THE LOUISVILLE CHAPTER

SFN SOCIETY for NEUROSCIENCE

32nd Annual Neuroscience Day

Thursday, April 11, 2024

Neurodegeneration & Repair

Program of Events

Irving Vega, PhD
Red Cedar Distiguished Faculty
Associate Professor
Department of Translational Neuroscience
Michigan State University

11:00 – 11:45	Check-in, Coffee and Light Refreshments
11:45 – 12:00	Welcome and Program Introduction
12:00– 12:30	DATA BLITZ • preview of selected posters: 3 slides, 3 minutes total

Nogo Receptor Knockout Extends Critical Period Plasticity and Visual Circuit Reorganization
Chris Brown • University of Louisville, Department of Anatomical Sciences and Neurobiology

Neurotransmitter differences in two genotypes of mice treated with benzo[a]pyrene during early brain development
Annika White • Northern Kentucky University, Department of Biological Sciences

Pathways to Mortality among Head and Neck Cancer Patients: Exploring Cortisol Rhythm and Immune Marker Relationships, and their Implications for Disease Progression
Isak Beck • University of Louisville, Department of Otolaryngology

Periaxonal swelling and loss of axo-myelinic connectivity causes secondary white matter injury after SCI
Spencer Ames • University of Louisville, Department of Neurological Surgery, KSCIRC

Effects of alcohol on Alzheimer's disease pathogenesis in 3xTg-AD mice
Lucy Sloan • University of Louisville, Department of Pharmacology & Toxicology

12:30 – 1:00	WHAT'S HAPPENING IN OUR OWN BACKYARD I?

Ultrasound Blood–Brain Barrier Opening for treatment of Alzheimer's Disease
Pierre D'Haese, PhD • West Virgina University, Associate Professor, Director of Digital Health and Imaging Analytics

1:00– 1:45	Lunch
1:45 – 3:00	POSTER SESSION AND JUDGING
3:00 – 3:30	WHAT'S HAPPENING IN OUR OWN BACKYARD II?

Therapeutic efficacy of Stereopure Oligonucleotides in a Pig Model of autosomal dominant Retinitis Pigmentosa (adRP)
Archana Jalligampala, PhD • University of Louisville, Postdoctoral Assocociate Department of Ophthalmology and Visual Sciences

3:30 – 4:30	PLENARY LECTURE

Alzheimer's disease: Understanding Molecules and People
Irving Vega, PhD • Michigan State University, Associate Professor, Red Cedar Distiguished Faculty, Department of Translational Neuroscience

4:30 – 5:00	Presentation of poster awards and chapter trainee awards, chapter business meeting, and closing remarks

Learn more about the Louisville Chapter of the Society for Neuroscience at: www.sfnlouisville.org • Questions, email us: SFNChap@louisville.edu

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About The Plenary Speaker

Irving Vega, PhD
Red Cedar Distiguished Faculty
Associate Professor
Department of Translational Neuroscience
Michigan State University College of Human Medicine

Dr. Irving E. Vega obtained his undergraduate degree in Biology from the University of Puerto Rico-Mayaguez Campus. He continued his research training in the Department of Cell Biology and Neuroscience at the Graduate School of New Brunswick, Rutgers University, earning his PhD. Dr. Vega completed a postdoctoral fellowship in the Neuroscience Department at Mayo Clinic Jacksonville, where he developed his research career focusing on the pathobiology of Alzheimer's disease. Dr. Vega joined the faculty at as an Associate Professor in the Department of Translational Neuroscience at Michigan State University College of Human Medicine campus in Grand Rapids, MI in 2014. His research focuses on molecular and biochemical mechanisms that modulate the accumulation of pathological tau proteins in Alzheimer's disease and related dementias. Dr. Vega is also working on ethnic disparities and the influence of ethnoracial factors on blood biomarkers in Alzheimer's disease.

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Neurodegeneration & Repair

SfN SOCIETY for NEUROSCIENCE Louisville Chapter

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Special Thanks

Lesley Roberson **Denise Hand** **All Poster Judges**

University of Louisville Participating Departments

Anatomical Sciences and Neurobiology
Biochemistry and Molecular Genetics
Computer Engineering and Computer Science
Otolaryngology
Neurological Surgery
Pediatrics
Pharmacology & Toxicology
Physiology
Psychiatry and Behavioral Sciences
Visual Sciences and Ophthalmology

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Learn more about the Louisville Chapter of the Society for Neuroscience at: www.sfnlouisville.org • Questions, email us: SFNChap@louisville.edu

Abstracts

UNDERGRADUATE STUDENTS

ABSTRACT # 1

Periaxonal swelling and loss of axo-myelinic connectivity causes secondary white matter injury after SCI

Ames S, Cortez-Thomas F, Brooks J, Jones E, Morehouse J, Desta D, Stirling DP

Department of Neurological Surgery, UofL
Kentucky Spinal Cord Injury Research Center

Ultra-structural studies of compressive and contusive SCI have shown that the most prominent acute changes in white matter are periaxonal swelling and separation of myelin away from their axon, axonal swelling, and axonal spheroid formation. However, the underlying cellular and molecular mechanisms that cause periaxonal swelling and the functional consequences are poorly understood. Utilizing in vivo longitudinal imaging of Thy1YFP+ axons and myelin labeled with Nile red, we have shown that periaxonal swelling significantly (ANOVA on Ranks, $p < 0.001$; post hoc Dunn's method, $p < 0.05$; n =2-11/ timepoint) increases acutely (24 hours) following a contusive SCI (T13, 30 kdyn, Infinite Horizons Impactor) and precedes axonal spheroid formation. In addition, using longitudinal imaging to visualize the fate of the same myelinated fibers acutely after SCI, we have determined that ~73% of myelinated fibers present with periaxonal swelling at one hour post SCI and ~51% of those fibers transition to axonal spheroids by four hours post SCI (Binomial proportion test, $p < 0.005$, n = 5). As cation-chloride cotransporters are localized to regions of the internode and regulate cell volume, we hypothesized that inhibiting NKCC1 or augmenting KCC2 would prevent periaxonal swelling after SCI. We found that inhibition of NKCC1 using bumetanide (30 mg/kg, 1h and 4h post-SCI) significantly (ANOVA on Ranks, $p < 0.05$) reduced acute periaxonal swelling and increased (One-way ANOVA, $p < 0.05$; Tukey HSD post hoc t-test, $p < 0.05$) axonal survival at 24h after T9, 50 kdyn contusive SCI versus vehicle controls (n=3-4/group). Furthermore, NKCC1 inhibition significantly improved finer aspects of locomotor recovery (Binomial proportion test, $p < 0.001$) and increased white matter sparing (One-way ANOVA, $p < 0.05$; Bonferroni post-hoc t-test, $p < 0.05$) at 6 weeks after SCI. Collectively, these data reveal a novel role for NKCC1 in periaxonal swelling and secondary axonal loss after SCI.

ABSTRACT # 2

The potential anti-hyperactivity and anxiolytic effects of CBD

Bailey A[1], Freudenberger R[1], Purcell L[2], Song Z-H[1]

[1]Department of Pharmacology and Toxicology, UofL
[2]School of Dentistry, UofL

Cannabidiol (CBD) is the main non-intoxicating phytocannabinoids. Recent research has identified G protein-coupled receptor 3 (GPR3) as a potential novel target for CBD. Previous studies have shown that CBD has therapeutic potential to reduce hyperactivity and alleviate anxiety, but the mechanism of action is unknown. We hypothesize that CBD produces anti-hyperactivity and anxiolytic effects through the GPR3 pathway. Our investigation involved observing the phenotypic responses using open field test (OFT) to assess the behavioral response to CBD in GPR3 -/- and wild-type C57BL/6J (B6) mice. The mice received an intraperitoneal injection of 25 mg/kg of CBD or vehicle. They were evaluated for 10 minutes for the OFT. Data from the behavioral studies were analyzed using one way ANOVA or T tests. We observed that GPR3 -/- and wild-type B6 mice exhibited same level of anxiety in the OFT, and CBD did not produce anxiolytic effects in either B6 or GPR3 -/- mice. However, comparing to B6 mice, GPR3 -/- mice demonstrated elevated locomotor activity, and CBD reduced the hyperactivity in GPR3 -/- mice. In conclusion, while CBD did not exhibit anxiolytic effects in our models, it reduced hyperactivity in GPR3 -/- mice, indicating this potential therapeutic effect operates independently of GPR3. Further investigations into the alternative molecular targets of CBD and different doses of CBD are needed to fully understand the roles of CBD in decreasing hyperactivity and producing anxiolytic effects.

ABSTRACT # 3

The Effect of Music Therapy on Anxiety Rates Among AP Students at North Oldham High School

Mathew, M

Neuroscience, University of Louisville

Since College Board developed the AP curricula, students around the world have been taking AP courses. Although these classes have many benefits, AP classes were also found to lead to an increase in anxiety symptoms. Based on official data, the students at North Oldham High School were found to have a higher average AP participation rate when compared to the national statistics. In turn, their anxiety rates were also found to be higher. Due to this influx of anxiety levels, a treatment technique known as Music Therapy was utilized and tested to prove that this method of anxiety treatment could help decrease anxiety among AP students. The test results indicated an average anxiety decrease of 12 points from the starting GAD-7 scale result of around 15 to the ending scale result of approximately 3. Due to the success of the music therapy sessions, if these anxiety treatment services are implemented in more high schools across America, then anxiety rates among AP students will substantially decrease.

ABSTRACT # 4

A review of the supraspinal mechanisms of SCS on chronic pain and cognition

Rustioni S, Vohar A, Zemmar A, Van Wouwe N, Steward T

Department of Neurological Surgery, UofL

Chronic pain is one of the leading causes of disability worldwide, with a myriad of debilitating factors, including physical and cognitive burden. Spinal cord stimulation (SCS) is a minimal-invasive treatment option for drug-refractory chronic pain. Although SCS can improve pain perception and related physical well-being, it is not well understood how SCS affects cognitive function in pain patients. Here, we review cognitive impairments arising from chronic pain and compare these with cognitive effects measured after SCS treatment. We focused on the involvement of supraspinal centers in SCS therapy and found increased activity in the anterior cingulate cortex and stronger connectivity between the thalamus and the insular cortex, as well as between the primary somatosensory cortex and emotional-processing areas. These observations suggest a role for SCS to influence and modulate the cognitive-emotional aspect of pain perception. Our study provides new insights to identifying potential cortical areas that can serve as biomarkers or neuromodulation targets for SCS treatment.

ABSTRACT # 5

Neurotransmitter differences in two genotypes of mice treated with benzo[a]pyrene during early brain development

White A, Feltner M, Good A, Clough K, Foster EG, Curran CP

Department of Biological Sciences, Northern Kentucky University

Benzo[a]Pyrene (BaP) is a widespread, carcinogen found in air pollution, cigarette smoke, wildfire smoke, and vehicle exhaust. BaP binds to the aryl hydrocarbon receptor (AHR) which then upregulates the production of metabolizing CYP1 enzymes. Exposure to BaP during neonatal development has been found to cause differences in the levels of neurotransmitters within the adult brain. To explore these differences, we used Cyp1b1(-/-) knockout and wild-type mice exposed to BaP during gestation and lactation. We collected the striatum, prefrontal cortex, hippocampus, and hypothalamus from the mice on postnatal day 120 (P120). We then quantified levels of neurotransmitters using high-performance liquid chromatography (HPLC). We found that BaP exposure significantly decreased dopamine ($P < 0.05$) and DOPAC ($P < 0.001$) in the striatum. There were no differences in the hippocampus for dopamine, but significantly higher serotonin levels in BaP-treated mice ($P < 0.05$). Genotype was highly significant in the hypothalamus with lower levels of DOPAC in Cyp1b1(-/-) mice ($P < 0.01$) and a trend for significance for dopamine ($P = 0.058$). Serotonin levels were also significantly lower in Cyp1b1(-/-) mice, but there was no difference in the levels of the metabolite 5-HIAA. There was no effect of BaP treatment in the hypothalamus. Together, these data suggest that BaP exposure during early brain development can have persistent effects on monoamine neurotransmitters in adults.

ABSTRACT # 6

Predictive Role of Increased Beta Power in Mitigating Intrusion and Avoidance Symptoms of PTSD Following Neurofeedback Training

Willgruber LJ, Im S

Department of Psychology , Western Kentucky University

Background: Post-Traumatic Stress Disorder (PTSD) may develop following exposure to a traumatic event, and the gold standard treatment is exposure-based therapy. However, this treatment approach often leads to high dropout rates due to its distressing nature for patients. In a previous investigation, neurofeedback was applied among participants with PTSD, resulting in significant symptom reductions such as intrusion and avoidance. Despite these positive outcomes, the specific brain regions responsible for mediating the beneficial effects of neurofeedback remained unclear. Methodology: Fourteen PTSD patients (11 females and 3 males) aged 19-48 years received 10 neurofeedback sessions along with three assessment sessions, pre-, mid-, and post-treatment, to evaluate trauma-related symptoms. Four electrode sites (F3, F4, P3, and P4) were selected, with each neurofeedback session lasting 20 minutes. During sessions, participants selected a video to watch, and training occurred through operant conditioning, where deviations from target thresholds in brain activity triggered dimming of the screen to prevent movie viewing. EEG data and PTSD Symptom Checklist for DSM-5 (PCL-5) scores were analyzed using MATLAB. Results: The findings revealed significant correlations between Beta power in the parietal region and PCL-5 scores. Specifically, intrusion scores were negatively correlated with Beta power ($p=0.020$ at P3 and $p=0.017$ at P4). Avoidance scores showed negative correlations with Beta power ($p=0.015$ at P3 and $p=0.034$ at P4). Discussion: These results suggest that the promising effects of neurofeedback in reducing intrusion and avoidance symptoms of PTSD may be attributed to reduced Beta activity in the parietal region. It is important to note, however, that the current study had a small sample size and lacked a control group, highlighting the need for further research in this area.

Abstracts

GRADUATE STUDENTS

ABSTRACT # 7

In Vivo Calcium Imaging to Shed Light on Neurocircuitry Alterations in the Prefrontal Cortex

Alsum AR, Turner JR

Pharmaceutical Sciences, University of Kentucky

In 2020, the United States National Institute on Drug Addiction reported approximately 2.7 million US citizens over the age of 12 had an opioid use disorder (OUD) in the past 12 months. Of this, 2.7 million, 2.3 million individuals had a prescription opioid use disorder. It is imperative for researchers apply new technologies to further unravel the secrets behind OUD and its complex mechanism and bring forth novel therapies to treat patients best in an individualistic manner. In vivo single photon calcium imaging in awake freely behaving mice is an innovative tool that has proven beneficial in examining neuronal activity and behavior in a variety of fields. Implementation of this technology allows for a more comprehensive understanding of OUD thus providing leads for novel therapeutics. The prefrontal cortex is a critical brain region in circuits underlying both reward and anxiety. A high anxiety phenotype is frequently reported in patients suffering from opioid withdrawal and is also listed as a principal culprit for return to use. Using in vivo calcium imaging, we can observe not only aberrant firing patterns present with periods of acute to chronic opioid use but also alterations to firing coordination with mice presenting an anxiety-like response while experiencing opioid withdrawal during behavioral assays frequently used to asses anxiety-like responses in preclinical models, open field and elevated zero maze. Perineuronal nets (PNNs) are primarily formed throughout development and are considered a contributing factor to maintaining synaptic rigidity in the adult brain. Synaptic plasticity has been an area of interest to substance use disorder (SUD) researchers, as an increase in synaptic plasticity is observed in SUD patients and this is thought of as a driving force in habit forming and SUDs. Lastly, cellular communication between the sheath that is PNNs, and microglia is an area lacking in information and will provide interesting insights into the functions of both PNNs and microglia in an OUD brain. The lasting effects of chronic opioid exposure are evident in neuronal firing rate and synaptic plasticity with a mediator of this mechanism being microglia's effects on perineuronal nets.

ABSTRACT # 8

An Examination of Visual Acuity, Retinal Function, and Structure in a Murine Model of P23H Retinitis Pigmentosa - Does Plasticity Play a Role?

Attaway CA[1], McCall MA[2], McGee AW[1]

[1]Department of Anatomical Sciences and Neurobiology, UofL
[2]Department of Visual Sciences and Ophthalmology, UofL

Retinitis Pigmentosa (RP) is an inherited retinal disorder where blindness is caused by rod and cone photoreceptor degeneration. Around 25% of cases are caused by a genetic mutation that results in autosomal dominant RP (adRP). We examined changes in visual acuity (VA), retinal structure, and function from early to late-stage disease in a murine P23H Rho 'knock-in' mouse model (RhoP23H/+), a model with the most common form of adRP in North America. To determine if additional plasticity of the visual system is beneficial during vision loss, we assessed the same measures in RhoP23H/+ mice lacking nogo receptor 1 (ngr1), a gene that restricts visual plasticity. We evaluated behavioral VA, using the visual water task, and retinal function using full field electroretinograms (ffERG) at the same scotopic and photopic levels. We quantified the thickness of the outer nuclear layer (ONL) in the retina. We constructed a natural history for each measure and compared differences between measures over time. We then generated RhoP23H/+; ngr1-/- mice and assessed VA, ffERG, and retinal morphology in RhoP23H/+; ngr1-/- and in ngr1-/- mice at similar ages. Compared to C57Bl6/J (WT), we find a significant decline in RhoP23H/+ scotopic VA at early-stage disease and in the photopic VA at late-stage disease. RhoP23H/+ scotopic VA decline is significantly slower than ERG decline and VA is retained even when the scotopic b-wave is absent. Between RhoP23H/+ and RhoP23H/+; ngr1-/- mice, the decline of scotopic and photopic VA and retinal structure is similar in early-stage disease. In late-stage disease, the RhoP23H/+; ngr1-/- mice decline significantly quicker for both photopic and scotopic VA in comparison. An acceleration in thinning of the ONL is also observed. ngr1-/- mice have a significant decline in both scotopic and photopic b-wave amplitudes compared to WT mice. A difference in VA or morphology is not observed. Our natural history shows that VA decline is slower than retinal decline in RhoP23H/+ mice. The absence of ngr1 in RhoP23H/+mice does alter the progressive loss of vision in a detrimental way. The absence of ngr1 alone does affect the function of the retina evident by the decline in b-wave amplitudes at older ages, although VA and morphology are unchanged.

ABSTRACT # 9

Introduction to Virtual Reality for Physiology Education

Ballard A, Lee J, Terson de Paleville D.

Department of Physiology, UofL

A new way of teaching using virtual reality can solve the knowledge gap between students and create an in depth understanding of physiology. Virtual reality can be defined as an interactive environment created by computerized systems to immerse the user (physically, emotionally, and mentally) into the artificial environment. The participant's senses, specifically sight, sound, and touch, are used to fully immerse them into the created environment. In addition to traditional teaching methods, virtual reality can be supplemented into the curriculum to facilitate student learning. Interactive 360° videos and virtual worlds for each body system will allow students to use the information learned in lecture and apply it to virtual scenarios. For instance, students learning immunology may struggle to understand antigen and antibody interactions, which is an essential fundamental concept to understand vaccine mechanisms. A virtual interactive video can demonstrate the different interaction types and allow students to make connections faster. This concept can be applied to other body systems in physiology—neurological action potentials, circulatory system, eye physiology, muscular system, etc. Active learning encourages students to be directly involved in the curriculum and develop new connections between subjects. Virtual reality can be implemented into physiology education to improve student engagement and increase the opportunities for active learning. This literature review and report of pilot implementation of VR for physiology education discusses the history of virtual reality, current teaching methods of physiology, current use of virtual reality in teaching, and how virtual reality can be incorporated into the standard curriculum for teaching physiology. Finally, a pilot study has been conducted on physiology students to determine how effective virtual reality is as an active learning exercise.

ABSTRACT # 10

Pathways to Mortality among Head and Neck Cancer Patients: Exploring Cortisol Rhythm and Immune Marker Relationships, and their Implications for Disease Progression

Beck IM[1], Cash ED[1,2], Harbison B[3], and Sephton SE[4]

[1]Department of Otolaryngology, UofL
[2]UofL Brown Cancer Center
[3]Medical College of Wisconsin
[4]Brigham Young Univ Psychology

Cortisol rhythm disruptions predict fatal outcomes in renal, colorectal, lung, and metastatic breast cancer. In head and neck cancer (HNC), various cortisol indices are known to correlate with adverse psychological and biological (e.g., inflammatory) outcomes, but links to mortality have yet to be demonstrated. We hypothesize that the association between diurnal cortisol aberrations and poorer progression-free survival will hold in HNC. Prior work moreover leads us to predict that aberrated diurnal cortisol profiles will associate with changes in serum immune marker expression in this population, and that these immune markers will themselves predict poorer progression-free survival. HNC patients (N eq 40) presented to our multidisciplinary clinic for treatment planning. Most patients presented with late-stage oral or oropharyngeal cancer, were older than 50 years, male, and received combined-modality treatment (surgery, radiation, and/or chemotherapy) with curative intent. Saliva was collected twice daily for six days to assess diurnal cortisol rhythm. Serum was assayed for an exploratory panel of immune markers. Two years post study entry, disease progression and survivorship status were abstracted from medical records. Cox Proportional Hazards models and linear regressions were used to test hypotheses. Cortisol level at bedtime and diurnal cortisol mean were significantly and inversely associated with progression-free survival (bedtime: HR eq 1.848, 95percent CI eq 1.057-3.230, p eq .031; diurnal mean: HR eq 2.662, 95percent CI eq 1.115-6.355, p eq .027). In serum, higher levels of the inflammatory marker IFN-gamma emerged as a correlate of bedtime cortisol (r eq .405, p eq .014) and diurnal cortisol mean (r eq .459, p eq .004). IFN-gamma expression in turn predicted poorer progression-free survival (HR eq 4.671, 95percent CI eq 1.409-15.484, p eq .012). This pilot study suggests that diurnal cortisol expression has prognostic relevance in HNC. These results may have immediate clinical relevance, but future work in larger samples could more appropriately characterize mortality-relevant links among cortisol and oncologic, immune, and psychosocial factors in this population. This study replicates similar findings in other cancers and demonstrates a valid approach to robustly measuring diurnal cortisol expression among patients with head and neck neoplasms.

ABSTRACT # 11

Nogo Receptor Knockout Extends Critical Period Plasticity and Visual Circuit Reorganization

Brown TC, McGee AW

Department of Anatomical Sciences and Neurobiology, UofL

During development, many systems in the brain require sensory experience from the environment to aid in proper formation. In many sensory systems periods of heightened sensitivity to experience known as “critical periods” govern the proper formation during development. During these critical periods the quality of this experience is crucial for the normal function of systems later in life. If the quality of experience is altered or manipulated during these critical periods many of the systems have enduring deficits in function. Extending or reopening critical periods has been a therapeutic target to treat many diseases and neurological conditions. Nogo receptor (NGR1) is a receptor on neuronal surfaces that has been shown to mediate the closure of critical periods. Ablation of NGR1 through knockout has been shown to extend critical period like sensitivity into adulthood. Here utilizing the well established assay Ocular Dominance Plasticity (ODP) in the visual system and 2-photon calcium imaging at cellular resolution we assess the role of individual neurons to plasticity in mice lacking NGR1. We find that NGR1 KO animals maintain critical period like circuit reorganization into adulthood after the closure of the classical critical period for ODP.

ABSTRACT # 12

Investigating Amygdala Circuits that Modulate Stress-Induced Anxiety in Alcohol Withdrawal

Do AL, Tyree JB, Kayat LS, Jaramillo AA

Pharmaceutical Sciences, University of Kentucky

The bed nucleus of the stria terminalis mediates anxiety-like behavior and is dysregulated in AUD. We hypothesize that withdrawal from alcohol increases stress- and anxiety-like behaviors in mice. First, male and female C57 mice were exposed to 4 days of repeated forced swim stress (FSS) and NSFT. Using fluorescent immunohistochemistry, we quantified c-Fos, a marker of neuronal activity, in the BNST. Next, female C57BL/6J mice underwent home cage 2 bottle choice (2BC) paradigm for 8 weeks. To establish drinking, we used an ethanol ramp with three days of 3% ethanol, 2 days of 7% ethanol, and 10% ethanol for the remainder of the experiment. During the 1st - 5th weeks of drinking animals were restricted to two hours of drinking. In week six, animals had 24-hour access to drinking with bottles being weighed daily in a 2-hour time window. In week 7, animals were abstinent for a week and did not voluntarily drink. In week 8 animals underwent the Elevated Plus Maze (EPM) test. Animals returned to 2BC in week 8 and had 24-hour access to drinking. In week 9, animals underwent one week of abstinence followed by the repeated FSS paradigm. Lastly, we used the novelty suppressed feeding test (NSFT) to measure anxiety-like behavior. Results from the FSS NSFT showed latency to consume was increased (unpaired t-test $p = 0.0132$), signifying an increase in anxiety-like behavior. Results from the cell quantification of the sum of cFOS cells showed FSS females had increased c-Fos in stress (2-way ANOVA $p = 0.0268$), signifying FSS increases BNST activity. Results from 2BC showed that animals had increases in ethanol intake after abstinence (2-way ANOVA $p=0.0105$). Therefore, the data supports the hypothesis that stress increases anxiety. Moreover, in alcohol exposed mice stress during withdrawal subsequently increased alcohol drinking. Future studies will use ex-vivo calcium imaging to identify cell type-specific changes in BNST activity of cells mediating anxiety-like behavior in withdrawal.

ABSTRACT # 13

Potential Fingolimod Efficacy in the Affective Withdrawal Phenotype of Nicotine Use Disorder

Elder T, Turner JR

Pharmaceutical Sciences, University of Kentucky

Nicotine Use Disorder (NUD) is a major worldwide issue that has had multiple failed treatment plans in the past. NUD causes a high rate of relapse due to the adverse effects of withdrawal phenotypes. This is due to glial cell dysfunction that causes an increase in neuroinflammatory effects within the central nervous system. Targeting glial cells directly, such as astrocytes and microglia, can dampen their activation with a proposed antagonist. A novel drug choice, Fingolimod, could be the answer to these problems. Fingolimod is sphingosine-1-phosphate functional antagonist that is currently on the market and being used for the treatment in Multiple Sclerosis. It has been shown to dampen microglia activation by antagonizing sphingosine-1-phosphate receptors located on astrocytes. This crosstalk between astrocytes and microglia leads to a long-term decrease in glutamate. Fingolimod's target of the ventral hippocampus could potentially have significant efficacy in controlling neuroinflammation.

ABSTRACT # 14

The Principles of Electrocardiogram and the Effects of Long-Term Vape Use: an Outreach Program to the Health Academy of Pleasure Ridge Park High School

Lee J, Ballard A, Thompson E Torres R, Carll A, Schuschke D, Maldonado C, Terson de Paleville D

Department of Physiology, UofL

An important aspect in the development of future healthcare providers is community engagement. According to the office of Community Engagement within the University of Louisville School of Medicine, "Community engagement and diversity represent essential components of the vision for the University of Louisville School of Medicine and play strategic roles in achieving our mission of improving the health of our patients and our diverse communities. The School of Medicine has a fundamental role and responsibility to improve the health of the community (broadly defined) and transform the delivery of healthcare that is complementary to and integrated with the school's other strategic pillars: Education, Clinical Services, and Research." Having the ability to understand intricate physiologic mechanisms is equally as important as having the ability to communicate your knowledge with the public and spreading awareness to others. In efforts to increase the understanding of cardiac physiology and aid with the prevention of vape use, the University of Louisville Department of Physiology orchestrated an educational outreach program with the Health Sciences Academy of Pleasure Ridge Park High School discussing the functionality of the heart, and hands-on use of an Electrocardiogram (ECG). Divided amongst 4 class periods, a total of 94 students from the 11th grade (Junior) class attended a 50-minute session regarding the pathway of blood through the heart, how action potentials cause the heart to contract, how to interpret an ECG, as well as how various breathing rhythms effect the heart rate. During each session, students were given a handout illustrating how vaping and air pollutants alter ECGs, experienced an oral presentation partnered with an animation for visual aid, engaged in educational games to recall the information presented, as well as rotated through 3 interactive Electrocardiogram (ECG) group activities. This presentation will discuss the details of the outreach program regarding ECG, and the learning objectives for the high school participants.

ABSTRACT # 15

Connections between the superficial and deep superior colliculus via narrow-field vertical neurons

Mason K, Masterson S, Slusarczyk A, Bickford M

Department of Anatomical Sciences and Neurobiology, UofL

The mammalian superior colliculus (SC) is a laminated midbrain structure and a site of sensorimotor integration. The superficial layers of the SC (sSC) receive visual information from retinal ganglion cells and other sources such as the primary visual cortex, while deep layers (dSC) receive information from other sensory modalities and motor-related areas such as the substantia nigra. Connections between the superficial and deep layers have been identified, but little is known regarding the connected cell types. To begin to address this, we have examined the intrinsic connections of superficial narrow-field vertical (NFV) cells. In mice, a subset of NFV cells can be specifically labeled in the KHGRP288 line ("NFV-cre"); these cells respond preferentially to rapidly moving visual stimuli and their inactivation disrupts the ability of mice to capture crickets (Hoy et al., Current Biology 2019 29:4130-4138). We stained sections from NFV-cre mice crossed with TdTomato reporter mice (Ai9) with an antibody against parvalbumin and found that NFV cells labeled in this line constitute a subset of parvalbumin neurons in the sSC. To examine the ultrastructure of NFV cells, we injected a virus to induce the expression of Apex2 in a cre-dependent manner and prepared the tissue for electron microscopy. Ultrathin sections were also stained with an antibody against gamma amino butyric acid (GABA) tagged with gold particles. Ultrastructural examination revealed that this subset of NFV cells receives synaptic input from retinal terminals (identified by their unique mitochondria), GABAergic terminals (identified by a high density of overlying gold particles), and terminals that contain dense core vesicles (a feature associated with cholinergic neurotransmission). Electron microscopy also revealed that the outputs of NFV cells preferentially contact nonGABAergic dendrites. Functional assays employing optogenetics and in vitro electrophysiology also show evidence of connections between NFV cells in sSC and cells in dSC. The identity of the deep layer neurons contacted by these sSC NFV neurons will be determined in future experiments. Collectively, these studies will help determine how SC circuits initiate the appropriate actions in response to visual motion.

ABSTRACT # 16

Establishing a mouse model of cerebral/cortical visual impairment (CVI)

Oakes DK[1], Cai J[2], McGee AW[1], Guido W[1]

[1]Department of Anatomical Sciences and Neurobiology, UofL
[2]Department of Pediatrics, UofL

Cortical/cerebral visual impairment (CVI) is a disorder most often caused by perinatal hypoxic injury to the developing brain. CVI is the leading cause of childhood visual impairment in developed nations, encompassing deficits in many aspects of vision including visual acuity, contrast sensitivity, and object recognition. The pathophysiology of CVI is not well understood because no animal model currently exists to study this disorder. Here, we developed a murine early postnatal hypoxic model of CVI by exposing mice to 9.5% O2 at postnatal day (P)3 for 14 days. As adults (>P40), we tested their motor function, visual acuity, and binocular depth perception. Then, we examined the pattern of eye specific segregation of retinogeniculate afferents in the dorsal lateral geniculate nucleus of the thalamus (dLGN) by using Cholera toxin subunit B as an anterograde tracer. Finally, we investigated the receptive field tuning properties of excitatory neurons in visual cortex (V1) using two-photon calcium imaging at cellular resolution in mice expressing the genetically encoded calcium sensor GCaMP6s. Motor performance was normal in mice receiving early postnatal hypoxia. In contrast, visual acuity was impaired on average and highly variable in hypoxic mice. A subset of hypoxic mice was unable to perform the task reliably. Binocular depth perception was also impaired by early postnatal hypoxia. On average, the pattern of eye specific segregation was largely unaltered in early postnatal hypoxic mice. However, there is greater variability in the segregation of ipsilateral and contralateral retinal projections in hypoxic mice. The orientation and spatial frequency tuning of visual cortical neurons were unaltered in the perinatal hypoxic mice. The ocular dominance of the hypoxic mice also resembled normoxic mice. These visual behavioral deficits resemble facets of human CVI. The establishment of an early postnatal hypoxic mouse model of CVI will provide a foundation for both characterizing this prominent visual disorder and developing rational treatment options.

ABSTRACT # 17

Effects of Prefrontal NRG3/ERBB4 Signaling on Nicotine and Withdrawal-Induced Responses

Prantzalos ER, Turner JR

Pharmaceutical Sciences, University of Kentucky

Our lab has identified region- and circuit-specific roles of the gene Nrg3 and its specific receptor tyrosine kinase, ErbB4, in the presentation of anxiety-like behaviors during nicotine withdrawal (WD). Nrg3 and ErbB4 are highly expressed in the prefrontal cortex (PFC), a region important for the regulation of thoughts, actions, and emotions. This study tests whether prefrontal ErbB4 is necessary for the presentation of behavioral deficits common to nicotine use or WD. Using an ErbB4-flox mouse model, we knocked down ErbB4 in the medial PFC of adult male and female mice. Chronic nicotine treatment was then administered via osmotic minipumps, at a dose of 18 mg/kg/day for 14 days. Removal of minipumps elicited spontaneous WD 24h prior to behavioral testing and tissue collection. Behavioral activities engaging the corticolimbic circuit assessed anxiety-like behaviors seen during WD via 1) Open Field Test (OF) and 2) Acoustic Startle Response (ASR). Pharmacological and genetic manipulations resulted in differential behavioral responses to nicotine and WD between males and females, suggesting sex-specific effects of prefrontal NRG3-ErbB4. Additionally, we show that NRG3 expression in the medial PFC is reduced with prefrontal ErbB4 KD. NRG3 and ErbB4 are implicated in several psychiatric disorders, notably schizophrenia and nicotine use disorder. Thus, these findings may lead to valuable insights regarding pharmacological treatment of nicotine use and comorbid psychiatric disorders, accelerating potential for personalized approaches to nicotine dependence by establishing a mechanistic model of gene x drug interaction of the NRG3-ErbB4 pathway.

ABSTRACT # 18

Expression of Cellular Senescence Markers in Glia and Macrophages from the Contused Mouse Spinal Cord

Rood B, Myers S, HodgesE , Slomnicki LP, Gao Y, Miller M, Andres K, Whittemore SR, Hetman M

Department of Biochemistry and Molecular Genetics, UofL
Kentucky Spinal Cord Injury Research Center

Cellular senescence is a response in proliferating cells to DNA damage which can promote tissue repair, but also chronic inflammation. While potential role of cellular senescence in SCI is unclear, this study aimed at testing for the presence of senescent cells after a moderate contusive SCI (50 kdyn, IH, T9) in C57Bl6 mice. Transcript levels for two widely used cell senescence markers (p16/Cdkn2a and p21/Cdkn1a) were increased both subacutely (3-7 days) and subchronically (6 weeks) after SCI. Moreover, SCI-associated upregulation of the p16 promoter-driven 3MR reporter gene was found in p16-3MR transgenic mice. p21 RNAScope as well as immunofluorescence staining showed both subacute and subchronic (6 week) increases of the respective senescence marker signals in ASPA-positive oligodendrocytes, GFAP-positive astrocytes and CD68- or IBA1-positive macrophages/microglia. Senescent astrocytes were found in the glial scar region bordering the injury epicenter. Senescent microglia/macrophages were also observed in the glial scar as well as in the fibrotic scar at the injury epicenter. In those regions, senescence marker-expressing astrocytes and microglia/macrophages were relatively abundant with a positivity rate ranging from 20-50%. These observations suggest a prolonged cellular senescence response to SCI that likely follows SCI-induced proliferation astrocytes and microglia/macrophages. Whether such a response is beneficial or detrimental for post-SCI recovery will be explored in future studies.

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ABSTRACT # 19

Characterization of the Gut-Brain Axis and Proinflammatory Status for the Presentation of Clinically Significant Depression in Patients with Alcohol Use Disorder

Said A, Jayanty D, Colson T, Singal A, Vatsalya V

University of Louisville School of Medicine

Background: Alcohol Use Disorder (AUD) and depression are comorbidities that are associated with greater severity and worse prognosis. This study explored the domain of depression using the Montgomery-Asberg Depression Rating Scale (MADRS) to classify the severity and evaluate the involvement of the gut-brain axis (GBA), pro-inflammatory status, and sex differences. Methods: 48 individuals (F=14, M=34) with AUD diagnosis were divided into two groups using MADRS score without any clinically significant (CS) level of depression (Gr.1, MADRS CS≤8; N=9 [F=1, M=8]); and those with CS depression (Gr.2, MADRS CS>8; n=36, [F=13, M=23]). Clinical charts, Standard of Care (SOC) labs, and research labs for gut dysfunction and pro-inflammatory biomarkers were assessed for relationships between depression and AUD. Gr.2 was further divided into mild (9-17) and moderate-severe (>17) by Mittman's criteria (and analyzed for response changes. Results: In Gr.2, Lifetime Drinking history was significantly increased among the males. In Gr. 2, TNF-α was significantly associated with +sCD14, a gut-dysfunction marker in the context of the heavy drinking marker HDD90, p=0.027 at R^2=0.221. Males showed a significantly higher chronic drinking index compared to females, p=0.015. Females of Gr.2 exhibited a significant 5-fold increase (p=0.025) in IL-8 levels than their male counterparts. Only in the mild MADRS group, depression scores could be predicted by the altered levels of gut-dysfunction markers, LBP, and +sCD14 (R2 adjusted=0.413, p=0.041). Subsequently with Adiponectin in context, the effects further increase to adjusted R^2=0.777, p=0.021; that gets augmented effects with IL-1β adjusted R^2=0.820, p=0.026. Such effects were absent in the clinically insignificant group, nor the moderate-severe group. Conclusions: Gut-brain response in mild depression shows sensitivity to the pathological arrangement of the candidate markers of gut dysfunction, and proinflammatory activity, and adiponectin response. Chronic alcohol drinking was high among the males who exhibited clinically relevant depression, showing sex dimorphism. AUD and depression share a corresponding response of the gut-brain axis, which is mediated by the candidate pro-inflammatory arrangement.

ABSTRACT # 20

Effects of alcohol on Alzheimer's disease pathogenesis in 3xTg-AD mice

Sloan LJ[1,2,3,4], Chilton PM[1,3,4,9], Rao A[1,3,4], Zhang J-W[1,3,4], Myers SA[1,3,4], Reddy S[1,3,4], Rodriguez WE[1,3,4], Gobejishvili L[1,3,4], Chariker J[5], Rouchka E[5,6], Ghare S[1,3,4,9], McClain C

[1]Department of Medicine, UofL
[2]Dept. of Pharmacology & Toxicology, UofL
[3]University of Louisville Alcohol Research Center
[4]Hepatobiology & Toxicology Center
[5]KY INBRE Bioinformatics Core
[6]Dept. of Biochemistry and Molecular Genetics, UofL
[7]Robley Rex VAMC
[8]Norton Neuroscience

Background: Alzheimer's disease (AD) is a neurodegenerative dementia marked by the progressive accumulation of neurotoxic proteins and loss of memory. It is becoming increasingly clear that excessive alcohol consumption leads to neurodegeneration. Indeed, recent meta-analyses identify chronic heavy alcohol consumption as a significant risk factor for developing various dementias, including Alzheimer's disease (AD). However, the effect of EtOH on early neuropathogenesis of AD is unclear. We hypothesize that chronic binge alcohol consumption accelerates the early development of AD neuropathology. Methods: We used the 3xTg mouse model of AD, expressing three genes associated with early-onset AD: human APPSwe, PS1M146V, and tauP301L. Female 3xTg-AD mice and non-transgenic (nTg) control mice were given 4g/kg EtOH binges twice/week by oral gavage from 6 to 10 months, while untreated controls received sham gavages. One-week after EtOH cessation mice were subjected to novel object recognition test (NORT) to assess hippocampal-dependent memory after which brain tissues were harvested for protein and RNA analysis. RNA-Seq was performed on the mid-brain region, containing the hippocampus, and validated with qPCR and western blot analyses. Data analyses were performed using GraphPad Prism, either two-way ANOVA (between genotypes) or one-way ANOVA (within genotype). Results were considered significant when p<0.05. Results and Conclusions: EtOH consumption caused a significant decrease in hippocampal-dependent memory in 3xTg-AD mice compared to untreated 3xTg controls, while nonTg mice did not exhibit significant deficits in memory with or without EtOH consumption. RNA-seq performed on the mid-brain region containing the hippocampus revealed that binge EtOH treatment significantly affected 8477 genes (4473 up- and 4004 down-regulated) in 3xTg mice. Enrichment analyses showed EtOH altered several processes associated with neurodegeneration in 3xTg mice including regulation of synaptic plasticity and autophagy. Lastly, plasma analyses showed a slight EtOH-induced increase of Neurofilament light (NfL) in 3xTg mice, but an EtOH-induced decrease in NonTg mice. Taken together, these data indicate that chronic binge EtOH consumption accelerated AD-associated memory deficits in 3xTg mice accompanied by significant changes in expression of genes contributing to AD pathogenesis in the hippocampus, a region affected early by AD neuropathology.

ABSTRACT # 21

Locomotor training enhances ejaculatory function triggered by epidural stimulation in spinal cord injured rats

Wilkins NL[1], Beasley K[1], Perez De Corcho Vazquez B[1], Hubscher CH[1,2]

[1]Department of Anatomical Sciences and Neurobiology, UofL
[2]Kentucky Spinal Cord Injury Research Center

Approximately 95% of men with spinal cord injuries (SCI) will exhibit sexual dysfunction with symptoms in males related to erection, ejaculation, and poor sperm quality. The current interventions focus on sperm harvest for in vitro fertilization; however, these interventions pose a risk of triggering autonomic dysreflexia and do not help individuals with physical intimacy or sexual satisfaction. Spinal cord epidural stimulation (scES) and activity-based recovery training (ABRT) are two interventions that have been found to improve bladder and sexual function in clinical and pre-clinical cases of SCI. In the current study, a clinically relevant rodent model of incomplete SCI was used to determine the efficacy of scES for ejaculatory function in animals that were non-trained (CX-NT) or received ABRT two times per week (CX-2DPWT) or five times per week (CX-5DPWT). A greater number of animals from CX-2DPWT and CX-5DPWT were responsive to scES for sexual function when compared to CX-NT, with CX-2DPWT displaying the most responses to scES. Electromyography revealed that CX-2DPWT and CX-5DPWT had significantly longer burst duration in the bulbospongiosus muscle ($P<0.01$) and CX-NT and CX-2DPWT had significantly greater excitation in the external urethral sphincter ($P<0.05$) during the urethrogenital reflex when compared to spinally intact rats. CX-NT and CX-5DPWT but not CX-2DPWT displayed a decreased trend in sperm counts relative to sham. ABRT twice a week has promise to improve sensitivity to scES for ejaculatory function in individuals with SCI, supporting the use of ABRT in conjunction with neuromodulation.

Abstracts

POSTDOCS, STAFF & RESIDENTS

ABSTRACT # 22

Semantic segmentation of OCT retinal layers in pigs using a trained U-Net network

Alston D[2], Jalligampala A[1], Prestigiacomo J[1], McCall M[1,2]

[1]Department of Ophthalmology and Visual Sciences, UofL
[2]Department of Anatomical Sciences and Neurobiology, UofL

The analysis of sdOCT (spectral domain ocular coherence tomography) b-scans can be time consuming and subjective. We sought an approach to provide more accurate, objective and quantitative analysis of sd-OCT using data from a transgenic pig model of P23H human rhodopsin (Tg P23H hRHO) Autosomal dominant Retinitis Pigmentosa. Methods: sdOCT was used to assess changes in Tg P23H hRHO pigs as a function of time. Sets of 1000 b-scans were averaged and registered using a custom Matlab script to produce 100 images/set (1000 x 1024 pixel images). Averaged images had retinal layers drawn manually using a modified version of a Matlab program called OCTSEG. Ground truth labels were drawn for the inner and outer nuclear layers (INL and ONL, respectively) and for the retinal pigment epithelium (RPE). A set of 274 averaged b-scans drawn from 27 pigs were selected and randomly split into training (206), testing (340), and validation (34) sets. Thirty-two patches of 48 x 1024 pixels were randomly extracted from each training image and formed the input to the model. A U-Net network was trained over 50 epochs using the Adam optimizer and the Matlab Deep Learning toolbox, validating its loss against the validation set every one third of an epoch. This final network was also exported to a Keras/Tensorflow model to allow for easy model sharing. Results: The final network was evaluated against the post validation test set (34 images). Five metrics were considered: global accuracy, per class mean accuracy, mean intersection over union (IoU), class weighted IoU, and mean boundary F1 score. For our purposes, the mean boundary F1 score was most critical since we are interested in layer edge locations. The final model achieved a mean boundary F1 score of 0.979 (SD=0.0378) with a per class mean accuracy of 0.896 (SD=0.0554). We are now comparing these quantified b-scans to quantified measurements from confocal images of the same retinas in the similar retinal locations. Conclusions: This network provides a way of easily segmenting averaged b-scans and significantly reduces the amount of time needed to measure retinal layer thicknesses. As more data is labeled, we expect the retrained model to further improve; eventually enabling fully automatic segmentation of pig b-scan data.

ABSTRACT # 23

NMDA Antagonists Use in Bipolar Depression: A Case Report

Ibrahim K, Abell S, El-Mallakh R

Department of Psychiatry and Behavioral Sciences, UofL

Background: Treatment of bipolar depression can be challenging for clinicians. Antidepressants have not been shown to be useful and can further destabilize bipolar patients and increase depressive episodes but remain the most frequently used class of drugs in these patients. While pro-dopaminergic and anti-serotoninergic doses of some antipsychotic medications have been found to be useful, glutamatergic interventions hold significant promise. Lamotrigine, which inhibits both voltage sensitive and N-methyl-d-aspartate (NMDA)-associated sodium channels has been found to have a significant antidepressant effect in bipolar patients. Similarly, ketamine and dextromethorphan, which also inhibit the NMDA-associated sodium channels are probably also effective in bipolar depression. Case: The patient is a 77-year-old Caucasian male with a psychiatric history of bipolar 1 disorder, who presented for outpatient follow-up with depressive symptoms. His psychiatric medication regimen at that time was Vraylar 1.5mg daily, Wellbutrin SR 450mg daily, Trintellix 20mg daily, lamotrigine 600mg qhs, modafinil 400mg daily, and Remeron 30mg qhs. He began treatment with s-ketamine shortly after this encounter. The patient had a notable clinical response to s-ketamine; citing it as “giving him his life back” and providing near complete symptomatic relief. On this regimen, the patient established euthymia and maintained it for several months thereafter. When he returned to the clinic for subsequent follow up, he reported recent cessation of s-ketamine treatments due to uncontrolled hypertension and tachycardia. In the absence of s-ketamine, depressive symptoms returned. Given the patient’s prior positive response to NMDA antagonists, Bupropion/dextromethorphan combination 105-45mg BID was started. He reported benefit from it the first several weeks before he returned to a depressed state. The dose was decreased to once daily, and remission was re-achieved. Discussion: NMDA-antagonists have a therapeutic window so that if NMDA inhibition is excessive the antidepressant effect can be lost. In this case the patient was on two separate medications that inhibited the sodium channel associated with the NMDA receptor. The combined administration of two agents that work by the same mechanism appears to have exceeded the therapeutic window, so that reducing the dose of one of the agents re-established the initial therapeutic response.

ABSTRACT # 24

Mobility task shows rescue of scotopic vision in a swine model for autosomal dominant Retinitis Pigmentosa after treatment with the meganuclease Rho 1-2

Kamboj K[1], Feist JE[1], Barone F[3], Jaikumar G[1], Jalligampala A[1], Wang W[1], Viles K[4], McCall MA[1,2]

[1]Department of Ophthalmology and Visual Sciences, UofL
[2]Department of Anatomical Sciences and Neurobiology, UofL
[3]National Eye Institute, NIH
[4]Precision Biosciences

Purpose - Retinitis pigmentosa (RP) is the most common form of inherited retinal disease with ~1:5000 people affected worldwide. The substitution of Proline to Histidine (P23H) at position 23 in the rhodopsin protein is the most common form of adRP in North America. We have shown that treating transgenic P23H human RHO pig model of adRP (TgP23H hRHO) with a gene-editing meganuclease Rho 1-2, recovers rod structure and restores rod function. We ran WT, Rho1-2 treated and untreated TgP23H hRHO (Tg) pigs through an obstacle course to quantify visually guided mobility under light- and dark-adapted conditions using motion analysis software. Methods - Rho 1-2 packaged in AAV5 with a GRK1 promoter was subretinally injected into one or both eyes of neonatal Tg pigs. After ~10 months, we tested visually guided behavior by running pigs through an obstacle course. Pigs were trained binocularly under light-adapted conditions. Pigs were food deprived (16hrs) and tested monocularly under light (150 lux) or dark (10 lux) conditions (30 mins dark adaptation). At the end of each run, pigs received a food reward. Barrier location was randomized between trials. Videos were recorded with an infrared handheld camera that moved along with the pig (outside of the course). From the videos, positions of the pig's front feet relative to obstacles were estimated using Kinovea motion analysis software. Data were plotted using SmartDraw charting software. Foot positions were imported into R and evaluated using its trajr package functions. Results - Under conditions that require rod function, Rho 1-2 treated Tg eyes led to significantly fewer collisions (~33%), shorter path length (~40%) and overall duration (~67%) in the run compared to untreated Tg eyes. The Tg pig's path through the obstacle course using the treated eye was less tortuous, compared to untreated Tg. In 1 Tg pig only one eye was treated and the visually guided behavior using its treated eye was better compared to its untreated eye. Conclusions - We developed an analytical tool that uses raw videos to quantitatively analyze foot position in large animals that quantifies maze mobility. Mobility mediated by Rho 1-2 treatment in TgP23H hRHO eyes was significantly improved under rod mediated conditions. These results extend Rho 1-2 mediated improvements shown in retinal rod function and structure in TgP23H hRHO pigs.

ABSTRACT # 25

Lupus Cerebritis Induced Catatonia Presenting with Stereotypy of Thought and Subsequent PTSD

Shah S, Nicholas B

Department of Psychiatry, UofL

Catatonia is a complex neuropsychiatric condition characterized by significant changes in psychomotor function and behavior. Although its pathophysiology is heavily debated, consistent evidence suggests that dopamine hypoactivity, loss of gamma-aminobutyric acid (GABA) transmission and glutaminergic hyperactivity play a role in its development. There is no agreed upon comprehensive model for catatonia, but two contenders are the fear hypothesis and depolarization hypothesis. The first hypothesis proposes that the primal fear response in humans has evolved into catatonia, whereas the second hypothesis proposes that catatonia is due to progressive elevations in resting membrane potential that leads to depolarization block. The association of catatonia with fear has long been well documented, but their relationship is not well understood. This case report sheds light on this topic by introducing the concept of a stereotypy of a thought, a symptom of catatonia that emerged during treatment of a catatonic patient with lupus cerebritis. This thought stereotypy presented with repetitive trauma flashbacks that lead to the development of post-traumatic stress disorder and subsequent psychosis. We believe the depolarizing nature of catatonia naturally selects for the preservation and reinforcement of neural circuitry which maintains its own polarity, in this case the adrenergic effects of the fear response. This report elaborates on this relationship.

ABSTRACT # 26

Increased hemorrhagic stroke and impaired hemostasis in mice deficient of the integrated stress response kinase HRI

Slomnicki LP, Owens R, Hodges E, McNeely J, Burke DA, Chariker JH, Rouchka EC, Saraswat Ohri S, Ding D, Hetman M

Department of Neurological Surgery, UofL
Department of Pharmacology and Toxicology, UofL
Department of Anatomical Sciences and Neurobiology,UofL
Department of Computer Engineering and Computer Science, UofL
Kentucky Spinal Cord Injury Research Center, UofL

After injury, the integrated stress response (ISR) reduces general protein synthesis and upregulates downstream ISR genes to promote cell survival or initiate cell death. In addition, ISR regulates various physiological processes, including immunity and synaptic plasticity. However, role of ISR in brain damage/functional recovery after hemorrhagic stroke has not been directly addressed. We report upregulation of multiple ISR genes in the peri-hematoma region one day after collagenase-induced intracerebral hemorrhage (ICH) in mice. Moreover, worsened functional impairment post-ICH was observed in knockout mice for the protein kinase HRI/EIF2AK1 that activates ISR in response to oxidative- or mitochondrial stress. In the hemisphere ipsilateral to the collagenase injection site, increased lesion area, elevated number of degenerating neurons, and greater staining area for the neuroinflammatory marker CD36 were also present on day 7 post ICH induction. However, such an enhancement of tissue damage was preceded by increased hemoglobin levels in the ipsilateral hemisphere one day after collagenase injection. Therefore, increased ICH severity in Hri-/- mice may be driven primarily by increased bleeding. In support of this notion, prolonged tail bleeding time was found in those mice together with a 50% reduction in blood platelet number. Our findings demonstrate the unexpected role of HRI in hemostasis and open an avenue for future studies into significance of pro-hemostatic ISR in pathogenesis of cerebrovascular disease. Financial support: R01NS108529