1 chemical activators of these neurons, demonstrating the selectivity of the interaction between these two TRP channels. Furthermore, when Ca2+ was removed from the extracellular solution, the synergistic effect of Cap and AITC on pulmonary sensory neurons was completely abrogated, clearly indicating a critical role of Ca2+ in mediating the action. These results suggest that this TRPA1-TRPV1 interaction may play a part in regulating the sensitivity of pulmonary sensory neurons during airway inflammatory reaction.

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31st Annual BGSFN Spring Neuroscience Day
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#151 Abstract Title: **Using an Economic Demand Function to Model the Opioid System's Effects on Cocaine Reinforcement in Environmentally Enriched and Impoverished Rats**

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Abstract: The endogenous opioid system has been implicated in motivational processes but its precise role in reward remains undetermined. Environmentally enriched (EC) and impoverished (IC) rats were pretreated with the opioid receptor ligands naltrexone and morphine before undergoing cocaine self-administration using a within session demand procedure. It was hypothesized that naltrexone would increase the essential value (α) of cocaine in both EC and IC rats. Additionally, because of their proposed higher opioid tone, EC rats were hypothesized to show greater increases in essential value after naltrexone pretreatment compared to IC rats. Thirteen male Sprague-Dawley rats were placed in EC or IC immediately after weaning. Upon reaching adulthood, all rats were trained on a within session demand procedure that measured cocaine consumption under changing cocaine price by decreasing the dose of cocaine earned throughout a 60 min session. Rats were able to self-administer cocaine on a FR1; every 10 mins the cocaine dose was systematically decreased (0.75 - 0.003 mg/kg/infusion cocaine). After 10 days of training on this procedure, rats were randomly pretreated with 0, 0.3, and 3 mg/kg morphine once every 3 days, followed by random pretreatments of 0, 1, and 3 mg/kg naltrexone once every 3 days. Morphine significantly increased α for both EC and IC rats. Additionally, EC rats had a significantly greater α compared to IC rats after morphine pretreatment. Naltrexone tended to increase α for EC but not IC rats, but this result was not significant. This study sheds light on the opioid system's contribution to reward value attribution and provides new insights into endogenous opioid functioning in EC and IC rats.

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31st Annual BGSFN Spring Neuroscience Day
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#152 Abstract Title:	**The protective effect of enrichment on drug abuse vulnerability may reflect a decrease in mood-based impulsivity using a rat model of negative urgency**
Author(s):	D.B. Vazquez-Sanroman, Dept of Psychology and Center for Drug Abuse Research Translation, U of Kentucky M.T. Bardo Dept of Psychology and Center for Drug Abuse Research Translation, U of Kentucky

Abstract: BACKGROUND: Impulsivity generally focus on: sensation seeking, lack of planning, lack of perseverance and negative urgency (NU). NU is a mood-based construct that refers to the tendency to act rashly in response to distress (Cyders and Smith, 2008). While NU has been shown to be a predictor of drug abuse, little is known if NU is modulated by environmental factors. The current study explored the effects of enriched and isolated housing in a behavioral rat model of NU. HYPOTHESIS: Rats raised in an enriched environment would display less NU than rats raised in an isolated environment. METHODS: 24 Male Sprague-Dawley rats were used in this study. Enriched condition (EC): 8 rats were housed in cage with 14 novel objects. Social condition (SC) 2 rats were rearing in NIH standard housing conditions. Isolated condition (IC): rats were placed singly housed. Rats were first trained in an operant conditioning chamber to expect a non-contingent food reward (US) upon presentation of a light (CS). They then received operant training for food reward on an FR10. After acquisition, the Pavlovian (PV) and operant (OP) components were alternated and the number of responses in the OP were measured. Randomly, the expected food reward in the PV was omitted and responding in the OP was measured. NU was defined by the increase in responding observed following reward omission compared to responding following reward presentation. RESULTS: To address differences in response rates a 2x3 (trial type x environment) ANOVA was conducted. A significant main effect for trial type [$F(1, 42)=13.15$, $p<0.0001$] and environment [$F(1,42)=19.59$, $p<0.0001$] and interaction effect [$F(1, 42) = 8.49$, $p <0 .0001$] was found. Tukey's HSD test revealed that IC rats increased their OP rates following unexpected reward omission ($p<0.01$). In contrast, neither EC nor SC rats modified their response rate after the omission trials. IMPORTANCE OF FINDINGS: The current results indicate that IC rats, but not EC nor SC rats, developed NU as modeled by a reward omission task. This results are important within the context of previous work showing that enrichment protects against drug abuse in preclinical models. We are performing immunofluorescence analysis in order to identify the possible neurobiological mechanisms involve in the expression of the environment-dependent NU phenotype.

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31st Annual BGSFN Spring Neuroscience Day
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#153 Abstract Title: **Inhibitory synaptic quantal and variability analysis in the dorsal motor nucleus of the vagus: does diabetes alter synaptic release?**

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Abstract: Variability in GABAergic synaptic transmission is related to the probability of quantal release, intrinsic properties of the receptor systems, and/or fluctuations in GABA concentrations. Changes in GABA currents have been identified in the dorsal motor nucleus of the vagus (DMV) after induction of diabetes. However, little is known about quantal GABA release or synaptic variability within the DMV, making it difficult to assess mechanisms underlying these altered GABA responses. The present study investigated synaptic release and response properties under both normal conditions and after the induction of hyperglycemia in mice. Individual DMV neurons demonstrate significant variability in GABAergic inhibitory postsynaptic current (IPSC) properties (amplitude, weighted decay time, and charge transfer). This variability was elevated after blocking glutamate release implicating presynaptic glutamatergic neurotransmission in IPSC synaptic variability. In normal aCSF, frequency, amplitude variability, and weighted decay time of IPSCs were altered after the induction of hyperglycemia. Blocking glutamate transmission eliminated these differences. Although these changes were not related to changes in quantal release, the mRNA expression of traditional synaptic receptor subunits was elevated. These results suggest that changes in GABAergic IPSCs after diabetes may be related to 1) increased GABAA receptor concentrations resulting in elevated numbers of unbound postsynaptic receptors and 2) increased synchronous release of GABA through presynaptic glutamatergic transmission at GABAergic terminals in the DMV. These findings indicate novel changes in the DMV after experimentally-induced diabetes that may lead to altered parasympathetic visceral regulation and prompts future studies to investigate quantal and synaptic variability properties in the brainstem's DMV.

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31st Annual BGSFN Spring Neuroscience Day
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#154 Abstract Title: Matrix-Metalloproteinases in Blood-Brain Barrier Dysfunction in Epilepsy

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Abstract: With more than 50 million patients worldwide, epilepsy is the most common neurological disorder. The blood-brain barrier (BBB) is severely altered in epilepsy and plays a critical role in seizure genesis and resistance against anti-epileptic drugs. One of the consequences of epileptic seizures is BBB leakage, which in turn triggers new seizures. Recent studies show that increased brain glutamate levels during seizures lead to barrier dysfunction including BBB leakage, increased efflux transporter and metabolic enzyme levels, and decreased influx transporter levels. One factor involved in BBB leakage is an increase in protein expression and activity levels of matrix-metalloproteinases (MMP). Here, we focused on MMP-2 and MMP-9, which are known to cause BBB leakage by digesting tight junction proteins as well as the basal lamina. We isolated brain capillaries from rats and exposed them to glutamate to mimic seizure conditions ex vivo, and used a novel combined in vivo/ex vivo approach of isolated brain capillaries from animal seizure models to study MMP expression and activity. We detected MMP-2 and MMP-9 protein expression and overall MMP activity in isolated capillaries and demonstrated that exposing capillaries to glutamate resulted in BBB leakage, decreased tight junction protein levels, and increased MMP-2 and -9 protein and overall MMP activity levels. We confirmed these findings in vivo in brain capillaries from rats that experienced status epilepticus. Our data support the hypothesis that glutamate released during seizures signals BBB leakage through MMP-2 and MMP-9.

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#155 Abstract Title:	**Persistent cognitive deficits following head injury in APP/PS1 knock-in mice are associated with increased amyloid pathology and altered glial responses**
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Abstract: Epidemiological studies show a history of head injury is associated with increased risk and earlier onset of Alzheimer's disease (AD) pathological and cognitive changes. Similarly, clinical findings show that neuroinflammation is chronically elevated after even a single head injury. However, little is known about how a single head injury can accelerate the onset and/or increase AD-related pathology. We hypothesized that an altered neuroinflammatory response following a traumatic brain injury might be a contributing factor to these pathological changes. Experimentally, we administered a closed head injury (CHI) to either APP/PS1 knock-in (KI) mice or wild-type (WT) control mice starting at 8 months of age, prior to cognitive deficits in the KI mice, and then measured various endpoints at 9h, 1d, 7d, 1m, and 2m post-injury. At 1m post-injury, injured KI mice exhibited a significant cognitive impairment in the radial arm water maze compared to sham KI mice or injured WT mice. There was also a significant injury-induced increase in amyloid plaques at 2m post-injury. Interestingly, we found that the temporal astrocyte and cytokine response in the injured KI mice was delayed compared to the injured WT mice. We also found that once activated, the glial injury response in the KI mice failed to resolve compared to the injured WT mice, resulting in chronic glial activation. Overall, our data support the hypothesis that CHI in the context of AD susceptibility can lead to greater cognitive impairment via mechanisms that involve glia neuroinflammatory responses.

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31st Annual BGSFN Spring Neuroscience Day
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#156 Abstract Title: Progress Towards Generating Zebrafish Models of Retinitis Pigmentosa

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Abstract: Retinitis pigmentosa (RP) is a genetically inherited disease that causes degeneration of photoreceptor cells in the eye. A number of cases are due to mutations in the G-protein coupled receptor rhodopsin, which plays a role in visual phototransduction. To better understand how different mutations in rhodopsin or RHO contribute to RP, we plan to generate constitutive and inducible transgenic lines in zebrafish that express human mutant RHO alleles previously identified in patients. Zebrafish provide an attractive model for retinal diseases because they possess a cone-rich retina and conserved retinal lamination similar to human. Also, because zebrafish regenerate photoreceptors, we can discover pathways promoting retinal regeneration and investigate novel approaches to induce regeneration in mammals. To generate these lines, we are using the Tol2 and Ac/Ds transposon systems and the Xenopus rhodopsin promoter (XOPS5.5) to drive expression of mutant RHOs in zebrafish photoreceptors. As a proof of principle experiment, we created a plasmid with XOPS5.5 driving mCherry to demonstrate promoter specificity in zebrafish photoreceptors. We have also generated constitutive and inducible constructs for five mutations (P23H, R135L, K296E, T58R, and P347S) along with wild-type human RHO. We have injected these constructs into zebrafish embryos and will raise them to screen for stable transgenic lines. Future experiments will include characterizing the different mutations including their role in activating cell death pathways, how they affect photoreceptor morphology and function, and whether zebrafish regenerate photoreceptors using similar or different mechanisms depending on the mutation.

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#157 Abstract Title: Age-related neuroinflammatory responses in spinal cord injury

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Abstract: The incidence of spinal cord injury (SCI) among older individuals has increased in recent years. In order to understand the impact of receiving an SCI at an older age, we compared locomotor and anatomical recovery in 4-month-old (4 MO) and 14-month-old (14 MO) mice after mild thoracic contusion SCI. We hypothesize that age will have a negative impact on repair and recovery after SCI. By 3 days post injury (dpi), there were significant differences in functional deficits between 4 MO and 14 MO mice that remained for 28 days as measured by the BMS, grid walk, and DigiGait analysis. Additionally, there was a significantly less spared tissue and longer lesion length in 14 MO mice as compared to 4 MO animals. Age is a key regulator of macrophage function and aging is associated with increased activation of pathological macrophage phenotypes. Therefore, we hypothesize that age-related differences in the macrophage response may contribute to worse recovery in 14 MO animals after SCI. Using a comprehensive gene array, we found a different pattern of macrophage activation between 14 MO and 4 MO animals. Specifically, 14 MO showed increased activation of pro-inflammatory macrophages and dampened activation of pro-reparative phenotypes. Collectively, these data demonstrate an important role for age in changes of inflammatory responses and functional recovery in the context of SCI. Our data highlight the potential for immunomodulatory therapies to have decreased efficacy in aged individuals receiving SCI, and the need to elucidate the cellular mechanisms contributing to age-related differences in functional recovery.

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31st Annual BGSFN Spring Neuroscience Day
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#158 Abstract Title:	**Surgical Hardware Modifications for Sural Nerve Graft Implants into the Rhesus Macaque Midbrain**
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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by a loss of dopaminergic function. There is currently no effective treatment to slow or prevent its progression. Studies have shown that neurotrophic factors can promote dopaminergic function in areas like the substantia nigra, which is affected in PD. It has also been shown that Schwann cells in peripheral nerves might be a source of growth factors, including GDNF, NDF, BDNF, and NT-3. An FDA-approved Phase I clinical trial is currently ongoing at the University of Kentucky to assess the safety and efficacy of implanting an autologous sural nerve graft into the substantia nigra of PD patients. Functional improvements have been seen in these patients post-implant. However, the exact effect the sural nerve implant has on surrounding brain tissue is unclear. To address this knowledge gap, similar procedures were performed in two normal, adult female rhesus macaques to study the histological and neurochemical effects from the implanted nerve grafts in the brain of a species relevant to humans. In order to perform the implants, surgical hardware needed to be adapted to the smaller rhesus brain. Thus, a modified cannula/stylet assembly and modified Nexdrive system were implemented. First, the tip of a stainless steel 18G cannula/stylet was cut down to have a tapered blunt end. Then, a 1x 5mm side window was created, 4mm up from the cannula tip to load the sural nerve tissue. Next, a Nexdrive system was adapted to hold the cannula while allowing both the cannula and stylet to be individually locked down for insertion into the brain parenchyma. It was also modified to allow retraction of the cannula while the stylet was locked down to deliver the sural nerve tissue into the substantia nigra. The instruments were successfully tested in gels for accuracy and delivery of nerve tissue, prior to surgery. Then, MRI-guided sural nerve grafts were performed in both animals without post-surgical complications. The animals were monitored for 8 weeks post-implant for changes in motor function and/or body weight, at which point they were necropsied and brain tissue collected for analysis. No significant changes in body weight or locomotor activity were observed over the course of the study. Histological and neurochemical analyses indicate sural nerve tissue delivery to the substantia nigra with no changes in dopamine function. We conclude that our modified surgical hardware can be safely used to successfully deliver sural nerve tissue to the rhesus midbrain to further understand the associated mechanisms of action and support further clinical development of this promising therapy.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#159 Abstract Title: **TRPV4, a Pancreatic Nociceptor, Potential Therapeutic Target for Relief of Visceral Pain**

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Abstract: Pain is a major clinical challenge. The pathogenesis of pain in pancreatitis is poorly understood and its treatment has been largely empirical. Surgical and other invasive methods have a variable and unsatisfactory outcome. There is a great need for discovery of pathogenesis of pain conditions in chronic pancreatitis and new therapeutic targets. Human and animal studies have indicated a critical role for neuronal mechanisms that result in peripheral and central sensitization. Pancreatic nociceptors seem to be significantly affected in these conditions. Among these nociceptors, the transient receptor potential (TRP) cation channel subfamily member, TRPV1 and TRPA1 have been extensively investigated for their roles in somatic and visceral hypersensitivity for decades. Recently, TRPV4 is evidenced to contribute to the pain associated with acute pancreatitis. But the role of TRPV4 in chronic pancreatitis needs to be further elucidated. In the present study, an alcohol/high fat diet (AHF) induced chronic pancreatitis rat model was employed to investigate the role of TRPV4 in visceral nociception. The results showed that rats with AHF pancreatitis developed referred visceral pain-like behaviors i.e. decreased mechanical threshold on the hind paw, shortened thermal withdrawal latencies on the abdomen and the feet. These secondary sensitization conditions associated with AHF chronic pancreatitis were effectively alleviated by TRPV4 antagonist, HC 067047. Furthermore, these conditions were also attenuated by a peripheral opioid receptor agonist, loperamide, in a naloxone reversible fashion. This study with strong evidence presents TRPV4 channel as pancreatic nociceptor, a potential new therapeutic target molecule for the treatment of visceral pain.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#160 Abstract Title:	**Exercise at Midlife Reverses Glial and Neurovascular Markers of Unhealthy Brain Aging**
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Abstract: Healthy brain aging and cognitive function are promoted by exercise. The benefits of exercise are attributed to several mechanisms, many which highlight its neuroprotective role via actions that enhance neurogenesis, neuronal morphology and/or neurotrophin release. However, the brain is also composed of glial and vascular elements, and comparatively less is known regarding the effects of exercise on these components in the aging brain. Here, we show that aerobic exercise at mid-age decreased markers of unhealthy brain aging including astrocyte hypertrophy, a hallmark of brain aging. Middle-aged female mice were assigned to a sedentary group or provided a running wheel for six weeks. Exercise decreased hippocampal astrocyte and myelin markers of aging but increased VEGF, a marker of angiogenesis. Brain vascular casts revealed exercise-induced structural modifications associated with improved endothelial function in the periphery. Our results suggest that age-related astrocyte hypertrophy/reactivity and myelin dysregulation are aggravated by a sedentary lifestyle and accompanying reductions in vascular function. However, these effects appear reversible with exercise initiated at mid-age. As this period of the lifespan coincides with the appearance of multiple markers of brain aging, including initial signs of cognitive decline, it may represent a window of opportunity for intervention as the brain appears to still possess significant vascular plasticity. These results may also have particular implications for aging females who are more susceptible than males to certain risk factors which contribute to vascular aging.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#161 Abstract Title:	**Altering the Progression of Parkinson's Disease: A Twelve Month Study of Peripheral Nerve Graft Implants into the Substantia Nigra in Participants Undergoing Deep Brain Stimulation Surgery**
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Abstract: In Parkinson's disease (PD), the substantia nigra undergoes a loss of dopaminergic cells and cell function that results in the motor symptoms of PD. Peripheral nerve grafts to the CNS may provide an opportunity to directly deliver neurotrophic factors in areas affected by neurodegenerative diseases. After DBS leads were implanted, a section of sural nerve (approximately 5mm in length) containing Schwann cells was excised and unilaterally delivered into the area of the substantia nigra contralateral to the most affected side. Adverse events were continuously monitored. Motor function was evaluated through assessment on the Unified Parkinson's Disease Rating Scale (UPDRS) before surgery and at 1, 3, 6, 9, and 12 months after surgery. We have implanted 8 of 8 participants (average age: 62.9 ± 9.2 years; duration with the disease: 9.8 ± 9.2 years; Mean ± SD) with no significant adverse events. Immediate, postoperative MR scans did not indicate evidence of abnormal tissue disruption. For five participants who have completed the study, motor scores off medication/off stimulation were 24.6 ± 13.5 points while at baseline they were 34.2 ± 8.0 points (moderate clinically important differences are defined as >5 points, Shulman et al. 2010). On medication/on stimulation scores were 14.8 ± 9.7 points at baseline and 9.6 ± 7.2 at 12 months. All the while, medication levels decreased from 775 ± 618 daily levodopa equivalents, pre-operatively, to zero after 12 months. Based on our initial safety outcomes and early efficacy results, combining Schwann cell delivery with DBS therapy may provide a means of offering neuro-regenerative therapy that may augment the benefits of DBS in patients with PD resulting in a change in the time course progression of this degenerative disease. Support provided by gifts to the Brain Restoration Center, Tom Dupree for Parkinson's Disease Research, University of Kentucky start-up funds (CVH) and the National Center for Advancing Translational Sciences, through grant UL1TR000117. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#162 Abstract Title:	**Human Deep Brain Stimulation Surgery as an Opportunity to Conduct Translational Neuroscience Research**
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Abstract: Deep brain stimulation (DBS) therapy has been approved for over a decade for the treatment of a variety of neurological and neurodegenerative diseases with the prospect of treating many more neurological disorders. The invasive nature of DBS surgery and the access to the deeper structures of the brain that DBS provides present unique opportunities for translational studies in neuroscience research. Typically, DBS surgery involves the formation of frontal bur holes through the skull and exposure of the cortical surface for electrode implantation. This is followed by electrophysiological recordings of deep areas of the brain such as the putamen, globus pallidus, subthalamic nucleus, and thalamus while the patient is conscious or under general anesthesia. Afterward, a four-electrode DBS lead is implanted and the DBS system is connected. DBS therapy to relieve symptoms then occurs over weeks or months as stimulation parameters are adjusted. Within each phase of DBS surgery and therapy, unique opportunities exist for translational neuroscience research.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#163 Abstract Title: **Region- and Time-Specific Intranasal Insulin Signaling in Young and Aged F344 Rats**

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Abstract: Metabolic syndrome is defined as a constellation of symptoms including insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, and central obesity. As insulin secretion begins to fail, the syndrome frequently converts to Type 2 diabetes mellitus (T2DM). While the impact of T2DM in aging is well-studied in the periphery, it is also becoming clear that central insulin resistance impacts brain function. To combat insulin resistance in the brain, several studies including ours, have used intranasal insulin delivery to offset memory impairment. However, the response of different brain regions to intranasal insulin as a function of time and age following delivery has not yet been determined in the F344 rat model of aging. We tested the impact of zinc-free insulin Apidra® on 8 different brain regions of young and aged F344 rats (n=8/age group). Animals received a unilateral intranasal dose of Apidra® at a concentration equivalent to those used in several clinical trials (0.0715 IU/rat) or saline. Olfactory bulbs and brains were removed at 30, 60, or 120 min after insulin delivery, and brains sectioned into 2 olfactory bulb, 3 dorsal, and 3 ventral regions. The activity of insulin was quantified with a focus on the canonical Akt and pAkt protein expression pathway. The pAkt:Akt ratio significantly increased at 30m in the right olfactory bulb, which was exposed to insulin, and went down to normal levels by 120 min. Dorsal and ventral signaling increases were noted at 60 and 120 min post delivery. These results provide novel insights for improved timing between insulin delivery and behavioral characterization.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#164 Abstract Title:	The Effect of Early-life Antipsychotic Drug Administration on Impulsivity in Adult Rats

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Abstract: The number of children receiving antipsychotic drugs (APDs) has risen over the past two decades. Of the APDs used to treat childhood behavioral disorders, risperidone is the most commonly used. Previous studies conducted by our lab have found that rats administered risperidone between postnatal days (PNDs) 14-42 were hyperactive in adulthood. The present study sought to determine if rats that received risperidone were also more impulsive during adulthood. Rats received daily administration of risperidone (1.0 or 3.0 mg/kg doses), or a control vehicle solution during PNDs 14-28. Rats began testing on the differential rates of low responding (DRL) task on PND 121. The purpose of the DRL task was to measure learning and impulsivity. The task rewarded rats with a single food pellet if they pressed a lever no less than every 15 seconds. If the rat responded before 15 seconds had elapsed since the last lever press, they did not receive a food pellet. During the first four weeks of testing, rats administered the high dose of risperidone were more impulsive than the low dose group and vehicle group, pressing the lever more often prior to 15 seconds since the last lever press. On the 7th and 8th weeks of testing, the low dose risperidone group displayed less impulsivity, and performed better on the task than the high dose and vehicle groups. The results of testing indicate that high doses of risperidone lead to changes in the developing brain that encourage increased impulsivity. These data raise concerns regarding impulsivity in young adults who have been exposed to APDs as children.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#165 Abstract Title:	**Effects of Impact Force and Duration on Functional Outcomes from Spinal Cord Injury**
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Abstract: Spinal cord injury (SCI) often results in life-long complications and tremendous healthcare costs. Long-term effects are largely due to the limited treatment options for SCI. One challenge to translational research and development of effective SCI therapy is the unique nature of each injury. Two unique and potentially clinically relevant factors in SCI are impact force and duration; a deeper understanding of the effects of these variables can help enhance treatment practices. We hypothesize that increased impact force and duration (as independent factors and when interacting) will decrease functional recovery and tissue sparing after SCI. We performed mild to moderate spinal cord impacts with or without compression (50dkyn, 50kdyn + 20s dwell, 75kdyn, and 75kdyn + 20s dwell) on mice and tested our hypothesis by grading functional recovery using the Basso Mouse Scale (BMS) and by immunohistochemical analysis of resultant lesions. In accordance with our hypothesis, increased impact force and duration decrease functional recovery and tissue sparing. In our model, 50kdyn + 20s dwell mice have similar functional recovery to 75kdyn mice, allowing for further investigation into the mechanical and cellular impact of compression as an independent factor. Continuation of this study will include functional recovery at later time points and investigations into the effects of impact force and duration on aspects of secondary damage. Specifically, it will investigate effects on macrophage phenotype, which can be either neurotoxic (M1) or neuroprotective (M2). Collectively, these data will provide valuable insight into the effects of impact force and duration that can aid in improving translational research and, ultimately, treating SCI.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#166 Abstract Title:	**Azithromycin Alters Macrophage Response to Spinal Cord Injury and Improves Functional Recovery**
Author(s):	W.M. Bailey, SCoBIRC and the Dept of Physiology, U of Kentucky B. Zhang, SCoBIRC and the Dept of Physiology, U of Kentucky D.J. Feola, Dept of Pharmacy Practice and Science, U of Kentucky College of Pharmacy J.C. Gensel, SCoBIRC and the Dept of Physiology, Kentucky Injury Prevention and Research Center, U of Kentucky

Abstract: Macrophages persist indefinitely at sites of spinal cord injury (SCI) and contribute to both pathological and reparative processes. More specifically, the classically activated macrophage phenotype (M1) is associated with cell loss and pathology whereas the alternatively activated phenotype (M2) is believed to promote cell protection, regeneration, and plasticity. Thus, identifying non-invasive, clinically viable, pharmacological therapies for altering macrophage phenotype is an important challenge for the SCI field. Azithromycin (AZM), a common clinical antibiotic, has been shown to increase M2 and decreases M1 macrophage activation and exhibit anti-inflammatory properties in lung infection and chronic airway inflammation such as cystic fibrosis (CF). We hypothesize that pre-treatment with AZM can polarize macrophages toward an M2 phenotype, increase tissue sparing and improve locomotor function after SCI. We have shown daily AZM treatment by oral gavage starting three days prior and continuing seven days post moderate spinal contusion improves tissue sparing and recovery in SCI mice. These improvements in histological and gross motor function measures correspond with additional improvements in fine locomotor function. Further, AZM increases M2 and decreases M1 macrophage activation in our mouse SCI model. Measuring this connection between phenotype and neuroprotection more directly in vitro, we have shown AZM treatment alters the phenotype and lowers neurotoxic potential of pro-inflammatory, M1 macrophages. Taken together, these data suggest that pharmacological intervention can alter macrophage phenotype in SCI. While further studies are needed to determine dose response and therapeutic window, AZM remains a strong candidate for a new non-invasive and clinically viable SCI therapy.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#167 Abstract Title:	**Measures of serotonin and dopamine dynamics within intact animals using in vivo electrochemistry**
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Abstract: Modulators, such as serotonin (5-HT) and dopamine (DA), are known to be present in crustacean (e.g. crayfish) and insect (e.g. Drosophila) hemolymph, and are well established to alter behavior and physiological function. Various behavioral responses in crustaceans are assumed to be due to release of modulators into the hemolymph as behavior can be correlated with injections of the same compounds. However, it has been challenging to obtain measures of these modulators in intact animals without stressing the animal to withdraw hemolymph thus, in vivo levels of DA and 5-HT associated with behaviors remain relatively unknown. We propose to use in vivo electrochemistry (chronoamperometry) to measure endogenous DA and 5-HT within intact crayfish and drosophilae. A recording electrodes consisting of 30 µm carbon fiber coated with nafion™ and a reference electrode (Ag/AgCl) are placed just under the cuticle over the heart and glued in place in the crayfish. For Drosophila larvae, the recording electrode will be placed within the larvae and the reference electrode placed on a saline soaked filter paper on which the larvae are placed. Square-wave pulses (200 ms) from 0.0 to +0.55 V are applied vs. an Ag/AgCl reference electrode at a rate of 1 Hz and the resulting currents (oxidation, reduction) are digitized using a FAST16 system (Quanteon LLC). Using this approach we proposed to study various behavior and physiology (e.g. movement, response to stimuli, heart rate) and examine endogenous release of the DA and/or 5-HTdirectly in the hemolymph. These studies will help us further our understanding of the role of these substances within the hemolymph in crustaceans and insects.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#168 Abstract Title: The Effects of TRPM8 Variants on Migraine

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Abstract: TRPM8 is a member of the transient receptor potential cation channel family. TRPM8 is a ligand-gated ion channel that is activated by cold or menthol. When activated, the TRPM8 protein lets Na+ and Ca2+ ions enter the cell, which depolarize the cell and generate action potentials. The somatosensory cortex in the brain perceives the incoming signal as the sensation of cold. Markus Schurks' research found that heredity is an important aspect in susceptibility to migraines. About 50% of effected individuals have a first-degree relative who suffers from migraine, which supports the idea that migraine risk is modulated by polymorphisms in the human genome. A single nucleotide polymorphism (SNP), rs10166942, was recently found to be associated with migraine risk in three large genome-wide association studies. People with the minor SNP allele have reduced risk of migraines. More recently, the minor SNP allele was also associated with lower sensitivity to cold. Two SNPs, rs13004520 and rs17868387, were found that are co-inherited with one another 100% in people and were in robust linkage disequilibrium with the migraine SNP. Both of these SNPs change TRPM8 amino acids (missense mutations). These mutations are predicted by poly-Phen to alter TRPM8 function. The minor and major alleles of the TRPM8 gene are being inserted to pcDNA5/FRT/TOPO, a tetracycline inducible vector, to avoid the toxicity found with long-term high TRPM8 gene expression in G418 selected AD293 cells. Using menthol or cold stimulus, the response of the two forms of the TRPM8 cells will be tested. When stimulated by cold or menthol, we hypothesize that cells with the minor allele form will import less Na+ and Ca2+ in response to cold or menthol. This is because people with the minor allele reported less intense cold pain. Elucidating the function of these two SNPs will thus show how we may be able to alter TRPM8 function to reduce the risk of migraine.

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Poster Presentation Abstracts

#169 Abstract Title:	**Role of cAMP in synaptic vesicle recruitment to synapses at high and low output neuromuscular junctions.**
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Abstract: Synaptic efficacy among neurons communicating to other neurons or to targets, such as skeletal muscle, is a dynamic process throughout development and for established synapses. The ability of synaptic function to increase or decrease in regulating the appropriate range of synaptic transmission is important in maintaining correct neural responses. Subtle changes in synaptic modulation can have pronounced acute and chronic effects. Vesicles are distributed inside a nerve terminal as a readily releasable pool (RRP) and a reserve pool (RP). The ability to mobilize the RP is known to be regulated by various second messengers (i.e. cAMP, IP3, PKA) depending on the type of preparation. Few studies have examined the differences in mobilizing the RP by cAMP following synaptic depression induced by high frequency stimulation; the same goes for synapses which are deemed high or low in synaptic efficacy. The hypotheses I am testing at the crayfish and larval Drosophila neuromuscular junctions (NMJs) are: (1) Low output synapses will show a greater degree of synaptic enhancement due to activation of cAMP as compared to high output synapses; (2) after induction of high frequency evoked depression, little recruitment of RP vesicle will occur in either synapse type; and (3) enhancing the cAMP production will lead to enhanced synaptic depression in the low output synapses as compared to high output synapses. Activation of cAMP by application of forskolin, an activator of adenylate cyclase, was used. Low output NMJs increased by 127.8% with prior 1hr incubation and only 36.16% without incubation of forskolin (N=5, $P< 0.05$). A 56.29% (n = 5) increase occurred after depression without incubation. Studies are underway with high output crayfish and Drosophila NMJs. These studies are significant as the results will inform us which types of synapses may be modulated by pharmacological agents for therapeutic targets.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#170 Abstract Title:	**A '3 trimester' mouse model to study the effects of Maternal Ethanol Exposure on the Elevated Plus Maze Mice**
Author(s):	R. Gupta, Dept of Psychology, U of Kentucky A. Hawkey, Dept of Psychology, U of Kentucky W. Xu, Dept of Pharmacology, U of Kentucky H. Li, Dept of Pharmacology, U of Kentucky G. Chen, Dept of Pharmacology, U of Kentucky S. Barron, Dept of Psychology, U of Kentucky

Abstract: Drinking ethanol (ETOH) during pregnancy can have adverse effects for the developing offspring. In humans, these adverse effects are termed Fetal Alcohol Spectrum Disorders (FASD). FASDs include deficits in behavioral regulation including hyperactivity and response inhibition deficits. Rodent models are used to examine the underlying mechanisms of ethanol's (ETOH) action on the developing CNS and to design interventions to reduce the damaging effects. Recently, a paradigm referred to as "Drinking in the Dark (DID)" was adapted to study the prenatal effects of ETOH in a mouse model. With the DID model, C57 BL/6J mice are given free access to ETOH during the dark cycle and allowed to voluntarily drink a 20% ETOH solution for 2 hr daily. This exposure period represents the human 1st and 2nd trimester of human pregnancy (in terms of CNS development). In a collaborative project with Dr. Gang Chen, we have been developing a model that includes voluntary drinking during pregnancy and in addition, neonatal exposure for the "3rd trimester" component. Pregnant dams consumed alcohol via DID and a subset of the pups received additional intubation treatments on PD 4-10 (3.0 g/kg/day in 2 feeds). Untreated litters were included as controls. On PD 24-25, activity and exploration for 10 min was measured in an elevated plus maze. Three-trimester ETOH treatment produced hyperactivity in male offspring and increased exploration of the open arms in all subjects, while maternal DID alone had little effect. This model may be very useful in improving our understanding regarding timing of ETOH exposure during development as well as potential underlying mechanisms.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#171 Abstract Title:	**Stereology in a biological context with the integration of mathematics, design and modeling**
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Abstract: Application of knowledge to real life problems in authentic scientific inquiry with active learning process along with construction of various models is a focus for the Next Generation Science Standards (NGSS). When researchers are examining mutations in proteins that alter ultrastructure of cellular organelles, knowing the error in measurements are important to understand if structural differences can account for altered function. The educational modules made of readily accessible materials help to allow students to take stereological measurements. The students can use the values they obtain to calculate a theoretical area or volume of objects, such as a triangle or triangular prism. Once they observe the 3D object they can calculate the potential error in estimations of area or volume compared to a 2D model. The modules are designed as an inquiry and problem based learning experience for the students. Physical models created by students will help in understanding the various concepts and provide useful objects for aid in classroom discussions. In addition, the freeware "Sketch up" allows some computational interaction and computer design to help illustrate various points the students may wish to discuss. The software provides a rapid means of altering structures and rotating them in 3D space with no cost of supplies. Students learn on their own accord through inquiry, model building and discussion in regards to errors in measurement which can vary depending on the structure and number of sections. Students will also learn that these concepts are important in authentic scientific investigations.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#172 Abstract Title:	**Acute and Chronic Effects of Inhibiting mTOR by Rapamycin on Development, Behvaior, and Physiology in Drosophila**
Author(s):	S.J. Potter, Dept of Biology, U of Kentucky R.S. Potter, Dept of Biology, U of Kentucky S.L.E. Blümich, V.M.F., U of Leipzig, Leipzig, Germany R.L. Cooper, Dept of Biology and Center of Muscle Biology, U of Kentucky

Abstract: Rapamycin is a compound that can specifically block mTOR signaling and is therefore used in experimental biology. It is being utilized clinically as an immunomodulator after transplantation procedures and treatment for some forms of cancer. Due to its many possible effects on different molecular pathways, it could have any number of impacts on synaptic transmission. This issue has not, however, been addressed in a developing system. We hope to address it by feeding second and third instar Drosophila larvae varying concentrations of rapamycin and monitoring larval stages, pupation, and survival. Typical larval behavioral assays being examined are mouth hook movement while eating and body wall movement while crawling on apple juice agar plates. Behaviors in the adults fed rapamycin include climbing, righting response, and movement assays. The results to date suggest 2nd instar larvae are more susceptible to rapamycin as compared to 3rd instar, based on a higher death rate. Adults fed rapamycin climb less over time and tend to fall off the wall when climbing. Dose-response studies are being established. This study is significant as we are starting to address the acute and long-term action of inhibiting the mTOR pathway on neuronal function and potential mechanisms to account for altered physiological function.

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31st Annual BGSFN Spring Neuroscience Day
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#173 Abstract Title:	**A undergraduate education module based on a research question: The effects of muscle injury on synaptic transmission, axon conduction and muscle physiology in relation to deep tissue injury.**
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Abstract: This laboratory exercise is to determine the consequences of damage muscle influencing healthy muscle and neuronal function. Students can develop variations to the experimental models presented in this laboratory exercise. The preparations presented are of multiple motor units and muscle fiber types (slow and fast) as well as a sensory-CNS-motor nerve circuit. These preparations are well known for student neurophysiology experimentation but novel to use for investigating an injury topic on muscle and CNS. In addition, this module lends itself for inquiry, team discussion, self-paced learning and focuses on authentic scientific research. These approaches are hall marks in student retention and understanding of novel concepts. Student feedback from use of this teaching exercise will be presented. The research questions on this topic are based on understanding the physiological problems with deep tissue injury of skeletal muscle and/or neurons. Primary skeletal muscle damage can produce secondary effects which can increase the spread of the damage zone. This can be caused by the additive effects of intracellular contents, particularly the ion K+, released from crushed muscle cells. Consideration in the exposure time and effects of restoring normal [K+] o on the health of skeletal muscle and synaptic transmission has not been fully addressed. The synaptic responses return slower than recovery of skeletal muscle potential. At present we are conducting further investigations on the crayfish opener muscle and Drosophila larval body wall muscles as models for effects on synaptic transmission with muscle injury. It appears the axon becomes blocked in conduction with raised [K+] o which is likely due to the inactivation of the NaV channels. Thus, a nerve close to a site of injury may not necessarily be physically injured but conduction of electrical signals may be hampered, due to a localized raised [K+] o. The goal of these research studies is to use these findings to help establish rodent models and development of experimental paradigms which may lead to better treatment and assessment of DTIs in urgent care centers for humans.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#174 Abstract Title:	**Assessing a Novel Model of Developmental Ethanol Exposure on Locomotor Activity in Mice**
Author(s):	A. Manuel, Dept of Psychology, U of Kentucky A. Hawkey, Dept of Psychology, U of Kentucky W. Xu, Dept of Pharmacology, U of Kentucky H. Li, Dept of Pharmacology, U of Kentucky G. Chen, Dept of Pharmacology, U. of Kentucky S. Barron, Dept of Pharmacology, U. of Kentucky

Abstract: Drinking during pregnancy can cause serious consequences for the developing brain. Even with the available knowledge on the effects of prenatal ethanol exposure, drinking during pregnancy remains the leading preventable cause of birth defects. Behavioral characteristics often observed include hyperactivity, problems with learning, attention and executive function; collectively termed Fetal Alcohol Spectrum Disorders (FASD) in humans. Rodent models of these deficits have replicated many of these findings and are often used to better understand mechanisms and develop interventions to reduce these problems. This study was designed to evaluate a novel model of FASDs in rodents that capitalizes on voluntary alcohol consumption. In collaboration with Dr. Gang Chen, the “Drinking in the Dark” (DID) paradigm was used to study the effects of prenatal ETOH exposure with C57 BL/6J mice given free access to 20% ETOH during 4 hrs of their daily dark cycle. Treatment groups included, mice exposed to ethanol solely through maternal DID, mice that received DID exposure and neonatal ethanol intubations (3 trimester model, 3g/kg), and untreated controls. Subjects were tested on postnatal days 20 - 21 in a circular open field for 30 min daily. Pre- and neonatal ETOH exposure resulted in hyperactivity relative to controls measured by distance traveled and time mobile in both sexes and on both days in open field. Maternal DID alone had no effect on activity. These results suggest that this “3 trimester” ethanol exposure model may be a useful tool for studying fetal ethanol effects. (Supported, in part, by AA020051to GC).

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#175 Abstract Title:	**3-Dimethoxybenzylidene-Anabasine (DMXB-A) Reduces Balance Deficits Following '3rd Trimester' Ethanol Exposure in Female but Not Male Rats**
Author(s):	E. Mirsky, Dept of Psychology, U of Kentucky L. Fields, Dept of Psychology, U of Kentucky M. Carter, Dept of Psychology, U of Kentucky A. Hawkey, Dept of Psychology, U of Kentucky S. Barron, Dept of Psychology, U of Kentucky

Abstract: Prenatal ethanol (EtOH) exposure can have long-term effects on motor coordination. The present study examined whether 3-dimethoxybenzylidene-anabasine (DMXB-A), an α-7-nicotinic-acetylcholine receptor (α7nAChR) agonist, could reduce balance deficits following EtOH exposure during a period of development equivalent to the 3rd trimester human “brain growth spurt. Neonatal male and female Sprague Dawley rats received EtOH (6g/kg/day) on postnatal days (PND 1-7). There was also an intubated and a non-intubated control. On PND 8, pups were injected with DMXB-A (10 mg/kg) or saline 24 hours after the last EtOH treatment. On PND 31-33, rats were tested on a dowel rod paradigm in which the rat has to run down a dowel to reach an “escape box”. With each successful entry into the escape box, the distance to reach the box was increased by 13cm. Each subject received 3 trials/day for 3 days. Female rats treated with EtOH showed significant balance deficits while females treated with EtOH that additionally received DMXB-A on PND 8 performed at levels similar to controls. Male rats that received EtOH and DMXB-A performed more poorly on the balance task relative to all other treatment groups, including EtOH alone. These results suggest that there may be sex differences in the sensitivity to EtOH and/or DMXB-A on this rodent task. DMXB-A appeared effective in reducing balance impairments in female rats exposed to prenatal ethanol.

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31st Annual BGSFN Spring Neuroscience Day
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#176 Abstract Title:	**Can DMXB-A reduce the damaging effects of prenatal ethanol exposure on spatial learning in rats?**
Author(s):	M. Cruse, Psychology Dept, University of Kentucky L. Fields, Psychology Dept, University of Kentucky M. Carter, Psychology Dept, University of Kentucky S. Barron, Psychology Dept, University of Kentucky

Abstract: Fetal Alcohol Spectrum Disorders (FASD) can cause a range of behavioral and cognitive disabilities that have long-term effects for the individual, their family, and society at large. Studies have shown that choline, a precursor of acetylcholine (ACh) and an alpha-7 nicotinic ACh receptor (nAChR) agonist, can reduce some of the damaging effects of prenatal ethanol (ETOH) exposure. Choline plays a number of critical roles during early CNS development and so to better understand the possible mechanisms for its neuroprotective effects, the current study used a more specific alpha-7 nAChR agonist, 3-2,4 dimethoxybenzylidene anabaseine (DMXB-A). This study examined whether DMXB-A, could improve spatial learning and memory following ethanol (ETOH) exposure during the third trimester “brain-growth” spurt in a rodent model. ETOH was administered (6 g/kg/day) on postnatal days (PND) 1 through 7 and DMXB-A dose (0, 3, or 10 mg/kg) once on PND 8. Offspring were tested in a Hebb style water maze for acquisition and 24 hr retention during early adolescence. ETOH exposed male rats needed significantly more acquisition trials than the control to learn the task, but the group that received ETOH+DMXB-A did not differ from controls (p=.001). DMXB-A alone had little effect on acquisition. No treatment effects were displayed by females from these neonatal groups, nor in 24 hr retention for either males or females. These results support our hypothesis that DMXB-A reduces deficits in acquisition of a spatial task in male rats. Further research is ongoing to see if these results generalize to other behaviors.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#177 Abstract Title:	The Effect of Sox4 on Fgf Signaling during Ocular Development and the Generation of Sox4-deficient Zebrafish Using CRISPR/Cas9 System
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Abstract: Congenital ocular coloboma, a malformation caused by failure of choroid fissure closure during eye morphogenesis, leads to childhood blindness and other associated defects in humans. Such visual defects can be explored by studying zebrafish, an ideal model organism due to its highly conserved ocular development. Sox4 is a SoxC family transcription factor. We previously discovered its effect on Hedgehog (Hh) signaling and ocular coloboma. To better understand the cross-talk between multiple cell-signaling networks mediating embryonic development, we examined the impact of sox4-deficiency on the fibroblast growth factor (FGF) signaling pathway. We studied the expression of fgf3, fgf8, and fgf19 in sox4-deficient embryos, and found that fgf3 and fgf19 were up-regulated in response to sox4 knockdown, whereas fgf8a and fgf8b expression levels were not altered. In addition, due to the loss of effectiveness of morpholinos over time, we applied the novel and highly effective CRISPR/Cas9 technique to generate permanent sox4-deficient zebrafish lines through targeted mutagenesis. Through microinjection, F0 screening and outcrossing, we identified three founder fish with germline mutations in the sox4a-CRISPR1, sox4a-CRISPR2, and sox4b-CRISPR2 gene loci. Generating a sox4 knockout transgenic line will enhance the study of sox4 function during ocular development with broad applications, such as examining its role in adult retina during normal neurogenesis or under retinal injury conditions.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#178 Abstract Title:	**Oral administration of Vesicular Monoamine Transporter-2 (VMAT2) Inhibitors JPC-077 and JPC-141 Reduce Methamphetamine-Induced Reinstatement in Rats**
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Abstract: While abuse rates for methamphetamine have been steadily declining, studies indicate a third of all abusers will relapse into addic9on at some point during treatment. Thus there is significant need for a drug which directly addresses the issue of relapse. Several newly synthesized 1,4---diphenylethyl analogs of lobelane (a defunc9onalized deriva9ve of lobeline) have been found to be potent and selec9ve vesicular monoamine transporter---2 (VMAT---2) inhibitors, indica9ng poten9al to aid in reducing methamphetamine (METH) abuse and preven9ng relapse. In this study we test the therapeu9c poten9al of two of these analogs (JPC---077 and JPC---141) on METH---induced reinstatement of self--- administra9on behavior in male adult Sprague Dawley rats following ex9nc9on. ARer surgical implanta9on of a jugular catheter, rats learned that methamphetamine infusions (0.05mg/kg) could be earned via comple9on of a simple task (lever pressing), followed by 10 days of ex9nc9on (no methamphetamine). METH seeking behavior was then induced by a pretreatment with METH (0.5mg/kg, i.p) on 3 sessions, where two doses of either compound (constant across subjects) were randomly administered 15 minutes prior to the session. Results showed that JPC---077 (100 and 170 mg/kg) and JPC---141 (130 and 170mg/kg) significantly blocked METH---reinstatement behavior. Further, these results were achieved at doses lower than those required to produce a decrease in locomotor ac9vity (previous work in our laboratory) indica9ng that results were not due to nonspecific suppressant effects. These results indicate that JPC---077 and JPC---141 are poten9ally viable drugs for the treatment of METH abuse and relapse; however further pharmacokine9c and toxicological research must be conducted before transla9ng these findings to human counterparts.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#179 Abstract Title: Cholinergic System Regulation on Behavior in Drosophila Larvae

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Abstract: We investigated the role of acetylcholine in the Drosophila melanogaster larval CNS to identify how this neuromodulator regulates locomotion and feeding behaviors. We combined pharmacological and genetic approaches in order to deduce the cholinergic receptor subtypes that play a role in mediating these behaviors and to gain a better understanding of the pharmacological profile in this model. Genomic screens have revealed that there are ten receptors in Drosophila that are very similar to the nicotinic acetylcholine receptors (nAchRs) of mammals. In Drosophila, acetylcholine is a neurotransmitter within the CNS and is the neurotransmitter for sensory neurons but not motor neurons, as in mammals. A distinctive advantage of Drosophila larvae is the short developmental time (~4 days) in which the development of the CNS can be investigated. The alteration in neural activity related to circuits is particularly important during neural development for formation and stabilization of neural connections. In addition, the proposed experimental design allows for a multitude of options for future experimentation including investigation of regulation of olfaction and response to light upon altering the cholinergic system. All of these are testable for proof of concept and will provide the degree of inhibition in sensory responses. This study will help to establish the role of acetylcholine in regulating simple motor behaviors and will help to identify the functional role of specific receptor subtypes within the larval CNS

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#180 Abstract Title:	JR-220 Reduces Ethanol- and Hypoxia-Induced Damage in Neonatal Hippocampal Cells
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Abstract: Prenatal ethanol (ETOH) exposure has a variety of adverse consequences for the developing brain. One hypothesis that we have been examining is that prenatal ETOH exposure can make the brain more susceptible to any additional challenges that the organism might experience. More specifically, we have shown that prenatal ETOH exposure increases the damaging effects of a mild hypoxic challenge in a neonatal organotypic hippocampal slice model. This study examined whether polyamine modulation of the n-methyl-d-aspartate glutamatergic receptor (NMDAr) by a novel aryliminoguanidine, JR 220, which reduces polyamine potentiation of the NMDAr, was neuroprotective against ETOH and/or hypoxia. Organotypic hippocampal slice cultures were prepared from 8-day-old Sprague-Dawley rat pups. Slices were exposed to 100mM ETOH or control culture media for 10 days followed by a brief hypoxic challenge using oxygen-glucose deprivation (ODG) treatment or control (air) for 30 min. Immediately after exposure, subsets of slices were treated with 0, 50, 100, or 125 µM JR220. After 24 hours, damage was measured in the CA1, CA3, and dentate gyrus regions of the hippocampus using propidium iodide (PI; a marker for non-specific cell damage). At 125 µM, JR220 reduced PI uptake in CA1 and CA3 regions to control levels in OGD and ETOH + OGD treated slices. We have previously shown that JR220 rescues cell damage and behavioral deficits following third trimester ETOH exposure: the current findings suggest that a similar mechanism and treatment may be effective for ETOH followed by a hypoxic challenge. These findings also support the role of polyamines in both ETOH- and hypoxia-induced hippocampal damage.

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31st Annual BGSFN Spring Neuroscience Day
Poster Presentation Abstracts

#181 Abstract Title:	**Effects of early-life risperidone on dopamine transporter densities in the mesolimbic dopamine system**
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Abstract: Risperidone is an atypical antipsychotic drug approved to treat schizophrenia, bipolar disorder, and behavioral concerns related to autism spectrum disorder. It is also frequently prescribed off-label to treat Attention Deficit Hyperactivity Disorder and some behavioral disorders in children. Risperidone primarily functions to block dopamine and serotonin receptors. Previous studies have found young adult rats administered risperidone early in life demonstrate greater levels of locomotor hyperactivity after injection of D-amphetamine, which targets dopamine transporters. This study examined the effects of early-life risperidone on dopamine transporter densities in the mesolimbic dopamine system in adult Long Evans rats. Thirty subjects, 12 male and 18 female, were administered one of three doses of risperidone (vehicle, 1.0, or 3.0 mg/kg) daily from postnatal day 14 through 42. Locomotor activity was measured pre- and post-administration, revealing accentuated activity. Brains were collected on PND 72 and autoradiography using 3H RTI-55 was performed to reveal dopamine transporter sites in sagittal sections. Dopamine transporter densities in the medial frontal cortex, nucleus accumbens shell, and ventral tegmental area were measured with Image J. Results revealed no dose-dependent changes resulting from early-life risperidone administration; however females had high transporter densities in the nucleus accumbens shell and ventral tegmental area. These findings suggest that the enhanced behavioral sensitivity to amphetamine in adult rats exposed to risperidone early in life is not caused by changes in dopamine transporter density in the mesolimbic system. It remains possible that changes in the density of dopamine transporters in other brain regions or in transporters for other neurotransmitters, such as norepinephrine, could be associated with the behavioral changes induced by early-life risperidone. These ideas will be considered in future work.

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31st Annual BGSFN Spring Neuroscience Day
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#182 Abstract Title:	**Oral JPC-077 and JPC-141, Vesicular Monoamine Transporter-2 Inhibitors, Reduce Methamphetamine Self-administration in Rats.**
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Abstract: Recently, a series of 1,4-diphenethyl analogs that could potentially aid in reducing methamphetamine (METH) abuse and relapse have been synthesized from lobelane. These compounds are vesicular monoamine transporter-2 (VMAT-2) inhibitors. The effects of oral administration of from two of these compounds (JPC-077 and JPC-141) on METH self-administration in rats are reported here. After undergoing surgical implantation of a jugular catheter, rats learned that METH infusions (0.05 mg/kg) could be earned by emitting lever presses in an operant chamber. To assess the effects of JPC-077 and JPC-141 on METH self-administration, rats earned infusions of the drug 15 minutes after being gavaged. Over the course of multiple sessions, subjects were gavaged with semi-logarithmically increasing and decreasing doses of the compound; efficacy was defined as a >50% decrease in self-administration behavior compared to prior session responding. Results for JPC-077 and JPC-141 both showed a reduction in METH self-administration; however, JPC-077 may have a higher therapeutic index compared to JPC-141. Further, doses of JPC-077 that effectively reduced self-administration were approximately three-times lower than those required to significantly reduce locomotor activity (based on previous work conducted in the laboratory), which indicates that this compound selectively decreases responding for METH prior to inducing suppressant effects. Thus, JPC-077 and JPC-141 represent novel, orally bioavailable potential therapeutic agent for treating METH abuse.

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