Eastern Carolina Chapter of the Society for Neuroscience Presents:

23rd Annual Neuroscience Symposium
Catalyst for Collaboration

Featuring:
David Ginty, PhD
Edward R. and Anne G. Lefler Professor of Neurobiology
Howard Hughes Medical Institute
Harvard University

“Beauty is Skin Deep:
The Sensory Neurons of Touch”

Friday, October 29th, 2021
East Carolina Heart Institute (ECHI)
escsfn.ecu.edu

Funding for this event was made possible by contributions from:

INSCOPIX
AXION BIOSYSTEMS
LAB PEOPLE, INC.
ECU
SOCIETY for NEUROSCIENCE

Anatomy & Cell Biology
Physiology
Psychology
The Eastern Carolina Chapter of the Society for Neuroscience would like to express our sincere gratitude to the following entities for their generous support of the 2021 Neuroscience Symposium:

The Society for Neuroscience
Axion Biosystems
Inscopix
Lab People, Inc.
ECU Department of Anatomy and Cell Biology
ECU Department of Physiology
ECU Department of Psychology
Multidisciplinary Studies Program in Neuroscience, ECU
and Neuroscience Student Association, ECU

Emma Farmer, Yasmine Habal, Savannah Hall, Liz Harris, Ryan Hawkins, Joshua Taylor, Morgan Tedder, Ysabella Villacorte

Officers:
President: Dr. Karen Litwa
Past-President: Dr. Fadi Issa
Treasurer: Dr. Tuan Tran
Secretary: Dr. Erzsebet Szatmari

Council Members:
Dr. Philip Boyer
Dr. Jeffrey Eells
Dr. Jessica Ellis
Dr. Chris Mizelle

Student Council Members:
George Cherry, Jr.
Faith Heagy
Luke Jackson
Cassandra Thomason
Madison Weeks
23rd Neuroscience Symposium Schedule  
October 29th, 2021  
East Carolina Heart Institute at ECU  
115 Heart Drive, Greenville, NC 27834

October 28th  
4:00PM-7:00PM Symposium Social at Pitt Street Brewing with food (provided by Sam Jones BBQ) courtesy of the chapter and its sponsors. Please RSVP through the symposium registration link.

October 29th  
8:00-3:35  
Check-In and Onsite Registration

8:30-9:00  
Breakfast and Chat with Keynote Speaker, Dr. David Ginty  
(for students, postdocs, and medical residents)

9:00-9:15  
Opening Remarks by ECCSfN Past-President, Dr. Fadi Issa

9:15-10:45  
Lightning Talks (5 min each, 3 min for questions, 10 total)

10:45-11:00  
Break

11:00-12:00  
Keynote Address by Dr. David Ginty, Harvard University  
“Beauty is Skin Deep: The Sensory Neurons of Touch”

12:00-12:30  
Lunch

12:30-3:00  
Invited Talks  
12:30-1:00  
Dr. Beth Lucas, NCSU  
“Ovarian Hormones Tune Amygdala Inhibition to Drive Anxiety-Like Behavior Across the Reproductive Cycle”

1:00-1:20  
Cody Hatchett, ECU  
“Slowed Opening and Closing Rates of Partially N-glycosylated Kv3 Channels Correlate with Abnormal Motor Neuron Structure and Locomotor Activity”

1:20-1:50  
Dr. Katie Baldwin, UNC-CH *virtual*  
“Unraveling Astrocyte Connectivity in Brain Development and Disease”

1:50-2:10  
Collin O’Bryant, ECU  
“Investigation of Nonhydrolyzable ATP Analogues and Cofilin-Derived Peptides for Inhibition of Cofilin-Actin Rod Formation”

2:10-2:40  
Dr. Elizabeta Gjoneska NIEHS *virtual*  
“Dissecting Mechanisms of Microglia Dysfunction in Neurodegeneration”

2:40-3:00  
Katie Clements, ECU  
“The Effect of Social Dominance on Modulation of Sensory-Motor Circuits”

3:00-4:00  
Poster Session

4:00-4:15  
Closing Remarks and Awards by ECCSfN President, Dr. Karen Litwa
Invited Talks
(in order of appearance)

Ovarian Hormones Tune Amygdala Inhibition to Drive Anxiety-Like Behavior Across the Reproductive Cycle

Beth Lucas, PhD
Assistant Professor of Neurobiology
Department of Molecular Biomedical Sciences
North Carolina State University
College of Veterinary Medicine

Slowed Opening and Closing Rates of Partially N-glycosylated Kv3 Channels Correlate with Abnormal Motor Neuron Structure and Locomotor Activity

Cody Hatchett
PhD Candidate
Department of Biochemistry and Molecular Biology
East Carolina University

Unraveling Astrocyte Connectivity in Brain Development and Disease

Katie Baldwin, PhD
Assistant Professor
Department of Cell Biology and Physiology
Neuroscience Center
University of North Carolina-Chapel Hill School of Medicine
Invited Talks (cont’d)
(in order of appearance)

**Investigation of Nonhydrolyzable ATP Analogues and Cofilin-Derived Peptides for Inhibition of Cofilin-Actin Rod Formation**

Collin O’Bryant  
Graduate Student  
Department of Chemistry  
East Carolina University

**Dissecting Mechanisms of Microglia Dysfunction in Neurodegeneration**

Elizabeta Gjoneska, PhD  
Principal Investigator  
Neuroepigenomics Group  
National Institute of Environmental Health Sciences

**The Effect of Social Dominance on Modulation of Sensory-Motor Circuits**

Katie Clements  
PhD Candidate  
Department of Biology  
East Carolina University
Flash Talk

Abstracts

(listed by presenting author in alphabetical order)
Secondary Neoplasms Following Therapeutic Cranial Irradiation: Radiation-Induced Meningioma After Successful Treatment of Leukemia, Langerhans Cell Histiocytosis, and Medulloblastoma During Childhood

Tijesuni Babalola1, Joel Nortey1, Sina Kazemzadeh1, J. Stuart Lee2, Kathleen E. Knudson2, Marwan Majeed1, Breann A. Zeches3, Jasmin Jo4, Philip J. Boyer3, Cathleen M. Cook5

1 Brody School of Medicine, East Carolina University, Greenville, NC
2 Vidant Neurosurgery, Greenville, NC
3 Department of Pathology and Laboratory Medicine, East Carolina University, Greenville, NC
4 Department of Internal Medicine, East Carolina University, Greenville, NC
5 Department of Pediatrics, East Carolina University, Greenville, NC

Background: Individuals treated for a neoplasm with radiation therapy or/and chemotherapy can develop secondary neoplasms due to genetic alterations induced by the treatment modality. We present three cases of individuals successfully treated for a neoplasm who developed intracranial meningiomas in the context of cranial irradiation.

Methods: Post-radiation meningiomas evaluated during the past seven years were compiled. A PubMed and Google literature search was undertaken.

Results: Three cases of meningioma arising years after therapeutic radiation to the skull were identified. Patient A received cranial radiation and chemotherapy for T-cell lymphoblastic leukemia at age 5 and presented at age 21 with headaches. A large bifrontal meningioma, World Health Organization (WHO) grade 2 was identified 17.5 years following treatment. Case B received cranial irradiation at age 13 for Langerhans cell histiocytosis. He presented at age 35 with new-onset seizures and dura-based lesions were identified in the right frontal and left cerebellopontine regions. The frontal lesion was resected and a WHO grade 2 meningioma was diagnosed, 22 years following treatment. Patient C was diagnosed with medulloblastoma at age 3 and received craniospinal radiation and chemotherapy. She presented at age 28 with headaches, nausea, emesis, and visual disturbances. A left parietal WHO grade 1 meningioma was identified and resected 25 years following therapy. A literature review identified multiple case reports and series of presumed radiation-induced meningiomas. Several studies identified a high recurrence rate of such neoplasms regardless of histologic grade.

Conclusions: These three cases represent presumed radiation-induced meningiomas occurring years following successful treatment of a neoplasm involving the brain or skull. Given their potential long survival following successful cancer therapy, children and young adults have an increased risk compared to adults for developing a post-therapy secondary malignancy. While secondary neoplasms arise in only a small number of patients who have undergone therapeutic cranial irradiation, this study emphasizes the potential risk of such therapy and justifies periodic surveillance even decades after cure of the original neoplasm.
Evaluating Neuroprotective Effects of Sulforaphane in a VPA-induced Autism Model

Riley Bessetti, Karen Litwa PhD

Department of Anatomy and Cell Biology, East Carolina University, Greenville, NC

In the last decade, there has been a substantial increase in U.S. Autism Spectrum Disorder (ASD) diagnosis reported by the Center of Disease Control. Pregnant women are commonly exposed to environmental factors that increase the likelihood of offspring developing an ASD. For example, fetal exposure to the anti-epileptic drug valproic acid (VPA) has been linked to an increased risk of developing an ASD. Fetal VPA exposure is associated with a range of detrimental consequences, including defective neural tube closure, altered neural differentiation, and changes in synaptic development. While VPA functions as an inhibitor of histone deacetylases, it is also known to increase oxidative stress. Therefore, a potential avenue for reducing the cytotoxic effects of VPA is to enhance the body’s own detoxification and antioxidant pathways. NF-E2-related factor 2 (Nrf2) is a transcription factor that promotes the expression of cytoprotective and antioxidant genes. The phytochemical, sulforaphane (SFN), is a potent inducer of the Nrf2 pathway. SFN prevents proteasomal degradation of Nrf2, increasing Nrf2 nuclear translocation and transcription. Thus, we hypothesize that SFN will protect developing neural circuits from the detrimental effects of VPA. To test this hypothesis, we grew human cortical spheroids (HCSs) and exposed them to VPA alone, VPA and SFN, SFN alone, or solvent control to investigate the neuroprotective effects of SFN in a VPA-induced autism model. We are also using CRISPR interference to establish whether sulforaphane’s effects are mediated via the Nrf2 pathway. Our preliminary data demonstrates feasibility of this approach to decrease Nrf2 expression. While our current results suggests that either VPA or SFN alone impairs synapse formation, together we observe a trend towards restored synapse formation. Based on these findings, we are currently testing the hypothesis that synapse formation requires a delicate balance between oxidative stress and antioxidant buffering, and that sulforaphane can restore oxidative homeostasis in the presence of pharmaceuticals and environmental stressors.
Understanding the Role of Rab10 in Neuronal Resilience

Wyatt Paul Bunner¹, Rachel Dodson¹, Lizzie Phipps¹, Denys Bashtovyy¹, Tuan Tran², and Erzsebet Maria Szatmari³

¹Department of Physical Therapy, East Carolina University, Greenville, NC
²Department of Psychology, East Carolina University, Greenville, NC

Purpose and hypothesis:
Advanced age and presence of ApoE epsilon allele are major risk factors for Alzheimer’s disease (AD). However, a small percentage of elderly and carriers of ApoE epsilon, do not develop AD (“AD resilient” individuals). The molecular basis of resilience to AD is not fully understood. Recently, a loss of function mutation in Rab10 gene was shown to confer a 40% reduction in AD risk, even in patients homozygous for ApoE epsilon allele. Rab proteins are small monomeric GTPases, belonging to the Ras superfamily. Rab10 is required for receptor trafficking during synaptic plasticity, axonal growth, and dendritic arborization due to its regulatory role in clathrin-independent trafficking and vesicle recycling. To elucidate the molecular mechanisms by which reduced level of Rab10 protein guards the aging brain against neurodegeneration, we created mice with reduced level of Rab10 protein (Rab10⁺⁻ mice). Here we describe our results on cellular, molecular and behavioral characterization of Rab10⁺⁻ mice, that we created to study the cellular and molecular mechanisms of Rab10-dependent neuronal resilience in a mouse model of AD on Rab10⁺⁻ background.

Results:
The level of Rab10 in the brain of Rab10⁺⁻ mice was reduced by approx. 50% compared to their Rab10⁺⁺ litter mates. Rab10⁺⁻ mice displayed no obvious abnormality in feeding, fertility and brain gross anatomy during a 12-month observation period. Interestingly, we noticed significant difference in body weight between genotypes, that was sex-dependent: female Rab10⁺⁻ mice had significantly higher body weight, than their Rab10⁺⁺ littermates. Next, we performed a battery of behavioral testing. Our results show that Rab10⁺⁻ mice perform significantly better in OIP task that tests hippocampus-dependent spatial memory. To elucidate the possible molecular basis of enhanced memory formation, NanoString profiling of the cerebellum was performed. Rab10⁺⁻ mice had a significant increase and decrease in the expression of multiple genes including Synaptotagmin-4 and Syntaxin 2 respectively.

Conclusions: Rab10 functions as a negative regulator of hippocampal learning and memory formation.

Clinical Relevance: Understanding the molecular mechanisms of neuronal resilience to disease may hold important clues for the design of novel neuroprotective strategies.
Determining the Role of Progesterone Nuclear Receptor in Modulating Aggression in Male Zebrafish (Danio rerio)

Skyler Carrell, Fadi A. Issa, Young Zhu

Department of Biology, East Carolina University, Greenville, NC

In many social animal species aggression is an essential element in forming stable dominance hierarchies. It serves as an organizing agent for resources allocation according to social rank. However, persistently high aggressive activity among a social group could be destabilizing and has long lasting physiological effects and detrimental to social cohesion. Though the importance of maintaining the balance of aggression has been explored, the biochemical underpinnings that maintain social homeostasis remains poorly understood. Our study utilizes zebrafish as a model organism to investigate the role progestin nuclear receptor (Pgr) and androgen nuclear receptor (Ar) play in regulating social aggression in adult male zebrafish. As a joint effort with colleagues, we show that Pgr plays an important role in regulating aggression. We demonstrate that Pgr knockout zebrafish display unusually high levels of aggressive activity that persist over an extend time compared to wildtype animals. By comparison, Ar knockout animals show reduced levels of aggression. To determine the neurophysiological bases that underlie hyper aggressiveness of PgrKO fish, we conducted morphological analysis of brain dopaminergic nuclei and blood hormonal measurements of testosterone and 11-ketotestosterone. We found that the Pgr knockout (PgrKO) transgenic line showed an increase in the number of dopaminergic neurons in the A15 nucleus as well as an increase in the steroidogenesis of 11ketotesterone (11KT) compared to WT zebrafish. Our results suggest that Pgr may work through the dopaminergic system to alter 11KT levels to modify social aggression.
**Increased Alpha Desynchronization During Dynamic Visual Assessments Within One Year of Mild Traumatic Brain Injury**

Riley Warlick¹, Joshua Lawton¹, Melissa Hunfalvay², Nicholas Murray¹

¹Department of Kinesiology, East Carolina University, Greenville, NC  
²RightEye, Bethesda, MD

**BACKGROUND:** Mild Traumatic Brain Injuries (mTBI) can lead to visual processing deficits, including decreased visual acuity, visual field impairment, eye movement dysfunction—including vergence, saccadic, smooth pursuit movements and an increase in mental workload during visual tasks. Previous studies have shown a general relationship between visual tracking performance and brain function, whereas brain-specific studies, as measured via electroencephalogram (EEG), indicated head-injury correlational differences between mTBI patients and healthy controls. Specifically, mTBI patients demonstrated decreased alpha activity with a corresponding, subsequent, increase in theta activity and an overall increase in cognitive effort during visual-tracking and motor tasks. The purpose of this project was to examine the relationship between brain activity and visual-motor deficit in participants with a recent mTBI compared to healthy controls. We hypothesized that participants with recent mTBIs (within the previous 13 months) would exhibit alpha desynchronization and perform worse on dynamic vision tests compared to healthy controls.

**METHODS:** To test these hypotheses, data from 10 concussed participants (age: 20.2 ± 1.87 yrs, post-injury: 8.0 ± 3.96 months) and 17 healthy participants (age: 20.7 ± 1.68 yrs) wore a 32-channel dry EEG cap while completing a series of RightEye dynamic vision tests. Participants' eye movements were tracked using an SMI Red-RE eye tracker, while MATLAB was used to analyze alpha and theta power within spectral analysis.

**RESULTS:** The mTBI group demonstrated a significant (p < .05) increase in alpha desynchronization during discriminant reaction time and smooth pursuit tasks.

**CONCLUSIONS:** These findings indicate that mTBIs results in increased cognitive workload in brain regions that negatively impact visual motor control and neurological functions during visual discrimination tasks within 1-year post-injury. Furthermore, the results demonstrate the need to assess the long-term impact of concussions on the visual-motor system.
Nurr1 is a nuclear transcription factor that is required for the development and maintenance of dopamine neurons in the ventral midbrain. Nurr1 is involved in the expression of tyrosine hydroxylase (TH), including regulating the circadian expression of TH. In addition to dopamine neurons, Nurr1 is also expressed in neurons located in other regions of the brain such as the hippocampus, subiculum, habenula and claustrum. Dysfunction in Nurr1 is associated with various neurological and neuropsychiatric disorders including anxiety, depression, schizophrenia, Parkinson's disease, and Alzheimer's disease. To better understand the role of Nurr1 across these diseases, we wanted to develop better techniques to visualize Nurr1 protein expression. Unfortunately, not all antibodies have been validated with Nurr1 knockout tissue or show the characteristic distribution of Nurr1 expression.

The purpose of the current study was to refine immunofluorescence (IF) to better describe Nurr1 protein expression and validate specificity. This study describes the parameters necessary to for Nurr1 immunofluorescence using Nurr1 wild-type and knockout tissue as well as the combination of the dopamine transporter promoter cre transgene with the cre dependent YFP reporter to label transitions of TH expression in dopamine neurons.

Using an optimized antigen retrieval procedure, we demonstrate protein expression in the brain and show specificity based on the lack of signal in Nurr1 knockout tissue. Nurr1, TH and YFP IF in DATcre-YFP mice revealed, in the ventral midbrain, that the most common cell populations were YFP+/Nurr1+/TH+ followed by YFP+/Nurr1+/TH-. Additionally, YFP+/Nurr1-/TH- and finally a smaller but significant population of YFP-/Nurr1+/TH- cells were also observed. Furthermore, the Nurr1 labeling was specific enough to delineate differences between Nurr1 localized to the cytoplasm or the nucleus.

There are two key findings of this study. First, a reliable method for staining Nurr1 protein in tissue with specificity and sensitivity validated in Nurr1 wild-type and knockout mice. Secondly, the ventral midbrain contains a heterogeneous population of both Nurr1+ and Nurr1- cells, many of which are confirmed to be “off” DANs in this transgenic mouse model. For the first time, at least four different populations of cells were identified with unique anatomical distribution.
Acute Presentation of Newly Diagnosed Multiple Sclerosis Associated with PCR Proven HHV6 CNS Infection: A Case Report and Review of Literature

Conor Pumphrey, Joshua Scarcella, Donald Price

Brody School of Medicine, East Carolina University, Greenville, NC

Objective: A link between the pathogenesis of MS and human herpesviruses has been thought to exist for decades. Despite several prevailing hypotheses, the role that HHV-6 plays in the onset of MS disease has yet to be clearly defined.

Background: We present the case of a 26-year-old male who was found to have human herpes virus 6 (HHV-6) in his cerebrospinal fluid (CSF) at initial presentation of Multiple Sclerosis (MS). Upon secondary evaluation at a large acute care center due to progression of symptoms, MRI revealed worsening plaque burden while CSF analysis was negative for HHV-6 DNA. This conflicts with previous literature that posited a link between HHV-6 infection and MS relapse.

Results: A 2017 meta-analysis included studies that collected blood, serum, CSF, peripheral blood mononuclear cells, tissue, and saliva specimens to detect infection. Only 9 of these 42 studies collected CSF samples and it was not specified when they were analyzed in the course of disease development.

Conclusions: Our observation is that inconsistent work-up of MS-like disease processes has contributed to the absence of a clear definition of the role of HHV-6 in acute MS diagnosis despite decades of research. We highlight the need for further research regarding the virus’s role in initial presentation of MS disease. A prospective cohort study that acquires CSF PCR at time of diagnosis of MS could further elucidate the role that HHV-6 infection plays in the development of MS in a previously undiagnosed patient. These proposed studies could be helpful in preventing or delaying onset of MS in at-risk populations.
Peripheral Nerve Injury Causes Central Sensorimotor Changes: Treatment with Dopaminergics and Opioids

Mandee Schaub and Stefan Clemens, Ph.D.

East Carolina University, Department of Physiology, Greenville, NC, USA

Chronic neuropathic pain (CNP) is a nervous system disorder that affects 12-15% of Americans. There is a lack of effective long-term treatments for CNP, and opioids serve as a last resort. We have shown recently that in an animal model of centrally-induced CNP (spinal cord injury), morphine can achieve and maintain analgesic relief if administered with the dopamine (DA) D3 receptor agonist pramipexole (PPX). We here wanted to explore if this novel drug combination would lead to similar positive outcomes in a peripherally-induced model of chronic pain. Male mice (C57BL/6, 10 weeks old) were subjected to a unilateral sciatic nerve ligation (SNL), with the contralateral side serving as control. A Hargreaves system was used to measure thermal pain withdrawal reflex latencies on both sides, under control and drug treatment conditions (i.p. injections of PPX and/or morphine). Following behavior testing, sciatic nerves were harvested to assess nerve conduction velocities (NCVs) and compound action potentials (CAPs), and spinal cords were harvested and probed for protein expressions of dopamine and mu-opioid receptor. We found that, when applied to this peripheral model, neither morphine (2 mg/kg) nor PPX (0.5 mg/kg) led to recovery of thermal pain withdrawal reflex latencies, while application of the drugs in combination (morphine 2mg/kg + PPX 0.5mg/kg) completely restored reflex latencies to control levels. In addition, a reduction of morphine to 1 mg/kg in the presence of 0.5 mg/kg PPX also restored normal reflex latencies. In vitro, NCVs were unaltered in SNL animals while CAPs were significantly reduced.

These data indicate that a combination treatment of morphine and PPX can restore normal reflex function in a peripherally-induced CNP model that is morphine tolerant, similar to the findings obtained from the centrally induced CNP model. Thus, we propose that this new pharmacological approach that combines an opioid with a dopaminergic may be a novel tool to treat CNP regardless of its origin. The proposed treatment would reduce opioid doses clinically, reducing negative outcomes due to opioid use.
Examining the Impact of Social Behavior on Host Gut Microbiome Composition in Male Zebrafish (*Danio rerio*)

Emily Scott, Fadi Issa, Ariane Peralta, Michael Brewer

Department of Biology, East Carolina University, Greenville, NC

The gut and the brain, both vastly different in physiologic function, have been linked in a variety of different neurological and behavioral disorders. The bacteria that comprise the gut microbiome communicate with other systems within the body including the immune and nervous systems. Specifically, the gut microbiome has been associated with the development and onset of many neurological disorders (i.e., autism spectrum disorder, anxiety, and depression), which have long lasting impacts. Understanding the mechanisms of onset and progression related to the gut microbiome is critical. Zebrafish (*Danio rerio*) form social relationships consisting of dominants and subordinates, but the relationship between social status and host gut microbiome composition is unknown. The purpose of this study is to determine if social status impacts the composition of the host zebrafish gut microbiome. We examined how the evolution of social status changed the composition and species diversity of the host gut. After initial isolation, male zebrafish were assigned to one of three experimental groups: pairs (n=12), isolates (n=6), or communal (n=6). Over the course of fourteen days, paired zebrafish self-established rank. To examine fish microbiomes, fecal samples were collected from each fish at four different times: during isolation, on day 0, day 7, and day 14 of pairing. After fecal sample processing and 16S rRNA amplicon (Illumina) sequencing, we found that social status does impact host gut microbiome community composition. In conclusion, this supports the hypothesis that social behavior can affect gut microbiome composition.
Determining the Role of Acsl6 in α-synucleinopathy

Amber Smaltz, Jessica M. Ellis

Brody School of Medicine at East Carolina University, Department of Physiology and East Carolina Diabetes and Obesity Institute, Greenville, NC

Docosahexaenoic acid (DHA) is an omega-3 polyunsaturated fatty acid highly enriched in the brain that has numerous neuroprotective benefits, yet a controversy exists regarding DHA’s role in α-synuclein biology. The α-synuclein protein can aggregate and accumulate in manners that are deleterious to neurological health and this is most known to occur in Parkinson’s Disease. Here, we assessed the role of DHA in α-synuclein biology using a mouse model-based approach. Specifically, we leveraged our novel model of neuronal membrane DHA depletion, due to the loss of a DHA-preferring fatty acid metabolizing enzyme Long-chain Acyl-CoA Synthetase 6 (Acsl6KO mice), combined with a model of α-synucleinopathy in which a human α-synuclein containing the genetic mutation of A53T, a mutation that was identified in individuals with Parkinson’s, is overexpressed (hA53Tsyn mice). As a result of combining Acsl6 loss with α-synuclein overexpression (Acsl6KO-hA53Tsyn mice), we observed a remarkable reduction in lifespan by 62.4%, average lifespan of 5 months in Acsl6KO-hA53Tsyn versus 13 months in hA53Tsyn. The early lethality of Acsl6KO-hA53Tsyn compared to hA53Tsyn alone, was accompanied by ~3-fold higher α-synuclein monomer protein abundance and increased oligomerization of α-synuclein in Acsl6KO-hA53Tsyn brains. These data demonstrate a critical role of Acsl6, a known DHA-metabolizing enzyme, in the pathogenesis and survival rates in a model of α-synucleinopathy.
Alone in a Crowd: Effect of a Nonfunctional Lateral Line on Expression of the Social Hormone parathyroid hormone 2

Alexandra Venuto1, Cameron Smith2, Timothy Erickson3

1Department of Biology, East Carolina University, Greenville, NC
2East Carolina University School of Dental Medicine, Greenville, NC
3Department of Biology, University of New Brunswick, Fredericton, New Brunswick, Canada

In larval zebrafish, parathyroid hormone 2 (ptth2) codes for a peptide hormone that is expressed exclusively in cells near the dorsal thalamus. Social isolation reduces ptth2 mRNA and protein levels, and expression recovers after returning isolated fish to a social environment. However, social interactions fail to stimulate ptth2 expression in previously isolated zebrafish whose mechanosensory lateral line has been chemically ablated. These findings suggest that ptth2 expression is regulated by social context and is acutely dependent on lateral line function. However, it is unknown how a chronic, genetic loss of lateral line function influences how zebrafish interpret their social environment.

We hypothesize that zebrafish born without a functional mechanosensory lateral line will be unable to sense their social environment and ptth2 expression will be low. To test this prediction, we used zebrafish mutants that either lack lateral line function only or lack both inner ear and lateral line function. We compared ptth2 expression in mutant and wild type (WT) zebrafish larvae raised in social or isolated environments. Like isolated WT larvae, all three types of socially raised mutants express low levels of ptth2 relative to their social WT siblings. Additionally, we created a transgene that is driven by the ptth2 promoter and found that both isolated and lateral line mutant zebrafish exhibit a decrease in ptth2-expressing cells compared to social WT siblings. These data support our hypothesis and suggest that lateral line mutants experience a chronic sense of isolation, even when raised in a social environment. Overall, this study offers insight into the sensory basis for social interactions in zebrafish.
Poster Session
Abstracts:
Research

(listed by presenting author in alphabetical order)
Involvement of miR-10 in Epigenetic Alterations of Behavioral Phenotypes in Offspring of the Western Diet Drosophila Melanogaster

Steven R. Bradley\textsuperscript{1}, Morgan E. Tedder\textsuperscript{1}, Elena S. Pak\textsuperscript{2}, and Alexander K. Murashov\textsuperscript{2}

\textsuperscript{1}Department of Psychology, East Carolina University, Greenville, NC
\textsuperscript{2}Department of Physiology, Brody School of Medicine, East Carolina University, Greenville, NC

Our lab has observed many detrimental effects of a Western Diet (WD) characterized by high fat, sugar, and salt, on Drosophila simulans and Drosophila melanogaster. Several of these deficiencies are behavioral, including sleep disturbance, hyperphagia, and decreased learning and memory. These flies also exhibit many ailments experienced by a large group of the general population today such as obesity, metabolic syndrome, and type 2 diabetes. Epigenetics has been found to play a large role in the obesity pandemic, but the mechanisms that underlay the inheritance of many traits are still not widely understood. qPCR of WD offspring shows a significant increase in miR-10, suggesting that this may play a role in some of these changes. To investigate this possibility, four stocks of transgenic flies will be used in crosses for the knockdown phase of this project. 7009 flies express GAL4 in dopaminergic and serotonergic neurons. 35014 flies express dsRNA for the knockdown of miR-10 under GAL4-induced UAS control. 61377 flies express a “sponge” RNA for the knockdown of miR-10 under GAL4-induced UAS control, and CS flies will be used as a control group. The four groups derived from these stocks will be 7009x35014, 7009x61377, CSx35014, and CSx61377. Locomotor activity tests will assess sleep disturbance over the course of 5 days. Feeding behavior is measured using the FLIC system which counts interactions between a fly and a 10% sucrose solution in a well. Learning and memory is measured using passive avoidance behavior assay. In this assay, flies are prompted to travel upwards by natural negative geotaxis, light, and odor. The number of times they are shocked when traveling upwards is measured along with latency – the time between entering the tube and the first shock. We have already completed the first round of testing which yielded significant results in the locomotor activity and learning and memory tests. Both experimental groups showed lower sleep disturbance than the controls and the 7009x35014 flies displayed superior learning and memory capabilities compared to their CSx35014 control group.
Neurophysiological Differences Between Healthy Young and Older Individuals in Cognitive Motor Control

Nikole B. Galman¹, Alexandra Shaver², J.C. Mizelle¹

¹Department of Kinesiology, East Carolina University
²Department of Kinesiology, University of Maryland

Introduction: Cognitive and physiological brain processes start to decline due to the wear and tear of natural aging. The ability to perform complex motor behaviors such as tool use is also known to decline with age. However, the reason for these declines is not well understood in the healthy aging population. The term used for the execution of goal-based actions is called praxis. The purpose of this study was to study neurophysiological differences between healthy young and old individuals in a cognitive motor task, and to observe how high-level cognitive motor functions like praxis may be susceptible to the aging process in healthy older adults.

Materials and Methods: 21 younger and 12 older healthy participants were recruited. Each was prepared with a 64-channel EEG cap which captured brain activity while black and white images showing normal tool use and plausible (unusual) were presented. Each trial started with a text prompt explaining the intended action-oriented goal. After a blank white screen appeared for a pseudorandom amount of time, the stimuli were then presented and participants selected their answers using a response pad. Stimulus-related EEG signals were then analyzed to identify group differences.

Results and Discussion: Functional connectivity and graph theory measurements were used to model networks of brain activation focusing on the Theta band (4-8 Hz). Our results show a loss of hemispheric dominance in older adults along with a more anterior focus of neural function.

Conclusion: Our results show that older individuals have altered neurophysiological functioning, with brain activation and neural networks largely generalized compared to the younger group. This may be related to neuronal alteration accompanies old age, which consequently leads to the recruitment of additional brain regions to perform cognitive motor tasks. In conclusion, older adults have more diffuse brain activity and neuronal network function to compensate for aging.
Adolescent Nicotine Exposure in the Zebra Finch has Lasting Impacts on Saliency and Anticipation of Conditioned Rewards

Yasmine Habal1, Alexis Papariello2, Ken Soderstrom2

1Department of Psychology, Neuroscience, East Carolina University
2Department of Pharmacology and Toxicology, Brody School of Medicine at East Carolina University

Nicotine administration during the peri-adolescent developmental stage of rats has been shown to significantly affect cocaine reinforcement in adulthood. In this experiment, a conditioned place preference experiment was conducted on zebra finches where half the birds were given nicotine, and the other half were given vehicle in the early peri-adolescent, sensorimotor vocal learning stage of development. Birds were given an initial preference test using a place preference apparatus where two chambers were distinguished by color and perch textures. Birds were then treated with vehicle in most-preferred, and cocaine (2.5 mg/kg IM in 50 mcl) in least-preferred chambers. After conditioning and final preference test, vehicle and control groups were subdivided into two groups: for placement into either the vehicle or cocaine-paired chambers for fifteen minutes. Densities of c-Fos-expressing nuclei (a marker of increased neural activity in the brain) were measured to determine which areas of the brain are associated with vehicle- or cocaine-conditioned environments. The specific brain areas that were measured were LMAN, Area X, Nucleus Taeniae (NT), amygdala, both medial and caudal striatum, HVC, and RA. The main regions of focus are Area X (a striatal regions that receives midbrain dopaminergic input and is necessary for song learning) and the amygdala (involved in fear and anxiety responses to sensory input) because they are associated with decision making, reinforcement, and learned behavior. It was hypothesized that developmental nicotine would increase reinforcing properties of cocaine and increase in c-Fos nuclei densities in Area X and amygdala. The c-Fos positive nuclei were counted via brightfield microscopy after immunohistochernistry staining. Significant differences in c-fos reactivity between VEH and NIC treated groups were found in Area X, HVC, LMAN, TN, and striatum (caudal and medial). No significant effects were seen in the amygdaloid region nor in vocal motor cortex (RA). Developmental nicotine treatment was associated with an increase in c-Fos nuclei when the bird is put into a vehicle-paired chambers and a decrease in c-Fos nuclei when the bird was placed into cocaine-paired chambers. In conclusion, this suggests that developmental nicotine changes sensitivity to cocaine place preference.
Involvement of Rab10 in Cognitive Dysfunction Using Trace Eyeblink Classical Conditioning

Liz Harris¹, Hailey Aldridge¹,², Luke Jackson¹, Kendra Brent³,⁴, Tuan D. Tran¹,²

¹Multidisciplinary Studies Program in Neuroscience, East Carolina University, Greenville, NC
²Department of Psychology, East Carolina University, Greenville, NC
³Department of Biology, East Carolina University, Greenville, NC
⁴Department of Anthropology, East Carolina University, Greenville, NC

Rab10 is a GTPase involved in vesicular trafficking. It is a substrate of leucine-rich repeat kinase 2 (LRRK2), a serine/threonine protein kinase associated with Parkinson's disease. Phosphorylation of Rab10 is prominently expressed in hippocampal tissues of Alzheimer’s disease (AD) patients (Yan et al., 2018). We are investigating the link between Rab10 and cognitive dysfunction using trace eyeblink classical conditioning (TECC), a form of learning mediated by cortical-hippocampal interactions. A learning task that assesses this neural circuit is used because it is highly susceptible to degeneration in AD. AD is characterized by progressive loss of many cognitive functions. It afflicts 5.1 million people aged 65 years and older in the US and tens of millions globally. Looking at Rab10 overexpression is a novel approach to understanding neuropathology of AD, as current treatments have yielded very little in terms of long-term efficacy. Elevated Rab10 may enhance AD progression and pathology, leading to cognitive impairments and its reduction is a potential target for experimental therapeutics. Adult male and female wild-type (WT) and Rab10+ mice are surgically implanted with recording electrodes and a stimulating electrode (after Tran et al., 2017). After recovery, they receive six days of TECC. Each day consists of 100 trials in which a 380-ms, 80dB tone conditioned stimulus (CS) is paired with a 100-ms, 1.6mA current (unconditioned stimulus, US) delivered to the periorbital muscle to elicit an eyeblink unconditioned response (UR). A trace period of 500ms in between the tone CS and shock US is imposed. The learning measure is the conditioned response (CR), an anticipatory eyeblink that is elicited by the tone CS and is emitted prior to the US. The trace period taxes the ability to time events properly and requires the integrity of cortical-hippocampal circuits. We compared whether the learning curves expressed by each group differed significantly. In n=6 Rab10+ mice, they showed impaired acquisition of CRs compared to n=6 WT mice, suggesting that elevated expression of Rab10 may disrupt learning performance.
The Hyaluronan Extracellular Matrix Critically Regulates Synapse Formation in Developing Neural Networks

Emily Wilson¹, Warren Knudson², Karen Litwa²

¹Brody School of Medicine Department of Physiology, East Carolina University, Greenville, NC
²Brody School of Medicine Department of Anatomy and Cell Biology, East Carolina University, Greenville, NC

The majority of neurodevelopmental disorders present with an imbalance in synaptic signal transmission. The delicate balance of excitatory to inhibitory synaptic transmission is regulated by multiple extracellular and intracellular factors. Specifically, our work demonstrates that the major extracellular component of the brain, hyaluronan, critically regulates synaptic formation and the emerging balance between inhibitory and excitatory neurotransmission. Furthermore, our results suggest that these effects are in part mediated by hyaluronan's interaction with its receptor, CD44, leading to actin cytoskeleton rearrangements that alter synapse formation and size. For the first time, we demonstrate that human brain models secrete an endogenous hyaluronan matrix through expression of hyaluronan synthetase. Hyaluronan is present at the synaptic cleft of nascent developing synapses. Through both genetic and pharmacological regulation of hyaluronan levels, we demonstrate that hyaluronan antagonizes excitatory synapse formation, preventing the emergence of hyperexcitability in developing neural networks. Furthermore, excitatory synapses contain the HA-receptor, CD44. In other tissue systems, the interaction between HA and CD44 activates RhoA signaling leading to actomyosin contractility. In our research, we demonstrate that similar to HA, RhoA signaling through its effector kinase, ROCK, also antagonizes excitatory synapse formation in developing neural networks. Together, our data supports a model in which synaptic HA suppresses excitatory synaptogenesis through interaction with CD44 and activation of RhoA/ROCK, resulting in the destabilization of synaptic contacts. We propose that HA-mediated regulation of synapse formation, critically regulates neural network development, and prevents the emergence of hyperexcitability in neural networks, which is characteristic of neurodevelopmental disorders.
Poster Session
Abstracts:
Clinical Case Studies

(listed by presenting author in alphabetical order)
Patients with neurofibromatosis type 1 can manifest cutaneous neurofibromas that transition to malignant peripheral nerve sheath tumors (MPNST). We present such a case which posed diagnostic and treatment challenges. A 68-year-old woman presented with a progressively enlarging nodule on the posterior aspect of her scalp that had existed for many years. During the previous three weeks the nodule had become firmer and caused increasing discomfort. Her past medical history was significant for breast cancer. Her family history included numerous relatives with neurofibromatosis type 1. She developed cutaneous lesions during adulthood and had not been offered genetic testing. The scalp lesion was 4.0 X 6.5 cm as evaluated by magnetic resonance imaging without definite skull involvement. The lesion was initially excised with simple closure in the event additional excision would be required if there were positive margins on pathology. Histopathologic evaluation revealed a malignant peripheral nerve sheath tumor with positive deep margins and 1 mm proximity to peripheral margins. In a second operation additional peripheral margins and pericranium was excised and bilateral parietal flaps were used to reconstruct the defect with a galeal flap in the central aspect. Histologic evaluation revealed neurofibroma and scar with no evidence of residual MPNST. Radiation of the resection bed was subsequently performed. The patient is scheduled for surveillance regularly with the oncology team. This unusual case underscores the potential for cutaneous neurofibromas to progress to MPNSTs and emphasizes the need for close monitoring of neurofibromas over time in patients with neurofibromatosis type 1.
Wernicke Encephalopathy in a Young Adult Following Severely Reduced Food Intake: Perils of Thiamine Deficiency

Peter G. Buccini1, Mohamed M. Maher2, Thomas Sporn2, Philip J. Boyer2

1Brody School of Medicine, East Carolina University, Greenville, NC
2Department of Pathology and Laboratory Medicine, East Carolina University, Greenville, NC

Chronic thiamine (vitamin B1) deficiency is associated with a range of neurologic disease processes including Wernicke-Korsakoff syndrome, cerebellar degeneration, and beriberi disease. We present a case of Wernicke encephalopathy in the context of a hunger strike. The patient was a 36-year-old man with a history of paranoid schizophrenia and obesity. He undertook reduction in his food intake resulting in the loss of over 50 pounds. He presented with altered mental status, generalized weakness, and foul-smelling urine. He was found to have bilateral pulmonary emboli by computed tomography angiography evaluation, possible urologic, pulmonary, or decubitus-ulcer associated septic shock requiring pressor support, and gastrointestinal bleeding with coffee colored emesis. His vitamin B1 level was <6 nmol/L (reference range 8-30 nmol/L), his vitamin C level was 0.1 mg/dL (reference range 0.2-2.1 mg/dL), and his vitamin D level was 26.3 ng/mL (reference range 30.0-100.0 ng/mL). Magnetic resonance imaging identified T2-bright signal around the third ventricle in the medial thalamus, in the fornix and mamillary bodies, and in the periaqueductal and peri-fourth ventricular regions involving the tegmentum. Cardiopulmonary resuscitation was unsuccessful, and he died. A full autopsy was performed. Neuropathologic evaluation identified marked vascular congestion and hemorrhage in the regions of imaging abnormality. The pattern of damage seen in the patient’s brain was diagnostic of Wernicke syndrome, acute in nature. Wernicke-Korsakoff-type changes in the central nervous system can develop in several settings, most commonly in the context of thiamine deficiency due to (1) reduction in intake, (2) reduction in absorption, or/and (3) increase in loss (e.g., via dialysis and diuresis). This report documents an unusual presentation of Wernicke encephalopathy and underscores the perils of non-medically supervised, severe reduction in food intake in the absence of vitamin supplementation.
Ameloblastomas are uncommon, primary neoplasms of the jaw. We describe a rare case of a maxillary ameloblastoma. A 39-year-old man was referred to our neurosurgery clinic because of a massive nasopharyngeal soft-tissue tumor extending into the anterior cranial fossa. He had been seen in another hospital and diagnosed with a nasopharyngeal tumor several years previously. He was scheduled for surgery, but his surgery was cancelled for unknown reasons, and he was lost to follow-up. The patient again presented after developing bilateral blindness. On examination the patient had marked proptosis and the right pupil was non-reactive to light. The tumor was visibly protruding from the right nostril. The patient underwent pre-surgical vascular embolization to debulk the tumor. Bicoronal frontal craniotomy was performed with removal of the neoplasm from both frontal regions and the skull base. Most of the floor of the anterior fossa had been eroded by tumor with encasement of both optic nerves, involvement of the sphenoid sinus, and compression of the right frontal lobe. The skull base was repaired and frontal region cranioplasty was performed with titanium mesh. Histologic evaluation of the resected neoplasm revealed a solid/multicystic subtype of ameloblastoma with follicular and plexiform growth patterns. Ameloblastomas, arising from odontogenic epithelium, are generally benign, slow growing, but locally aggressive neoplasms. Approximately 80% are found in the mandible while only 20% are found in the maxillary bone. Initial presentation is usually with painless swelling of the jaw or as an incidental finding on dental imaging. They are generally considered benign but are locally aggressive when untreated. Maxillary ameloblastomas require early diagnosis and prompt treatment as they may act more aggressively than those of the mandible. Ameloblastomas are known to have high rates of recurrence, up to 15-25% after radical resection and 75-90% after conservative resection. Long-term follow-up is necessary to identify and treat recurrences. Local invasion into the orbital region or skull base is very rare but poses serious lethal potential. Unfortunately, following the surgery the patient was again lost to follow-up.
Inflammatory Cerebral Amyloid Angiopathy (CAA) Initially in the Absence of Radiologic Evidence of Microhemorrhages and Responsive to Corticosteroid Therapy: CAA-Related Inflammation vs. Amyloid Beta-Related Angiitis

Marwan Majeed¹, Jasmin Jo², Breann Zeches³, Bushra Javed³, Sina Kazemzadeh⁴, Regis G. Hoppenot⁵, Anas Mohamed¹, Philip J. Boyer¹

¹Department of Pathology and Laboratory Medicine, East Carolina University, Greenville, NC
²Department of Internal Medicine, Hematology and Oncology Division, East Carolina University, Greenville, NC
³Department of Internal Medicine, Neurology Division, East Carolina University, Greenville, NC
⁴Brody School of Medicine, East Carolina University, Greenville, NC
⁵Vidant Neurosurgery, Vidant Health, Greenville, NC

Cerebral amyloid angiopathy (CAA) evokes an inflammatory response in a minority of cases manifesting as either CAA-related inflammation (CAA-ri) or amyloid beta-related angiitis (ABRA). Clinical and imaging criteria for the diagnosis of possible and probable CAA-ri have been proposed and validated. A 58-year-old woman presented with a 1-week history of a shuffling gait, falls, and intermittent confusion with acute-onset left gaze deviation progressing to generalized seizures. Magnetic resonance imaging of her brain identified non-enhancing lesions in the right parietal and frontal white matter in the absence of microhemorrhages. Lumbar puncture was negative by cytology and flow cytometry with normal protein and cell counts; three oligoclonal bands were identified; IgG index and myelin basic protein were within normal ranges. A course of corticosteroids was administered with reversal of neurologic deficits and improvement in imaging abnormalities. However, after tapering corticosteroids, while her neurologic examination remained normal, imaging documented interval recurrence and progression with confluent leukoencephalopathy now involving both cerebral hemispheres along with microhemorrhages, meeting criteria for probable CAA-ri. Biopsy of a lesion revealed extensive amyloid deposits in subarachnoid and cortical blood vessels with, in many vessels, associated inflammation including granulomatous features and evidence of previous vessel wall with recanalization, consistent with ABRA. This report illustrates a case of cerebral amyloid angiopathy that is at the interface of CAA-ri and ABRA with respect to clinical criteria and histopathologic features and contributes to the clinicopathologic correlation of radiologic and imaging studies. Despite clinical criteria, definitive distinction between CAA-ri and ABRA requires histologic evaluation.
Primary Central Nervous System Lymphoma as a Manifestation of Post-Transplant Lymphoproliferative Disease in Solid Organ Transplant Patients: Report of Four Cases

Christopher S. McMillan¹, Nupur Sharma², Jasmin Jo³, J. Stuart Lee³, Hassam Ali⁵, Richard T. Dalyai³, Hilal Kannan³, Breann A. Zeches², Philip J. Boyer²

¹Brody School of Medicine, East Carolina University, Greenville, NC
²Department of Pathology and Laboratory Medicine, East Carolina University, Greenville, NC
³Department of Internal Medicine, East Carolina University, Greenville, NC
⁴Vidant Neurosurgery, Greenville, NC
⁵Department of Internal Medicine, East Carolina University, Greenville, NC

Individuals who receive solid organ transplants need to be maintained on immunosuppressive medications to prevent transplant rejection. This immunosuppressed state can predispose to infection-associated neoplastic complications. We present four cases of central nervous system Epstein-Barr virus (EBV)-related posttransplant lymphoproliferative disorder (PTLD) in individuals with solid organ transplants. Patient A is a 62-year-old woman who received a kidney transplant 15 years previously. She presented with generalized weakness and falls. Magnetic resonance imaging (MRI) of her brain identified a left frontal lobe lesion. Patient B is a 71-year-old woman who is 15 years status-post renal transplant. She presented with progressive aphasia (word finding difficulty) and confusion. MRI of her brain revealed a left temporal lobe mass and a left frontal lobe mass. Patient C is a 72-year-old man who is 16 years status-post renal transplant. He presented with right hand weakness and wrist drop. An MRI study of his brain identified a medial left frontal lobe lesion. Patient D is a 70-year-old man who is 3 years status-post liver transplant. He presented with confusion. Imaging of his brain revealed a left frontal lobe lesion. In each case, biopsy of the patient’s brain lesion revealed an EBV-positive diffuse large B-cell lymphoma with no evidence of lymphoma elsewhere in their body, consistent with designation as primary central nervous system lymphoma. Combined findings are also consistent with designation of the lymphoma as a EBV-associated PTLD. This report summarizes the therapy and outcome for each patient. In solid organ transplant recipients, PTLD is the most commonly associated malignancy. The patient’s degree of T-cell immunosuppression in the context of an underlying, dormant EBV infection in the recipient or in the organ donor appears to be a critical risk factor for developing PTLD. PTLD can affect various sites with the CNS involved in 7-15% of cases, usually, as in these patients, with primary presentation in the brain rather than secondary involvement of the brain by a lymphoma arising in lymph nodes or an extranodal site. Primary central nervous system PTLD most commonly is associated with kidney transplants, often occurs years after transplantation, usually follows an aggressive course, and most commonly shows EBV expression in neoplastic cells.
Anti-HMG-CoA Reductase Myopathy in Patients Taking Atorvastatin: A Case Study

Stephen Orr¹, Ryan Patton¹, Donald Price², Philip Boyer³

¹Brody School of Medicine, East Carolina University, Greenville, NC
²Brody School of Medicine Department of Internal Medicine, East Carolina University, Greenville, NC
³Brody School of Medicine Department of Pathology and Laboratory Medicine, East Carolina University, Greenville, NC

Introduction: Statins are widely used medications for reduction of cholesterol levels in patients with risk factors for atherosclerosis. These medications function by inhibiting the enzyme HMG-CoA reductase, thereby inhibiting the conversion of HMG-CoA into cholesterol. In rare cases, the use of statins can cause the immune system to create antibodies to HMG-CoA reductase, leading to an autoimmune attack on muscle tissue known as anti-HMGCR myopathy.

Case Presentation: We compare the clinical presentations, demographics, risk factors, and response to treatment in three patients with anti-HMGCR myopathy, a subtype of immune-mediated necrotizing myopathy (IMNM) linked to statin use, to better understand this rare condition. All three patients had been taking atorvastatin for many years, initially presented with proximal muscle weakness and severe myonecrosis (30x greater than upper limit of normal) and tested positive for HMG-CoA reductase antibody.

Patient 1: 53-year-old Caucasian male with fatty liver disease with onset of symptoms several years after switching from pravastatin to atorvastatin. This patient developed a severe progressive necrotizing myopathy requiring several months of hospitalization as well as intubation and gastric tube placement.

Patient 2: 68-year-old African American female who had been taking several medications with known interactions with atorvastatin. This patient developed weakness and mild dysphagia that improved over 15 days with IV steroids and outpatient prednisone taper.

Patient 3: 62-year-old African American female with onset of proximal muscle weakness and cramps soon after doubling her dose of atorvastatin. Muscle cramps and myonecrosis resolved with combination of IV steroids and IVIG, although proximal muscle weakness persisted.

Discussion: Each patient was taking atorvastatin at the time of symptom onset and each had predisposing factors leading to elevations of statin levels. Atorvastatin is considered a high-risk statin for statin-induced myopathies because it is metabolized by CYP3A4, and therefore has many potential drug interactions. Anti-HMGCR myopathy is a rare condition that remains understudied. This case study adds to the literature supporting a higher risk of anti-HMGCR myopathy with increased levels of a high-risk statin.
Germ cell neoplasms of the central nervous system are rare lesions seen predominantly in the pediatric population. We report a case of a patient with an uncommon location of an intracranial germ cell neoplasm. The patient is a 9-year-old girl who presented with increased sleepiness, decreased activity, decreased appetite, and a few episodes of vomiting. Imaging of her brain identified a right frontal hemisphere mass, 4.9 X 3.7 cm, centered along the lateral margin of the frontal horn of the right lateral ventricle. The lesion was resected and histologic evaluation revealed a mixed germ cell neoplasm with yolk sac / endodermal sinus tumor features predominate and admixed regions of germinoma, second most prominent, and choriocarcinoma, minimal, very focal. Serum evaluation postoperatively (07/20/2021) identified elevated alpha-fetoprotein, 4354 ng/mL (reference range <8.4 ng/mL), and beta-HCG, 5.4 IU/L (reference range <1.0 IU/L). The identification of markedly elevated serum alpha-fetoprotein levels, collected after resection, is concordant with the predominance of yolk sac / endodermal sinus tumor in the lesion. Likewise, the mild elevation of serum beta-HCG is concordant with the relatively scant presence of choriocarcinoma. Her post-operative course was complicated by seizures, neuro-storming, and significantly altered mental status and disability. Central nervous system germ cell tumors comprise approximately 0.5-3% of primary neoplasms in the pediatric population with germinomas accounting for 65-75% of cases. A majority of central nervous system germ cell tumors present as midline lesions, affecting the pineal (more commonly in male patients), the hypothalamus and suprasellar region (more commonly in female patients), or both midline locations. Presentation in the basal ganglia, thalamus, ventricles, or brainstem is uncommon. Treatment is ongoing and will be summarized in the presentation.
Paraneoplastic Cerebellar Degeneration Associated with CV2/CRMP5 Antibodies in a Patient with Multiple Cerebral Venous Angiomas

Kevin Travia1, Alex Doherty1, Steven Vernino3, Ellen Marder4, Phillip J Boyer2

1Brody School of Medicine, Greenville, NC
2Department of Pathology, Greenville, NC
3Department of Neurology, University of Texas Southwestern Medical School, Dallas, TX
4Neurology Specialists of Dallas, P.A., Dallas, TX

Paraneoplastic autoimmune neurologic syndromes are rare disorders triggered by humoral and/or cellular immune activation by neoplasm antigens resulting in immune attack on specific nervous system regions. The primary neurologic symptoms and signs correlate with the nervous system region attached and include ataxia (cerebellum), cognitive dysfunction (limbic system), sensory deficits (dorsal root ganglia), and weakness (neuromuscular junction). Specific onconeural, paraneoplastic antibodies can be detected in serum; a paraneoplastic antibody screen serves as a diagnostic test. Anti-CV2/CRMP-5 antibodies can develop and be detected in patients with small cell carcinoma or thymoma and are predominantly detected in smokers. This report summarizes the clinical findings and histopathology of a patient with subacute cerebellar degeneration in whom serum anti-CV2/CRMP-5 antibodies were detected. The patient was a 66-year-old female with a five-month history of progressively worsening ataxia and vertigo to the extent of being wheelchair bound. Past medical history was significant for four grand mal seizures, three cerebral cavernous angiomas with other family members manifesting cavernous angiomas, and hypertension. MRI and MRA revealed cerebellar atrophy but no cerebellar vascular malformations were identified. A chest CT scan was negative for a neoplastic process. A paraneoplastic antibody screen identified anti-CV2/CRMP5 antibodies. The patient had a negative workup for hereditary cerebellar degenerative disorders or an underlying malignancy. She died of pneumonia and an autopsy limited to evaluation of her brain was undertaken. Cerebellar vermis and hemisphere sections revealed atrophy due to focally severe loss of Purkinje cells with prominent Bergmann gliosis and patchy parenchymal inflammatory cell infiltrates consisting of predominately CD3-positive T-cells and CD68-positive macrophages with prominent clusters of CD20-positive B-cells surrounding blood vessels and chronic inflammatory infiltrates in the subarachnoid space. Findings were consistent with paraneoplastic cerebellar degeneration most likely arising from an occult small cell lung carcinoma. Paraneoplastic disease with anti-CV2/CRMP5 paraneoplastic antibodies can include limbic encephalitis, peripheral neuropathy, myelopathy, and uveoretinal disease. This report documents autoimmune cerebellar degeneration as another possible outcome of individuals with an anti-CV2/CRMP5 paraneoplastic disease process. A paraneoplastic antibody screen is important in the clinical workup of a patient with a smoking history and ataxia.
Cerebellar Pilocytic Astrocytoma with Spinal Canal Extension and Drop Metastasis in a Young Adult: Late and Unusual Presentation with Novel PID1-BRAF Fusion

Alexander J. Trei\(^1\), Patrick M. Dugom\(^1\), Jasmin Jo\(^2\), Breann A Zeches\(^3\), Marwan Majeed\(^1\), Regis G. Hoppenot\(^4\), Andrew W. Ju\(^5\), Philip J. Boyer\(^3\)

\(^1\)Brody School of Medicine, East Carolina University, Greenville, NC
\(^2\)Department of Internal Medicine, East Carolina University, Greenville, NC
\(^3\)Department of Pathology and Laboratory Medicine, East Carolina University, Greenville, NC
\(^4\)Vidant Neurosurgery and Spine Center, Greenville, NC
\(^5\)Department of Radiation Oncology, East Carolina University, Greenville, NC

Pilocytic astrocytomas of the cerebellum most commonly present in childhood and most are shown to have a KIAA1549-BRAF fusion. We present a patient with a late-presenting pilocytic astrocytoma with a novel BRAF fusion. A 23-year-old man presented for ophthalmologic evaluation with progressive vision loss and gait ataxia of approximately three months duration with chronic headaches, years duration. Ophthalmologic evaluation identified papilledema. Emergent magnetic resonance imaging (MRI) of his brain identified a cerebellar / fourth ventricle mass, heterogeneously contrast-enhancing, extending through the foramen magnum to the C4 level of the spinal cord with mass effect on and deformity of the upper cervical spinal cord along with hydrocephalus was identified. MRI evaluation of the lower spinal cord revealed a curvilinear enhancement along the surface of the cord, T1-T3, and punctate enhancement in the cauda equina. Resection of the lesion was undertaken. Combined histologic and immunohistochemical findings in this case are diagnostic of a glial neoplasm and are consistent with designation as a pilocytic astrocytoma. A complete molecular evaluation identified a PID1-BRAF fusion along with a TET1 gene mutation of uncertain significance. Between 75-80% of posterior fossa pilocytic astrocytomas manifest a KIAA1549-BRAF fusion; while other BRAF fusions, BRAF mutations, and other molecular abnormalities can be seen they are considerably less common. While the nature of this fusion with respect to function has not been characterized, the loss of the BRAF auto-regulatory domain and maintenance of an intact in-frame BRAF kinase domain suggest that the fusion is likely to generate a functionally significant and pathogenic fusion protein. As such, this fusion protein may represent an addition to the group of BRAF fusions that can be seen in pilocytic astrocytomas. No histologic or molecular findings that would suggest an alternative diagnosis were identified (e.g., brainstem glioma, other astrocytoma variant, oligodendroglioma, etc.). Craniospinal radiation was undertaken. The patient is being closely followed. This case is unusual due to (1) late presentation, (2) extensive spread from the posterior fossa into the spinal canal with apparent drop metastases, and (3) a novel BRAF fusion.
Spectrum of Intracranial, Bone, Hematopoietic, and Extracranial Neoplasms Presenting as a Skull-Based Lesion: Radiologic-Pathologic Correlation

Breann A. Zeches1, Rufus B Aderounmu2, K. Stuart Lee3, Jasmin Jo4, Marwan Majeed1, Regis G. Hoppenot3, Richard T. Dalyai3, Philip J. Boyer1

1Department of Pathology and Laboratory Medicine, East Carolina University, Greenville, NC
2Brody School of Medicine, East Carolina University, Greenville, NC
3Vidant Neurosurgery, Greenville, NC
4Department of Internal Medicine, East Carolina University, Greenville, NC

Background: A wide range of lesions can be identified in association with the skull, presenting variably with neurologic symptoms, scalp pain and tenderness, and / or a palpable lesion. This study illustrates the spectrum of skull lesions seen at a single academic medical center.

Methods: Skull-based lesions evaluated during the past seven years were compiled. A PubMed and Google literature search was undertaken.

Results: A total of 30 lesions associated with the skull, from patients evaluated at our institution were selected as representative of the range of disease processes seen at this medical center. Ages ranged from from 9 months to 78 years with four lesions identified in children and the remainder identified in adults. Intracranial lesions invading the bone consisted of meningioma variants, both presenting as large dura-based, extraaxial lesions and en plaque and osseous variants not recognized as meningiomas radiologically and included World Health Organization grade 1 and 2 neoplasms. Hematopoietic neoplasms involving the skull included Langerhans cell histiocytosis, histiocytic sarcoma, multiple myeloma, plasmacytoma, and diffuse large cell B-cell lymphoma. Skull-based lesions included epidermoid cyst, hemangioma, fibrous dysplasia, osteoma, osteosarcoma, chondrosarcoma, and chordoma. Metastatic lesions included those originating from neuroblastoma, lung, liver, and rectum. Sinus-based lesions invading the skull included squamous cell carcinoma and Ewing sarcoma. Skin-based lesions invading the skull including nuchal fibroma with metaplastic ossification and squamous cell carcinoma. A literature review identified several radiology reports summarizing and illustrating radiologically the range of skull-associated lesions and a summary of primary skull lesions in the pediatric population, but no report providing a comprehensive review of skull-associated lesions with radiologic and pathologic illustrations and correlations was identified.

Conclusions: This study provides a comprehensive illustration and review of the wide range of neoplasms that can occur in association with skull. It emphasizes the need for clinical-radiologic-pathologic correlation on such lesions and the challenges in generating the differential diagnosis clinically, prior to histologic evaluation.