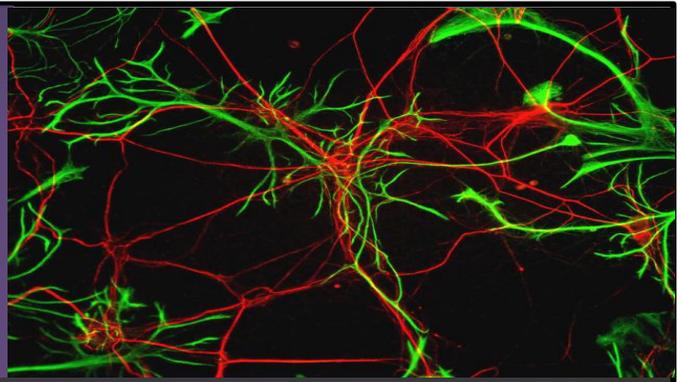


*Eastern Carolina Chapter
of the Society for
Neuroscience Presents:*



16th Annual Neuroscience Symposium Catalyst for Collaboration



Featuring:

David L. McKinzie, PhD

Senior Research Advisor

Eli Lilly and Company

*“A Primer on the Drug Development Process and Challenges
Facing the Pharmaceutical Industry”*

Thursday, October 30th, 2014

East Carolina Heart Institute

9:00 am – Registration

9:00 am – Poster Session 1

11:45 am – Opening Remarks

12:00 pm – Keynote Address: Dr. McKinzie

1:30-2:45 pm- ECU Faculty/Student Presentations

2:45 pm – Poster Session 2

4:00 pm – Closing Remarks and Awards

Registration and program information at: www.ecu.edu/neurochapter

The Officers and Council Members of the Eastern Carolina Chapter of the Society for Neuroscience would like to express their sincere gratitude to the following for their support of the 2014 Neuroscience Symposium:

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Proposed 2014 Neuroscience Symposium: Catalyst for Collaboration

October 30th, 2014

Presented by:

The Eastern Carolina Chapter of the Society for Neuroscience

Schedule of Events:

- 9:00-11:45 **Registration: ECHI Hallway**
- 9:00-10:15 **Poster Session 1: ECHI Hallway**
- 10:30-11:30 **Brunch** with Keynote and Students: ECHI Classroom
- 11:45-12:00 **Opening Remarks:** William Downs, PhD, Dean, Harriot College of Arts and Sciences
- 12:00-1:15 **Keynote Address:** David L. McKinzie, PhD, Senior Research Advisor, Eli Lilly & Company
- “A Primer on the Drug Development Process and Challenges Facing the Pharmaceutical Industry”**
- 1:15-1:30 **Break & Vendors w/snacks**
- 1:30-1:55 Dorothy Dobbins, MS Candidate
- “Neurological Effects of Blast Overpressure Exposure: Examining Changes in miRNAs and Behavior”**
- 1:55-2:20 Fadi Issa, PhD, ECU Department of Biology
- “The Effects of Spinocerebellar Aataxia Type-13 Mutations on Zebrafish Cerebellar and Spinal Cord Neuron Development and Excitability”**
- 2:20-2:45 Chia-Cheng (James) Lin, PhD, ECU Department of Physical Therapy
- “Functional Near-Infrared Spectroscopy Neuroimaging of Sensory Integration During Balance in Older Adults”**
- 2:45-4:00 **Poster Session 2/Vendors** (w/ hors d'oeuvres)
- 4:00-4:15 **Closing Remarks and Awards**

Oral Presentations

A Primer on the Drug Development Process and Challenges Facing the Pharmaceutical Industry

David McKinzie, PhD

Senior Research Advisor / Head of In Vivo Pharmacology

Neuroscience Discovery Research, Lilly Corporate Center, Eli Lilly & Co., Indianapolis, IN 46285

Despite tremendous advances in biomedical technology and in our understanding of brain function, considerable attrition exists within pharmaceutical drug development for central nervous system (CNS) disorders. A failure to translate animal models of psychiatric and neurological disease into demonstration of clinical efficacy is often cited as a contributing factor. As a result of such failures, many pharmaceutical companies have reduced or ceased investment in CNS disorder research. This presentation will provide a high-level overview of the drug discovery process and highlight challenges that have led to the discontinuation of new clinical compounds. Moreover, current strategies to improve preclinical-to-clinical translation of therapeutic activity will be discussed.

Neurological Effects of Blast Overpressure Exposure: Examining Changes in miRNAs and Behavior

Dorothy Dobbins, BS, MS Candidate

Dorothy Dobbins and Xiaoping Pan

Department of Biology, East Carolina University, Greenville NC 27858

Blast overpressure exposure is the leading cause of mild traumatic brain injury (mTBI) in veterans returning from combat. Exposures to shockwaves from explosive devices create a variety of cellular and biochemical changes causing lingering neurological problems. While mTBIs can have a good prognosis, over 50% lead to persistent long-term deficits. This study aims to understand the microRNA-mediated molecular mechanisms of blast overpressure - induced mTBIs and resulting neurological alterations. Rodent models of mTBIs were generated using an advance blast simulator. Sprague Dawley rats were subjected to a single blast overpressure of 10-12 psi. Biochemical, histological, and behavioral differences were observed between blasted and sham controls. Samples of whole blood were used for total RNA extraction. Microarray and quantitative real-time PCR (qRT-PCR) were used to profile aberrantly expressed microRNAs (miRNAs). The collection of miRNAs exhibiting altered expression targeted many neurological pathways including inflammation, neutrophin signaling, and long-term potentiation. The Morris water maze was used to examine the behavioral/functional alternations that may relate to the identified biochemical alterations. Findings initially revealed learning and memory deficits and an increase in depression-like symptomology. Continued behavioral testing indicated a significant improvement of impairments/behaviors overtime. Results from this study link miRNAs to altered neurobehavioral status, aiding the understanding of mTBI sequela. Observed changes in miRNA expression and behavioral assessments also suggested novel targets that are useful for improving therapeutic approaches.

The Effect of Spinocerebellar Ataxia Type 13 Mutation on Zebrafish Cerebellar and Spinal Cord Neuron Development and Excitability

Fadi A. Issa, PhD

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Spinocerebellar ataxia type 13 (SCA-13) is an autosomal dominant disease that leads to the neurodegeneration of the cerebellum and spinal cord. SCA-13 patients experience progressive severity in incoordination of the limbs accompanied by irregularity of speech and eye movements. Underlying this disease is two mutations in the Kv3.3 channels. The Kv3.3 channel promotes high frequency firing in cerebellar Purkinje and spinal cord motor neurons. Thus, SCA-13 alters the Kv3.3 channel function suggesting that changes in excitability initiate pathogenesis. The disease exists in two forms: infant-onset characterized by severe mal-development of the cerebellum and persistent motor deficits or adult-onset characterized by progressive cerebellar degeneration and ataxia. The age of onset is strongly correlated with the causative mutation in unrelated families. In this presentation, we will explore the effects of the SCA-13 mutations on the zebrafish cerebellum and spinal cord. Using electrophysiological recordings and in vivo imaging, I will present evidence that shows genetically targeted expression of the SCA-13 mutations alter the excitability and morphological development of the zebrafish spinal cord motor and cerebellar Purkinje neurons. These cellular changes lead to behavioral motor deficits in swimming abilities. Also, I will show that the infant onset form of the disease exerts significantly more detrimental effects on neuronal development. We propose that infant onset SCA13 is associated with changes in cerebellar development that reduce neuronal health and viability, resulting in the withered cerebellar architecture seen in affected children.

Functional Near-Infrared Spectroscopy Neuroimaging of Sensory Integration During Balance in Older Adults

Chia-Cheng Lin, PhD

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Functional near-infrared spectroscopy (fNIRS) is a neuroimaging method which is able to monitor brain hemodynamic changes during upright dynamic movements. Compared to traditional neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET), fNIRS can be used to measure brain activities without any restriction of body position and movement. This novel neuroimaging method will help us investigate human brain function during daily activities.

Human balance control is reliant on the sensory integration of the visual, somatosensory and vestibular information. Studies have shown the sensory integration process deteriorates in old age. Little is known about changes in brain activities that accompany a decline in balance performance during aging. In our study, four different sensory integration conditions (vision conditions (eyes open or closed) x somatosensory feedback conditions (fixed or sway-referenced platform)) were used to investigate the brain activity in older adults.

After a brief introduction of fNIRS, this presentation will review current evidence for the sensory integration process for balance control during aging using fNIRS. Our results suggest that older adults demonstrate widespread areas of increased brain activity in response to changes in sensory information to maintain balance control. In the conditions which require vestibular processing, older adults used different patterns of brain activation compared with young adults. These results suggest that the sensory integration process may change during aging.

Poster Session 1

(in alphabetical order by first presenting author)

Heat Shock Proteins (Chaperones) For Intervention in Neurodegenerative Diseases

Atta Ahmad

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Chaperones assist in maintenance of functional proteome *in vivo*. However, they seem to be either ineffective or overwhelmed in the case of protein mis-folding diseases like Parkinson's, Huntington's or Alzheimer's. We have investigated effects of one of the chaperones namely "Hsp70 system" in particular. The members of Hsp70 system exhibit conflicting effects on the aggregation propensity of α -synuclein, a protein implicated in Parkinson's disease. While some members alleviated the aggregation propensity other members were stabilizing when studied individually. When all members were present the system as whole showed a stabilizing effect. These results inspired us to further pursue the importance of protein quality control in neurodegenerative diseases and if they could be effective drug targets.

We carried out screening of different chemical libraries on Hsp70 system and have found compounds that can inhibit or activate this system. Further, we identified compounds that could replace some members of Hsp70 system in the knockout models. Though far from conclusion, these data provide us the bases of carrying out further experimentation as we study the folding efficiency triggered by these and other similar drugs. These results as we envisage can then be directly applied to rescuing dying cells and prevent degeneracy associated with neurodegenerative diseases.

(Repetitive) Head Trauma: Histopathologic Distinction between “Traumatic Axonal Injury” (TAI, Affecting Long Axons Tracts) and “Chronic Traumatic Encephalopathy” (CTE, Affecting Cerebral Cortex) - An Illustrative Case Report

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²Rocky Mountain Forensic Services, Loma, CO

Recognition of the adverse effects of head trauma, both immediate and long-term, has emerged during the past decade and distinction between the two major forms of non-contusion injury can now be made postmortem. **(1) Traumatic axonal injury (TAI)** (also known as diffuse axonal injury (DAI)) results from axon damage, primarily within long white matter tracts (e.g. corpus callosum and ascending and descending fibers). Axon damage has been correlated with the effects of acceleration-deceleration on the long white matter tracts. TAI manifests clinically as a “concussion.” Histologic and amyloid precursor protein immunohistochemical examination for TAI highlights the axon damage. **(2) Chronic Traumatic Encephalopathy (CTE)** affects the cerebral cortex and is now recognized as the long-term sequela of multiple traumatic head injuries experienced over time. First described in former professional football players, it has subsequently demonstrated post-mortem in individuals who suffered repetitive traumatic injuries while playing hockey, soccer, and other sports. Clinically, CTE presents years after the head injuries as early-onset dementia and behavioral changes. Histopathologic diagnosis is made by identification of abnormal accumulation of phosphorylated tau protein within cortical neurons.

Case Report: A 25-year-old man suffered closed head injury and thoracic trauma while performing tricks on a snowmobile during the 2013 X Games in Aspen, Colorado. He suffered a cardiac contusion-related cardiac arrest six hours following the accident with an anoxic time of 15-20 minutes and succumbed to severe hypoxic-ischemic injury seven days after the accident. He had participated in “extreme sports” for over a decade and had suffered at least five previous “concussions.” Neuropathologic examination identified both (1) recent traumatic axonal injury and (2) early-stage chronic traumatic encephalopathy. This highly informative case highlights and distinguishes these two trauma-induced disease processes and underscores the immediate and chronic effects of head trauma in a young athlete. Acknowledgement: The patient’s father has encouraged the publication of this case with the goal of advancing the understanding of the pathophysiology of head trauma.

Fatigue-Related Shifts in Median Frequency of Quadriceps EMG in Prolonged Steady State Running

Brooke R. Catanzarito¹, Kelly A. Best¹, Klarie M. Ake¹, Laura A. Scott¹, Jennifer A. Bunn¹, Douglas W. Powell¹

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Fatigue is a complex phenomenon associated with changes in muscle environment and descending neural drive. Mechanically, it is associated with reductions in sport performance; however, the neurophysiological underpinnings of fatigue have not been fully elucidated. The response of the neuromuscular system to a sustained, submaximal effort is theorized to be associated with increased motor unit activation. However, few studies have directly investigated fatigue during a prolonged bout of exercise with a common EMG-driven measure of fatigue, median frequency (MDF). The purpose of this study was to investigate changes in MDF in response to a prolonged steady state running task.

METHODS: Eleven participants aged 18 to 35 years performed a 35-minute treadmill running task at a self-selected velocity. Electromyography (EMG) was recorded from the right (dominant) vastus lateralis for eight 15-second trials in five-minute intervals (i.e. 0 min, 5 min, etc.). EMG was recorded using wireless EMG electrodes (2000 Hz, Delsys Trigno, Delsys Inc., Boston, USA). Using custom software (MatLab 2013a, Mathworks, Natick, MA), EMG signals were band-pass filtered (20 Hz – 500 Hz) then converted to the frequency domain using a Fast Fourier Transform and the MDF was selected. Paired samples t-tests were used to compare changes in MDFs via three measurements: 0 to 15 minutes, 0 to 35 minutes and 15 to 35 minutes. A Bonferroni adjustment was used to compensate for multiple comparisons. Alpha level was set at $p < 0.05$ (adjusted: $p < 0.017$).

RESULTS: The statistical analysis revealed significant increases in MDF between the 0 and 15th minutes ($p=0.004$; 0-minute: 52.2 ± 10.9 ; 15-minute: 63.1 ± 7.2) and between the 0 and 35th minutes ($p=0.001$; 0-minute: 52.2 ± 10.9 ; 35-minute: 64.1 ± 7.0). No significant differences were observed between the 15th and 35th minute ($p = 0.370$).

CONCLUSIONS: These data reveal that fatigue is induced during a prolonged exertion such as a 35-minute running task, as evidenced by significant increases in MDF. Further research should be conducted on methods by which one may reduce MDF to improve performance and to determine the underlying mechanisms responsible for increases in MDF associated with exertional fatigue.

Cocaine Produces Conditioned Place Preference in Zebra Finches

Nariman Emadzadeh and Ken Soderstrom

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Zebra finches learn a form of vocal communication during their adolescent development. This allows these animals to be used to assess the effects of abused drugs on development of a learned behavior. In avian species it is difficult to measure drug self-administration, which is a disadvantage of the model. We have worked to create a conditioned place preference method that measures the reinforcing properties of abused drugs. A two-sectioned chamber, separated by a divider, was constructed from standard birdcages, along with colored cardboard sidings (yellow and green). Pre-treatment preferences were determined by placing finches in between chambers without a divider and measuring the amount of time freely spent in each chamber for a period of fifteen minutes for five consecutive days. During the conditioning stage, a divider was used to keep animals in a particular chamber. Half of the birds were injected with cocaine and placed in their preferred chamber, and the other half in their non-preferred chamber for a period of fifteen minutes for eight consecutive days. Following conditioning, preference tests were done by placing birds between chambers and allowing them to freely choose a preferred chamber for fifteen minutes without any injection of cocaine. Investigation of the dose-response relationship between cocaine and the amount of time spent in the cocaine chamber is ongoing. Currently we have results from 10 mg/kg (% time spent in cocaine chamber = 100.0 +/- 0), 5 mg/kg (= 99.4 +/- 0.99) and 2.5 mg/kg (= 73.6 +/- 40.5). These results clearly demonstrate that cocaine produces a place preference in zebra finches. Furthermore, results show that the reinforcing properties of abused drugs can be measured through conditioned place preference methods in zebra finches. We are currently working to clearly establish the dose-response relationship and half-maximal effective dosage of cocaine (EC50). Determination of EC50 will allow potential increasing and decreasing effects of other treatments on the reinforcing properties of cocaine to be assessed.

Survival and Differentiation of New Cells in the Hippocampus of Adult and Aged Mice Following an Immune Challenge

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University of North Carolina Wilmington

Prior research shows that normal aging induces alterations in immune function. This causes an elongation of the neuroinflammatory response to an immune challenge. Neuroinflammation can decrease hippocampal neurogenesis. For instance administration of the bacterial endotoxin lipopolysaccharide (LPS) reduces both new cell formation and neuronal differentiation in adult animals (Ekdahl et al., 2003; Bastos et al., 2008). The age-related changes in the neuroinflammatory response have been associated with exaggerated cognitive and behavioral deficits; however, if these age-related deficits cause a greater suppression of neurogenesis following the administration of LPS is still unknown. The present study assessed whether aged mice would show greater reductions in hippocampal neurogenesis following an acute immune challenge with LPS. Further, we assessed whether aerobic exercise would protect against the effects of LPS. Adult (3 months) and aged (20 months) male C57BL/6J mice were individually housed with or without a running wheel for a total of 9 weeks. Mice received a single intraperitoneal (ip) LPS (250 µg/kg) or saline injection 5 weeks into the exercise/sedentary housing. To label dividing cells, all mice received four daily ip injections of Bromodeoxyuridine (BrdU; 75 mg/kg) starting 2 days prior to the LPS or saline injection. Tissue was collected 4 weeks later and immunohistochemistry was conducted to measure new cell survival. Preliminary findings confirm that aging reduces new cell survival and exercise increases survival in both adult and aged mice. LPS had no effect on the total number of new BrdU positive cells. Data collection is currently in progress to determine whether aged mice show alterations in the proportion of new cells that differentiate into neurons following LPS administration. Presently, findings indicate that voluntary wheel running promotes cell survival in both adult and aged animals.

Exercise Slows the Development of Early Sensorimotor and Cognitive Symptoms in the Triple-Transgenic Mouse Model of Alzheimer's Disease

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Alzheimer's disease (AD) is a neurodegenerative disease characterized by a progressive decline in cognitive function; however, recent evidence suggests that several non-cognitive sensorimotor symptoms accompany early stages of the disease. Although exercise is emerging as a major therapeutic to combat AD progression, little is known about the effect of exercise on both non-cognitive and cognitive domain functions. The purpose of this study was to determine if non-cognitive sensorimotor symptoms accompany early AD pathology. We also sought to determine if exercise could protect against non-cognitive and cognitive decline. Animals were assigned to the following groups: sedentary (SED) WT controls (n=8), exercise (Ex) WT (n=5), sedentary (SED) 3x-Tg AD (n=9), and exercise (Ex) 3x-Tg AD (n=8). Exercise was initiated in 3 month old animals. Moderate intensity exercise was administered for 12 weeks at an intensity of 8.0 m/min for 60 minutes. At 6 months of age, animals underwent a series of sensorimotor and cognitive behavioral tests. Sedentary 3x-Tg AD mice displayed significant reductions in sensorimotor function compared to WT controls in the beam traversal, spontaneous activity, and adhesive removal tests. Interestingly, 3x-Tg AD animals exhibited significant increases in freezing behaviors and demonstrated atypical shaking/tremoring behaviors that were not displayed by WT controls. Furthermore, 3x-TG AD mice showed deficits in hippocampal dependent spatial learning compared to WT controls. 3x-Tg AD mice that exercised showed attenuated sensorimotor deficits, improved spatial learning and significant reductions in freezing and shaking behaviors. Our study shows that sensorimotor symptoms coincide with early cognitive decline exhibited in this Alzheimer's disease model. These results indicate that exercise can mitigate both non-cognitive and mild cognitive deficits associated with early stages of Alzheimer's disease.

Aerobic Exercise Reduces Markers of Painful Neuropathy in Rats Exposed to a High Fat/High Sucrose Diet

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Diabetic neuropathy is a secondary complication affecting up to 70% of those with diabetes. Neuropathy is often characterized by loss of proprioception; however, early features of pre-diabetes are painful symptoms. A Western style diet of high fat and high sucrose (HFHS) induces a group of conditions known as Metabolic Syndrome, which includes hyperglycemia, a diabetic hallmark that likely contributes to early peripheral neuronal damage. We hypothesized that prolonged exposure to a HFHS diet would induce oxidative stress and nociceptive expression changes in peripheral sensory neurons and that exercise can help reverse the effects of this neuronal damage. In this study, Sprague-Dawley rats were assigned to these groups (each n=4): control diet (standard chow), 4 week HFHS diet, 8 week HFHS diet, 12 week HFHS diet, 12 week HFHS diet + exercise (aerobic interval training 5 days/week). DRGs were collected bilaterally from L4-5, fixed in paraformaldehyde, and sectioned for immunohistochemistry. DRGs were stained for malondialdehyde (MDA, oxidative stress), ATF-3 (neuronal injury) and nociceptive markers (CGRP). Images were captured and analyzed for changes in fluorescence intensity.

Twelve weeks of HFHS diet induced a pre-diabetic state as evidenced by increases in fasting blood glucose, insulin and homeostatic model assessment scores, as well as an altered cholesterol profile. Exercise attenuated but did not restore these metabolic changes. Significant increases in DRG ATF-3 expression were evident as early as 4 weeks following consumption of a HFHS diet. MDA was elevated after 12 weeks of exposure to HFHS diet compared to controls. Markers for neuronal stress were primarily expressed in CGRP positive neurons, suggesting a preferential targeting of nociceptive neurons. Exercise significantly decreased ATF-3, MDA, and nociceptive expression in the DRG. These data suggest that a HFHS diet results in early increases in neuronal stress and nociceptive expression in DRG neurons, suggestive of ongoing peripheral nervous system pathology in a pre-diabetic state. A decrease in oxidative stress and nociceptive expression with exercise supports prescription of exercise as a therapeutic tool to protect against these pathological changes. Further studies are needed to determine if pain related behaviors accompany the increase in neuronal stress following HFHS diet.

Block of Spinal Dopamine D3 Function Increases Locomotor Activity and D1 Receptor Expression in the Spinal Cord

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Restless Legs Syndrome (RLS) is a chronic and disabling sensorimotor disorder of the nervous system that is associated with insomnia (difficulties of sleep initiation, sleep maintenance, or excessive sleep fragmentation) and periodic leg movements during sleep (PLMS). Primary treatment is aimed at reducing the symptoms through treatment with dopamine (DA) receptor agonists that preferentially target D3 and D2-like receptors. Here, using interventional and immunohistochemical approaches, we assessed the possible role of the spinal D3 receptor system in the emergence of the PLMS phenotype. Wild-type rats were implanted with electrodes for recording the sleep/EEG and electromyogram (EMG) of postural (nuchal) and bilateral tibialis anterior (TA) muscles, and animals received repeated i.p. injections of the D3-receptor-preferring antagonist, U-99194A, or saline (sham) over one week. Following the behavioral assessments, spinal cords were harvested and analyzed for protein expression levels of D1, D2, and D3 receptors. We found that animals treated with U-99194A stayed awake longer and expressed an increased locomotor activity when compared to sham controls, and that this difference was most prominent during the early night time phases of the animals. Subsequent Western blot analyses suggested that blocking D3 receptor activation had no effect on D2 or D3 receptor protein expression. In contrast, we observed a significant increase in D1 receptor protein expression in the cervical cord, which was accompanied by slightly increased D1 receptor protein expression levels in the thoracic and lumbar areas of the cord. As D3 and D1 receptors are often coupled as heterodimers and as D1 receptors generally mediate excitatory actions, our data suggest that the increase in PLMS activity observed in the D3-dysfunctional rodent model may arise from associated changes of the D1 receptor system.

Continuous Movement Trajectory Modulates Stretch Reflex Amplitude in Parkinson's Disease

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Parkinson's disease (PD) is associated with exaggerated rigidity created by aberrant reflex responses and alterations in the stiffness of passive tissues. Exaggerated stretch reflexes have been shown to mediate rigidity in PD; however, no research has quantified the effect of different movement trajectories on rigidity in PD. The purpose of this study was to compare reflex responses during continuous compared to discontinuous movement trajectories. It was hypothesized that continuous movement trajectories would be associated with greater reflex amplitudes than discontinuous movement trajectories.

METHODS: Twelve individuals with PD participated in a protocol in which their wrist joints were passively flexed and extended (50 deg/sec) through a range of motion (± 45 deg) using two movement trajectories: continuous and discontinuous. The continuous movement trajectory was characterized by a passive wrist flexion movement followed immediately by a passive wrist extension movement. Conversely, the discontinuous movement trajectory was characterized by a one-second pause between passive flexion and extension movements. Participants were tested after a 12-hour withdrawal from medication (OFF-MED) and one hour following administration of their normal dose of dopaminergic medication (ON-MED). Electromyography signals were recorded from the wrist flexors and extensors. EMG signals were rectified and smoothed using the root mean square with 20 ms smoothing window and normalized to background EMG amplitudes in the 100 ms prior to the onset of passive movement. Mean RMS EMG of the wrist flexors and extensors were used to quantify stretch reflex amplitude. Two paired samples t-tests were used to compare mean stretch reflex amplitudes in CONT vs. DISC movement patterns in the OFF- and ON-MED conditions. Significance was set at $p < 0.05$.

RESULTS: The continuous movement trajectory was associated with significantly greater stretch reflex amplitudes compared to the discontinuous movement trajectory in both the OFF-MED ($p = 0.039$; CONT: 3.5 ± 0.9 ; DISC: 3.2 ± 0.7) and ON-MED conditions ($p = 0.013$; CONT: 3.7 ± 1.2 ; DISC: 3.4 ± 0.8).

CONCLUSIONS: These data demonstrate that a continuous movement trajectory enhances stretch reflex amplitudes in PD. These results suggest that the stretch reflex may be primed by the exaggerated pre-stretch shortening reaction that has been previously reported in individuals with PD.

Lexical Diversity in Early Stage Parkinson's Disease

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Parkinson's disease (PD) is a neurodegenerative disease estimated to affect 4-6 million individuals worldwide. PD centers on neuroanatomical areas of the basal ganglia (BG) which is critical to cognitive and motor performance. Models of BG function suggest there should be predictable expressive language deficits in BG diseases. A number of recent studies indicate there is compelling evidence that subtle language deficits consistently exist among individuals with PD. However, few studies have examined expressive language performance at the level of discourse among individuals with PD. Narrative discourse is used to describe an experience, events or episodes and may be sensitive to language changes in PD. Lexical diversity or the range of vocabulary used is an element of discourse that may be disrupted in PD, suggesting difficulty with access to and retrieval of target words from a relatively intact knowledge base. We hypothesized that lexical diversity would be reduced during discourse production in individuals with PD.

We examined lexical diversity in 12 individuals with early stage Parkinson's disease and 12 age and gender matched controls. We collected three discourse samples related to (1) a typical day, (2) a memorable vacation, and (3) family for a minimum of 3-minutes. We calculated lexical diversity based on two measures (type token ration and number of different words) for group comparisons using Systematic Analysis of Language Transcripts (SALT). A MANOVA indicated no significant differences between groups on measure of lexical diversity ($F=1.06$, $p=.42$). Our findings suggest lexical diversity may be preserved in early stage PD.

EMG Normalization Masks Medication-Based Reductions in Reflex Amplitude in Individuals with Parkinson's Disease

Laura A. Scott¹, Klarie M. Ake¹, Brooke Catanzarito¹, Anburaj Muthumani², Rui-Ping Xia³, Douglas W. Powell¹

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Rigidity is a hallmark symptom of Parkinson's disease (PD). This rigidity has been attributed, in part, to exaggerated stretch reflexes. Common methods of quantifying stretch reflex amplitudes involve the normalization of reflex EMG to background EMG amplitudes. However, it is known that dopaminergic medication reduces underlying hypertonia through diminished background muscle activation. The purpose of this study was to investigate the effect of normalizing to background EMG on the efficacy of dopaminergic medication in reducing stretch reflex amplitudes.

METHODS: Twelve individuals with PD participated in a protocol in which their wrist joints were passively flexed (280 deg/sec) through a range of motion (± 45 deg) while EMG was recorded from the wrist flexors and extensors when participants were off medication (OFF-MED) and on medication (ON-MED). To enhance stretch reflexes, participants performed a contralateral activation maneuver of a gripping contraction equal to 20% of their maximal grip force. EMG signals were rectified and smoothed using the root mean square with a 20 ms smoothing window. Raw EMG signals (rEMG) were normalized to mean background EMG amplitudes collected 100 ms prior to the onset of passive movement (nEMG). The effect of medication was assessed for nEMG and rEMG amplitudes using paired samples t-tests. Alpha level was set at $p < 0.05$.

RESULTS: The statistical analyses revealed no significant differences in nEMG amplitudes of the flexors ($p = 0.107$; OFF-MED: 3.89 ± 1.45 ; ON-MED: 3.50 ± 0.78) or extensors ($p = 0.098$; OFF-MED: 2.98 ± 0.52 ; ON-MED: 2.83 ± 0.52) between the OFF- and ON-MED conditions. For rEMG, a significant effect of medication was observed for both flexors ($p = 0.025$; OFF-MED: 0.044 ± 0.028 ; ON-MED: 0.036 ± 0.018) and extensors ($p = 0.023$; OFF-MED: 0.039 ± 0.012 ; ON-MED: 0.034 ± 0.012).

CONCLUSIONS: Normalizing EMG magnitudes to background EMG masks reductions in stretch reflex and shortening reaction associated with dopaminergic medication in individuals with PD. The use of repeated measures designs circumvents the limitations associated with normalizing to background EMG. Further research should address alternate methods of EMG normalization.

PSYCHOGENIC POLYDIPSIA, HYPONATREMIA AND OSMOLAR MYELINOLYSIS – Case Report and Brief Review

Corneliu Stanciu

Department of Psychiatric Medicine and Behavioral Health, BSOM, East Carolina University

Compulsive water drinking (psychogenic polydipsia) is commonly observed among patients with chronic mental disorders. A minority of them develop clinically significant hyponatremia with associated confusion, delirium and ataxia that may progress to seizures, coma and death. Destruction of myelinated brain structures may develop in patients with chronic hyponatremia or have had rapid correction of hyponatremia - central pontine myelinolysis when affecting mid-brain structures and extrapontine myelinolysis when affecting areas outside the pons.

We describe a case of extrapontine myelinolysis presenting in a 49 year-old individual with a history of severe Schizoaffective disorder and psychogenic polydipsia with extreme hyponatremia. A syndrome of delirium and gait dysfunction with characteristic enhancement of T2 MRI images within extrapyramidal structures is documented. A gradual improvement in cognition and motor function occurred over a period of weeks following the insult. Importantly, the patient's psychiatric status was also improved following the insult and recovery to the point where he was free of psychotic symptoms off all psychotropic medications.

This individual had complete recovery of cognitive function with no appreciable residual deficits in balance and gait. It is interesting to note that the patient has been free of psychotic symptoms that had previously plagued him for his entire life since completing stabilization of his electrolytes.

Epigenetic Effect of Modified Diet and Exercise on the Metabolic Phenotype of *Drosophila Melanogaster*

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Obesity is a growing world-wide epidemic. Overweight population is prone to variety of morbid conditions including diabetes type 2, cardiovascular diseases, and cancers. The catastrophic increase in obesity rates is largely attributed to sedentary life style and a poor diet. Epigenetic studies show maternal obesity is a risk factor for metabolic syndrome in offspring; furthermore, evidence suggests obese and diabetic fathers may also contribute to offspring metabolic phenotype, so we questioned whether a modified paternal diet and exercise may produce transgenerational effects on offspring metabolic phenotype using *Drosophila Melanogaster* as a model because of its exponential population growth rate, making it ideal for genetic studies. Specifically, this research sought to look at the effects of a modified diet and exercise on whole body composition, development, cardiovascular health, and the change in expression of various metabolic genes and microRNAs in *Drosophila* F0, and F1 generations. To test the effects of diet, male virgin flies were exposed to either 14 days of a high-fat, a high-sucrose diet, a high-fat/high-sucrose, or a control diet and then mated with control virgin females overnight. Offspring were collected after hatching and subjected to a normal or modified diet challenge for 14 days. After 14 days, animals were analyzed for triglyceride content and trehalose/glucose levels in F0 and F1 generations. Fruit flies were also subjected to exercise for 14 days to measure effects of exercise on phenotype. Developmental data was also collected for *Drosophila* on modified diets every day until enclosing. Cardiovascular health was measured by submitting *Drosophila* in an artificial hemolymph solution to measure heart beats per minute and then were analyzed for arrhythmias. Preliminary results indicate a trending increase in amount of triglycerides in flies on a modified diet in both generations and a concomitant change in expression of metabolic genes and microRNAs dependent upon phenotype.

Dopamine 3 Receptor Knockout (D3KO) Mice Show Age Dependent Morphine Tolerance Possibly Mediated via Increased D1 Receptor Expression

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Dopamine (DA) is a major catecholaminergic neurotransmitter that modulates nociceptive pathways in the spinal cord. We have shown recently that dopamine D3 receptor knockout mice (D3KO) were resistant to morphine both in vivo and in the isolated spinal cord in vitro, and that spinal D1 expression was upregulated in D3KO.

Here, we addressed the question if D3KO truly are resistant to morphine, or if they are tolerant instead. Additionally, we hoped to determine if by modulating D1 receptor activities, we could improve the efficacy of morphine administration in D3KO.

We tested withdrawal latencies for two different age groups of D3KO (2 month and 1 year) with varying dosages and/or combinations of morphine and D1 antagonist. We first established baseline withdrawal latencies and then began our treatment groups, which included intraperitoneal (i.p.) injections of saline control, morphine at varying doses (2 mg/kg; 5 mg/kg respectively), D1 antagonist (0.1 mg/kg), and morphine-D1 antagonist combinations (2 mg/kg + 0.1 mg/kg; 5 mg/kg + 0.1 mg/kg) respectively.

We found that at higher doses of morphine (5mg/kg), withdrawal latencies in 2 month D3KO increased significantly as opposed to 2 mg/kg morphine, but that neither concentration was sufficient to significantly alter withdrawal latencies in the 1 year D3KO cohort. Further, in young but not old animals, co-administration of the D1-antagonist and low-dose morphine increased withdrawal latencies. However, D1-antagonist co-administration was only effective in the old animals with the higher dose of morphine.

Together, these data suggest that the D3KO animal may be model to study morphine tolerance in the spinal cord, and that the interaction between morphine and D3 receptors might be mediated via the D1 receptor system.

Poster Session 2

(in alphabetical order by first presenting author)

The Design and *in silico* Analysis of Novel Cdc42 Inhibitors

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Cdc42 is an important signaling protein involved in various biological processes such as actin filopodia formation, cell motility, directional migration, and cell growth. As a member of the Rho GTPase family, Cdc42 cycles through its active, GTP-bound state and inactive, GDP-bound state for proper protein function. Dysregulation of Cdc42 may have dire consequences. For instance, Cdc42 has been found to be highly active in neurodegenerating brain tissues. Thus, inhibiting Cdc42 activity in neurodegenerative diseases may be of therapeutic value. ZCL278 is a novel selective, small molecule inhibitor of Cdc42. The purpose of this study was the design and *in silico* analysis of novel ZCL278 with increased drug-like properties.

The *in silico* analysis of Cdc42 revealed eight unique potential binding sites that can be subcategorized into three groups based on location. The A-sites are located near the GTP binding pocket, the B-sites are located on the opposite face of the protein, and the C-sites are located in between. Compound ZCL193 was observed to have high affinity for all sites. ZCL369 showed considerably more favorable interactions with A-sites than both B- and C-sites. ZCL351 showed increased selectivity for C-sites while AZA1 showed only slightly more affinity for B-sites. Taken together, these compounds may be valuable inhibitors of Cdc42 that prevent the interactions with the effectors responsible for cell signaling while not interrupting interactions with regulators. Supported in part by NIHCA165202 and The Wooten Foundation.

Training Paradigm is Associated with Unique Sway Velocities during Quiet Standing

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Research has shown that athletes exhibit greater postural stability across the lifespan compared to non-athletes (NON). However, few studies have addressed the unique demands of stable (SSA; i.e. basketball or football) versus negative surface sports (NSA; i.e. surfing or snowboarding). Previous research has suggested that SSA and NSA may employ divergent postural control patterns. However, this research was conducted using measures of sway magnitude and sway variability. It is possible that a higher order variable could provide greater insight into postural control mechanisms. The purpose of this study was to determine the effect of training paradigm on sway velocities.

METHODS: Twenty-four individuals (8 NON, 8 SSA, 8 NSA) performed three 30-second standing trials on a balance platform while ground reaction forces (GRFs) were recorded (200 Hz, Neurocom, Inc.). Center of pressure was calculated from raw GRF data. Sway excursions and velocities were calculated as described by Prieto et al. (1996) for the anteroposterior (AP) and mediolateral (ML) directions, independently. Peak sway velocity was defined as the maximum of the sway velocity signal. Two univariate ANOVAs with follow up t-tests were used to compare sway velocities between the three groups. Alpha was set at $p < 0.10$.

RESULTS: Significant main effects of group were observed in both the ML ($p = 0.068$; NON: 20.18 ± 8.86 ; SSA: 20.18 ± 11.20 ; NSA: 29.49 ± 4.79) and AP directions ($p = 0.020$; NON: 11.42 ± 4.77 ; SSA: 5.90 ± 3.17 ; NSA: 7.19 ± 3.01). Follow up t-tests revealed that the NSA group had significantly greater sway velocities in the ML direction compare to the NON ($p = 0.010$) and SSA ($p = 0.024$). In the AP direction, the NON exhibited significantly greater sway velocities compared to the SSA ($p = 0.008$) and NSA ($p = 0.026$).

DISCUSSION: These data demonstrate that training paradigm significantly effects sway velocities during quiet standing. Balance control is a global process that requires sufficient sensorimotor integration. While these results may demonstrate unique motor responses to quiet standing, greater challenges to balance may exacerbate these differences or may further elucidate the unique strategies employed by these functionally different groups.

Duration of Sickness Behavior Following LPS Injections in Aged and Adult Animals

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Activation of the peripheral immune system induces the release of proinflammatory cytokines from immune cells that reside within the brain, called microglia. Activation of microglia and the subsequent release of proinflammatory cytokines induces many transient behavioral changes collectively termed sickness behavior. With normal aging, microglia reside in a partially activated or primed state. In response to an immune challenge, microglia in the aged brain show prolonged cytokine release and sickness behavior. Our objective was to determine the duration of the sickness behavior response by assessing burrowing behavior in aged and adult mice 1, 3, 5, or 8 days after an acute immune challenge. Data indicate that immune activation initially suppressed burrowing in adult mice. Aged mice showed prolonged sickness behavior following an immune challenge as burrowing was still suppressed 8 days after immune activation. These findings demonstrate that aging increases susceptibility to cytokine-induced behavioral deficits. Additional work is currently in progress to assess whether increased microglia activation and proliferation accompany the prolonged sickness behavior response in aged mice.

Mean Electromyography Amplitude is not Indicative of Fatigue during Submaximal Steady State Running

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Fatigue is a physiological response to repeated and prolonged exertion that is associated with reductions in performance. Submaximal fatigue is generally associated with increased amplitudes of surface electromyography (EMG) signals. However, most studies investigating fatigue associated with submaximal effort are single-joint in nature and conducted in a controlled, non-physiological movement paradigm such as open-chain knee extension. Activities of daily living, however, occur using complex multi-joint movements. Therefore, the purpose of the current study was to quantify changes in EMG amplitude associated with fatigue during a common multi-joint movement. It was hypothesized that EMG amplitudes would increase significantly throughout the duration of a 35-minute running task.

METHODS: Eleven participants aged 18 to 35 years performed a 35-minute treadmill running task at a self-selected velocity. Electromyography (EMG) was recorded from the right (dominant) vastus lateralis for eight 15-second trials in five minute intervals (i.e. 0 min, 5 min, etc.). EMG was recorded using wireless EMG electrodes (2000 Hz, Delsys Trigno, Delsys Inc., Boston, USA). Using custom software (MatLab 2013a, Mathworks, Natick, MA), EMG signals were bandpass filtered (20 Hz – 500 Hz), then smoothed and rectified using the root mean square with a 20 ms smoothing window. The mean EMG was calculated across the 15-second trial. Three paired t-tests were used to compare mean EMG values across three measurements: 0 minute to 15 minute, 0 minute to 30 minute and 15 minute to 30 minute. A Bonferroni adjustment was conducted to compensate for multiple comparisons. Significance was set at $p < 0.05$.

RESULTS: Statistical analysis revealed no significant changes in mean EMG amplitude across the running trial (0-15 minutes: $p = 0.117$; 0 – 30 minutes: $p = 0.063$; 15 – 30: $p = 0.086$). Mean EMG values were as follows: 0-minute: 0.026 ± 0.006 ; 15-minute: 0.028 ± 0.008 ; 30-minute: 0.030 ± 0.010 .

CONCLUSIONS: These data suggest that mean EMG amplitude does not increase significantly during a submaximal prolonged running trial. Other measures of fatigue from the EMG signal may be more indicative of the neuromuscular aspects of fatigue.

Effect of Compression Garments on Lower Extremity Fatigue during a Steady State Run

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Neuromuscular fatigue is associated with reduced performance during competition. Athletes adopt sport-specific training paradigms to counteract the deleterious effects of fatigue on competitive performance to improve competition outcomes. While targeted training is associated with improved fatigue resistance, many athletes are seeking external modalities to improve training and fatigue resistance. One modality that has been suggested to improve fatigue resistance in athletics is compression garments. The purpose of this study was to directly compare changes in surface electromyography (EMG) signal content associated with fatigue when running with and without compression garments. It was hypothesized that compression garments would serve a fatigue resistant purpose and reduce changes in median frequency (MDF) and signal amplitude (iEMG).

METHODS: Eleven participants aged 18 to 35 years performed a 35-minute treadmill running task in each of two conditions: while wearing compression garments (COMP) and without compression garments (NO COMP). Running trials were performed at a self-selected velocity and EMG was recorded from the right (dominant) vastus lateralis for eight 15-second trials in five minute intervals (i.e. 0 min, 5 min, etc.). EMG was recorded using wireless EMG electrodes (2000 Hz, Delsys Trigno, Delsys Inc., Boston, USA). Using custom software (MatLab 2013a, Mathworks, Natick, MA), EMG signals were band-pass filtered (20 Hz – 500 Hz) then converted to the frequency domain using a Fast Fourier Transform where the MDF was selected. EMG signals were also rectified and smoothed using the root mean square with a 20 ms smoothing window. Integrated EMG (iEMG) amplitude of the RMS EMG signal was calculated across the trial. A series of paired samples t-tests were conducted to assess the effectiveness of compression pants on the changes in MDF and mEMG from the first to 35th minute of the treadmill run. Alpha was set at $p < 0.05$.

RESULTS: The statistical analysis revealed that no difference in MDF was observed with the compression pants compared to normal running ($p = 0.121$; NO COMP: 9.81 ± 5.22 ; COMP: 11.83 ± 6.75). Further, the NO COMP condition was associated with greater increases in iEMG compared to the COMP condition ($p = 0.042$; NO COMP: 31.14 ± 10.54 ; COMP: 24.09 ± 11.65).

CONCLUSIONS: These data reveal that compression pants may reduce neuromuscular fatigue during a prolonged treadmill run. Further research should be conducted to focus on the underlying mechanisms and biomechanical manifestations of this reduced fatigue including lower extremity stiffness.

Spinal Cord Injury Induced Hyperalgesia is Associated with Increased Levels of Let-7 Family of microRNAs

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Spinal cord injury (SCI) results in chronic pain syndromes that are refractory to treatment with opioids, and may represent a dysfunction of the mu opioid receptor (MOR). MicroRNAs, small noncoding RNAs, play a central role in gene regulation by binding to target mRNA, leading to translational repression or mRNA degradation. The Let-7 family of microRNAs has been shown to target MOR, suggesting it may play a role in opioid tolerance. We hypothesized that excitotoxic SCI increases levels of Let-7 family miRNAs, preventing the analgesic effects of morphine. Burrowing behavior (spontaneous pain) and thermal thresholds (evoked pain) were assessed in Long Evans rats before & after excitotoxic SCI with (1.2 μ L) quisqualic acid (QUIS) or sham laminectomy. 21 days after surgery, thresholds were re-tested after a single dose of morphine (5mg/kg, i.p.). Levels of Let-7 family of miRNA were determined using RT-PCR and qRT-PCR on spinal cords segments caudal to lesion at 7 and 22 days after injury. Spinal cords from the level of injury were histologically examined for damage in QUIS animals. Thermal thresholds decreased significantly at day 21 in QUIS animals compared to baseline thresholds. Morphine significantly increased thresholds for both QUIS and sham animals. Burrowing behavior was not found to be affected by QUIS injury. At 7 days post-injury, prior to the development of pain, Let-7 levels were not significantly different from baseline. SCI increased the levels of three members of Let-7 family by 21 days, and resulted in a loss of deep dorsal horn neurons at the site of QUIS injection. Let-7 family of miRNA levels were similar to baseline at 7 days post-injury, but increased compared to sham animals at 21 days, after the onset of pain. Contrary to previous results, morphine provided analgesia in both QUIS and sham animals. Our data suggest that increased levels of Let-7 family of miRNAs are involved in the behavioral response to spinal cord injury, but their specific role remains unknown. Future studies will determine time frame of miRNA increase and examine if inhibition of let-7 family of miRNAs alters the behavioral and cellular response to spinal cord injury.

Repeated Restraint Stress Alters Adult Zebra Finch Song Performance Differently in Female or Male Social Contexts

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Male zebra finches learn a complex song developmentally in a similar process as human language acquisition. At adulthood, the critical learning window is closed, and the song is stereotyped and crystallized. The song has significance for both inter- and intrasexual communication, and zebra finches are highly social. Song performance directed to female or male zebra finches involve different neural song pathways. Song in a female social context uses a direct motor pathway, and song in a male social context uses a more indirect pathway that involves basal ganglia song regions that also have important functions in developmental song learning. In the current study, we hypothesize that psychological stress will alter the performance of the learned, stable song of adult zebra finches. Adult male zebra finches (>100 days) were administered 4 days of 30 minute restraint stress, and their vocalizations were recorded for 2 hours following the cessation of each stressor. To maximize song activity during the recording period, the recorded zebra finch was paired with an audience bird as a stimulus. The sex of the audience bird may influence the effects of stress on song performance due to the different neural circuitry implicated in song in female or male social contexts. For all recorded birds, half of the post-stress recording sessions had female audience birds, and half had male audience birds. In the female-directed context, stress stimulated song activity, resulting in a significant increase in quantity of song production compared to non-stressed controls ($p < 0.05$), but in the male-directed context, no effects were detected ($n = 3 - 5$ birds). Song for courtship is postulated to have evolved as an indicator to the female of male quality, and the increase in song quantity following stress in the female social context may represent a strategy to promote courtship that compensates for stressed song. In further analysis of the recordings, we will assess the effects of stress on temporal (i.e., syllable duration) and spectral (i.e., pitch) features. In future studies, we will co-administer stress and a cannabinoid agonist to assess possible modulation of stress-induced changes in song performance and associated neuronal effects.

The Effects of Complex Learning on Hippocampal Neurogenesis in a Mouse Model of Alzheimer's Disease

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Much research is dedicated to further the understanding and treatment of Alzheimer's disease (AD). AD is a neurodegenerative disease, characterized by cognitive disturbances such as learning difficulties and memory loss. These cognitive dysfunctions are the result of AD-related pathology in a handful of memory systems, most notably the medial temporal lobe memory system that includes the hippocampus. In recent years, mice which bear PS1-M146V, APP-Swe, and tauP301L gene mutations (3xTg mouse model) have provided a valuable research tool in understanding the molecular, physiological, and neurobehavioral features of AD in humans. The research literature shows that a large proportion of effort is funneled into examining pharmacological approaches that potentially mitigate cognitive disturbances in AD. On the other hand, less attention has been given to non-pharmacological approaches (NPAs). Despite the lower frequency of their examination, NPAs have been shown to yield promising results. Indeed, one particular NPA, complex cognitive training, has been shown to enhance hippocampal neurogenesis, which in turn, may underlie positive changes in synaptic plasticity that supports new learning and memory formation. To test this latter idea, the current study compares two forms of associative learning, one simple and the other complex, and their effects on inducing hippocampal neurogenesis in 3xTg mice.

We examined eye blink conditioning (ECC), a form of associative learning that can be varied to assess the functional integrity of different neural circuits. The simple form of ECC, delay, is easier to acquire for mammals due to the optimal arrangement of test stimuli, and is supported by an intact cerebellum. The more complex form, trace ECC, is more difficult to acquire because it requires the organism to resolve the awkward timing of stimuli used in this procedure. It has been well-demonstrated that an intact hippocampus supports this form of learning. Adult 3xTg mice and controls received 4 injections of bromodeoxyuridine (BrdU; 50 µg/g IP) on alternating days. On Day 9, they were implanted with stimulating and recording electrodes for ECC. From Days 11-16, they underwent simple ECC (delay) or complex ECC (trace). A separate group of 3xTg and control mice did not receive ECC to serve as training controls. On Day 21, brains were extracted and examined using BrdU immunohistochemistry. We hypothesized that if complex learning mitigates the neurodegenerative effects of AD, then hippocampal neurogenesis would be enhanced in mice that had received the trace ECC procedure, compared to mice that received delay ECC. Non-pharmacological approaches may be beneficial in ameliorating cognitive disturbances in AD as they are inexpensive, easy to administer, and can potentially facilitate neural plasticity underlying enhanced cognitive function.

Cognitive Deficits are Weakened in Diet-Induced Obese Mice Following Endotoxin Administration

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There have been multiple studies that have shown activation of the immune system impairs hippocampus dependent cognitive tasks. Diet-induced obesity (DIO) can modify the activity of the immune system. Whether diet-induced obesity (DIO) influences the cognitive impairments associated with brain inflammation has not been addressed previously. The present study evaluated whether DIO alters the development of cognitive deficits following an immune challenge with the bacterial endotoxin, lipopolysaccharide (LPS). Female C57BL/6J mice were fed a high fat (60% fat) or control diet (10% fat) for a total of five months. After consuming their respective diets for four months, mice received an LPS or saline injection and were assessed for alterations in spatial learning. One month later, mice received a second injection of LPS or saline and tissue samples were collected to assess the inflammatory response within the periphery and central nervous system (CNS). Results showed that LPS administration impaired spatial learning in the control diet mice, but had a reduced effect in DIO mice. This dampened cognitive deficit in the DIO mice is likely due to a blunted inflammatory response within the brain. While cytokine production within the periphery (i.e., plasma, adipose, and spleen) was similar between the DIO and control mice, the DIO mice failed to show an increase in IL-6 and CD74 in the brain following LPS administration. Collectively, these data indicate that DIO can reduce aspects of the neuroinflammatory response as well as blunt the behavioral reaction to an immune challenge.

Central Nicotinic Acid Administration Increases Blood Pressure in Conscious Rats

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The hypolipidemic drug nicotinic acid (NA) elicits prostaglandins (PGs)-dependent flushing reaction via GPR109A activation. There are no reports on GPR109A expression or function in the rostral ventrolateral medulla (RVLM), despite evidence that NA reaches the brain. We present the first evidence for GPR109A expression in the RVLM (Western blot). Next, we showed in conscious rats that intra-RVLM NA (estimated doses to reach the RVLM following systemic administration) increased BP and reduced HR, which resembled responses elicited by intra-RVLM L-glutamate. The pressor effect of NA was abolished by selective NMDAR blockade (2-amino-5-phosphonopentanoic acid; AP5) and enhanced by L-glutamate uptake inhibition (L-trans-Pyrrolidine-2,4-dicarboxylic acid; PDC). Further NA elevated L-glutamate level in culture medium of PC12 cells, which exhibit neuronal phenotype and express GPR109A. These novel findings suggest that L-glutamate release is involved in RVLM GPR109A-mediated brief pressor response. Ongoing integrative and molecular studies will elucidate the role of PGs and oxidative stress in the delayed pressor response caused by intra-RVLM NA. The findings are clinically relevant because they elucidate the mechanisms of a centrally mediated deleterious effect of NA on BP, and yield new insight into the potential use of concurrent therapeutics to circumvent such deleterious effect.

Neurophysiological Behavioral Activation (BAS) and Behavioral Inhibition (BIS) Systems are Associated with Quality of Life and Adherence in Patients with Obstructive Sleep Apnea (OSA)

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Continuous Positive Airway Pressure (CPAP) is a highly effective treatment for obstructive sleep apnea (OSA); however, adherence rates are extremely poor and inconsistent, resulting in increased healthcare costs and morbidity. Utilizing the Reinforcement Sensitivity Theory (RST), previous research has identified which patients are more likely to adhere to treatment, which may ultimately offer differing interventions. RST is comprised of neurophysiological systems with distinct neural pathways that regulate approach and withdrawal behaviors, including the Behavioral Activation System (BAS) and the Behavioral Inhibition System (BIS). BAS is associated with left frontal alpha activity (measured through EEG) and approach behavior, while BIS is associated with right frontal activity and withdrawal behavior. Prior research in our laboratory has indicated that individuals with higher BIS are less likely to adhere to CPAP. Moving forward, the relationships between BIS, BAS, frontal EEG asymmetry, and health-related quality of life (QoL) using the SF-12v2 were investigated in 105 patients with OSA.

It was hypothesized that BIS would be negatively associated with the Physical Component Summary (PCS) and the Mental Component Summary (MCS) of the SF-12v2, while the opposite relationship would be observed for BAS. It was further predicted that PCS and MCS would be negatively associated with CPAP compliance at 30 days. These hypotheses were partially supported. BIS was found to be associated with MCS of the SF-12v2, $r(102)=.27$, $p<.01$), and a weaker association was observed for a subscale of BAS (BAS-D) and MCS, $r(105)=.17$, $p<.05$). Likewise, higher MCS scores were associated with adherence at 7 days, $r(49)=.26$, $p<.05$) and at 30 days, $r(55)=.27$, $p<.05$). Additionally, higher PCS scores were found to be associated with adherence at 60 days, $r(36)=.28$, $p<.05$). These findings indicate that MCS of QoL is related to BIS and adherence to CPAP among patients with OSA, a finding with potential implications for clinical intervention.

The Tolerogenic Activity of Interferon- β is Associated with Direct Antigen-Dependent Induction of FOXP3⁺ Regulatory T Cells

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Fusion proteins comprised of interferon-beta (IFN- β) and an encephalitogenic neuroantigen (NAg) represent an effective means to couple the beneficial anti-inflammatory actions of IFN- β with the induction of NAg-specific tolerance. The purpose of this study was to test IFN- β -NAg fusion proteins for tolerogenic efficacy in murine models of experimental autoimmune encephalomyelitis (EAE) and to resolve underlying tolerogenic mechanisms. The IFN- β -PLP fusion protein that contained the encephalitogenic PLP139-151 epitope was tested for prophylactic activity. This fusion protein was effective as a preventative vaccine that inhibited the subsequent induction of EAE in SJL mice. The IFN- β -MOG fusion protein that contained the MOG35-55 epitope was tested as a therapeutic intervention in the chronic model of EAE in C57BL/6 mice. This fusion protein was effective as a therapy that reversed EAE when treatment was initiated after onset of paralytic EAE. In both systems, covalent linkage of the IFN- β domain and the NAg domain was needed for inhibition of EAE. Unlike the covalently-linked cytokine-NAg fusion proteins, equimolar mixtures of IFN- β and NAg did not inhibit EAE. These fusion proteins were administered in saline by subcutaneous injection and were without apparent adverse side-effects. The tolerogenic activity of IFN- β -NAg was associated in vitro with the ability of IFN- β to directly mediate NAg-dependent induction of FOXP3 in MOG35-55 specific T cells. Overall, these data indicate the IFN- β -NAg fusion proteins represent an effective approach to couple the anti-inflammatory activity of IFN- β with tolerogenic vaccination to ameliorate pathogenic autoimmunity in CNS demyelinating diseases. IFN- β based tolerogenic vaccines may represent a novel therapeutic modality for treatment of the human demyelinating disease multiple sclerosis. This work was supported by grants from the National Institutes of Health (R15-NS075830 and R01-NS072150) and The Harriet and John Wooten Laboratory for Alzheimer's and Neurodegenerative Diseases Research.

Anger is Associated with Greater Left than Right Hemisphere Baseline Electroencephalographic Activity

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Anger is an emotional phenomenon that has received negative attention in the literature. Associated with hostility and aggression, these experiences are often thought to be major influencing factors of numerous negative health behaviors and outcomes. To date, research has attempted to understand the role of these negatively portrayed experiences through the creation of experimental models relying on respective biological and psychological evidence. The present study aims to further understanding by conceptualizing anger, hostility, and aggression within the Reinforcement Sensitivity Theory (RST), a biobehavioral- and neuropsychologically-based framework, with particular emphasis on related baseline alpha asymmetry correlates.

The current study employed electroencephalographic recording or baseline resting alpha asymmetry, for averaged eyes open and eyes closed conditions, and examined the data in respect to self-reported emotional (anger, hostility, and aggression) and personality (Behavioral Inhibition and Behavioral Activation; BIS/BAS) characteristics. Thirty-six undergraduate participants were assessed on measures of personality, state and trait affect, and baseline anterior alpha asymmetry. Results of the present study revealed a significant positive correlation between self-reported anger and baseline alpha asymmetry at the F8-7 electrode site for the eyes closed, $r = .438$, $n = 36$, $p = .008$, and eyes open conditions, $r = .414$, $n = 36$, $p = .012$. Findings demonstrate conceptual differences among anger, hostility, and aggression. Further, these results aid in a better understanding of the complexity of the three phenomena as well as provide insight into the relationship between cortical asymmetry and the harboring of anger, hostility, and aggression.

Re-evaluation of Classical Rho GTPase in Alzheimer's Disease

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Altered intracellular protein transport and synaptic remodeling are two of the most prominent cellular processes that are affected in Alzheimer's disease (AD) as well as other neurodegenerative diseases. Rho subfamily of the small GTPases within the Ras superfamily is essential for modulating these functions. Although the literature has established that the RhoA, Rac1, and Cdc42 subclasses of small G-proteins are controlling elements of secretase trafficking, A β production, neurotransmitter receptor signaling, and the synaptic cytoskeletal dynamics, direct links between these Rho GTPases and AD are lacking. We took genetic and imaging approaches to re-evaluate the association between the classical Rho GTPases and AD. Our other studies employ isolated primary cortical neurons from triple transgenic (3xTg) mice expressing AD-like mutations in presenilin 1 (M146L), APP (695), and Tau301. In the 3xTg neurons filamin, G-actin, and Cdc42 showed redistribution in the soma and the axonal or dendritic processes, further validating the potential significant involvement of actin cytoskeleton in AD pathogenesis. The discovery of ZCL series chemicals could form a novel compound base to potentially develop into AD modifying therapeutics. Supported by grants from NIH and the Wooten Foundation for Alzheimer's Disease Research.