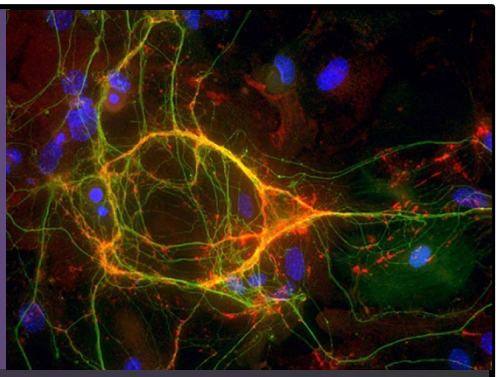
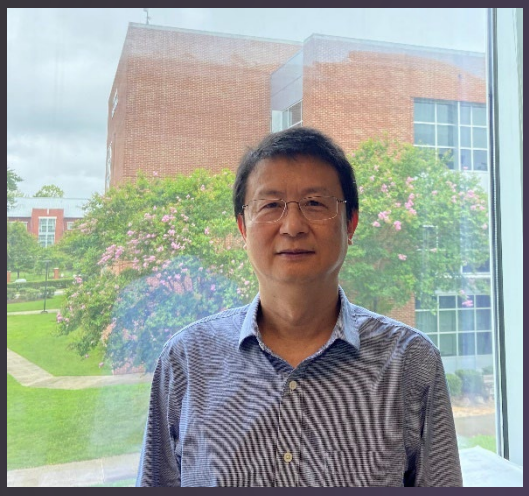
Eastern Carolina Chapter of the Society for Neuroscience Presents:



26th Annual Neuroscience Symposium



Featuring:

Bin Xu, PhD

Principal Investigator | BRITE Research Institute
Associate Professor of Pharmaceutical Sciences at North Carolina Central University

"Translational Neuroscience: Early Alzheimer's Disease Diagnosis and Aging-Related Inhibitor Discovery"

Thursday, October 31st, 2024
East Carolina Heart Institute
eccsfn.ecu.edu

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The Eastern Carolina Chapter of the Society for Neuroscience would like to express its sincere gratitude to the following sponsors for their generous support of this year's symposium:

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26th Neuroscience Symposium Event Schedule
Thursday, October 31st, 2024

9:00-3:00 **Check-In / Walk-In Registration**

9:00-10:00 **Breakfast and Chat with Keynote Speaker:** Bin Xu, PhD
(for students, postdoctoral fellows, and medical students/residents)

10:00-10:05 **Opening Remarks:** Tuan Tran, PhD, ECCSfN Interim President

10:05-10:55 **Podium Talks** (10 min each, including time for questions)
10:05-10:15 Drew Theobald
10:15-10:25 Jonathan Carver
10:25-10:35 Carrie Adams
10:35-10:45 Abigahill Simon
10:45-10:55 Natalie Clark

10:55-11:05 **Break**

11:05-11:50 **Keynote Address:** Bin Xu, PhD, Principal Investigator at the BRITE Research Institute and Associate Professor of Pharmaceutical Sciences at North Carolina Central University
"*Translational Neuroscience: Early Alzheimer's Disease Diagnosis and Aging-Related Inhibitor Discovery*"

12:00-12:45 **Lunch** (courtesy of our sponsors)

12:00-12:30 **VWR /Avantor**

12:45-2:25 **Guest Faculty Presentations**
12:45 – 1:30 **Leon Coleman, Jr, MD/PhD, UNC-Chapel Hill**
"*The Role of Microglia and Extracellular Vesicles in Behavioral and Neurobiological Pathology in Alcohol Use Disorder*"

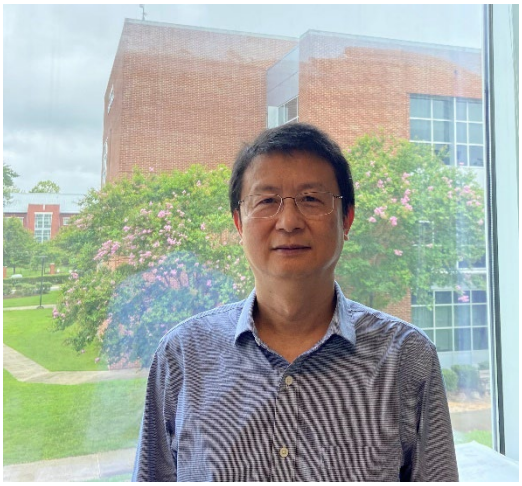
1:40 – 2:25 **Richard Lamb, PhD, University of Georgia**
"*Prediction of Student and Client Cognitive Status Using Neurological and Machine Learning Technologies*"

2:35-3:45 **Poster Session**

3:55-4:15 **Closing Remarks and Awards:** Tuan Tran, PhD, ECCSfN Interim President

Invited Talks

(in order of appearance)



Translational Neuroscience: Early Alzheimer's Disease Diagnosis and Aging-Related Inhibitor Discovery

Bin Xu, PhD
Principal Investigator | BRITE Research Institute
Associate Professor of Pharmaceutical Sciences at North Carolina Central University

Dr. Xu is also faculty Co-Director of the Neurobehavioral Core at NCCU and an affiliated faculty at the Duke-UNC Alzheimer's Disease Research Center. After earning his PhD in Biomedical Sciences at Case Western Reserve University School of Medicine, Dr. Xu did a postdoctoral research fellowship at Fred Hutchinson Cancer Research Center. Prior to joining BRITE of NCCU, he was a faculty of Biochemistry and Neuroscience at Virginia Tech. His research group focuses on translational aging research, in particular, Alzheimer's disease biomarker discovery for early diagnosis, and drug discovery for Alzheimer's and diabetes-induced neurodegeneration.

The Role of Microglia and Extracellular Vesicles in Behavioral and Neurobiological Pathology in Alcohol Use Disorder

Leon G. Coleman, Jr, MD/PhD
Assistant Professor
Department of Pharmacology
The University of North Carolina at Chapel Hill

After completing his graduate training, Dr. Coleman completed two years of general surgery residency followed by a postdoctoral fellowship where he studied the role of central and peripheral immune signaling in pathology associated with alcohol use disorder and severe burn injury. His research goal is to identify novel therapeutic targets for immune-related conditions such as alcohol use disorder, Alzheimer's disease, cancer, and trauma.

Prediction of Student and Client Cognitive Status Using Neurological and Machine Learning Technologies

Richard Lamb, PhD
Associate Professor
Department of Physiology and Pharmacology and
Department of Clinical and Administrative Pharmacy in the
College of Veterinary Medicine and College of Pharmacy
University of Georgia

Dr. Lamb is currently the director of the Neurocognition Science Laboratory at the University of Georgia. He earned his PhD from George Mason University, College of Education and Human Development in 2013 in Science Education and Measurement. His research focuses on the identification of cognitive markers of learning, increasing efficacy and performance of information processing, and cognition using novel technologies such as machine learning and artificial intelligence in digital environments.

Podium Talk Abstracts

(listed by presenting author in alphabetical order)

Effects of Social Dominance on the Morphological and Functional Activity of the Diencephalic Posterior Tubercular Nucleus

Carrie L Adams, Feliciti Gunter, Fadi A Issa

Department of Biology, East Carolina University, Greenville, NC

Social dominance is prevalent among many social species. It allows animals to allocate limited resources according to social rank. However, social interactions during dominance formation are accompanied with aggression, anxiety and stress that may have significant impact on brain structure and function. However, our understanding of the neurophysiological consequences of social dominance remains poorly understood. Here we examined the effects of social dominance on the morphological and functional organization of the diencephalic Posterior Tubercular Nucleus (PTN) in zebrafish (*Danio rerio*). The PTN is dopaminergic and is implicated in modulating motivated behaviors and spinal motor circuits (startle escape and swim). Moreover, the zebrafish brain organization shares many of the mammalian brain organization, and they form stable dominance relationships with easily identified dominant and subordinate individuals. Thus, zebrafish are suitable organisms to study the neurobiological bases of social dominance. Here we show social status-dependent differences in PTN cell number and cellular activity. Dominant animals display a higher number of PTN cells compared to subordinates and communal (control) fish. Similarly, dominants' PTN cells show higher biochemical activity compared to subordinates. These differences emerge between 7-14 days of social interactions. To examine the neural bases underlying morphological differences, we are testing the hypothesis that plasticity in PTN cell number is due to either neurogenesis by measuring expression in BrdU and PCNA activity, shift in cell neurotransmitter identity using genetic approaches, or an increase in cellular death because of apoptosis or elevated levels of oxidative phosphorylation. Preliminary results in communal animals demonstrate that PTN cells display enhanced levels of neurogenesis and oxidative phosphorylation suggesting that the PTN could be prone to socially induced cellular plasticity. However, our results do not show significant differences in a shift in cellular identity in socially dominant and subordinate fish. Results from this project provide new insights to help us understand the neural bases of social dominance on nervous system function the neurobiological principles of which might also be applicable to other social species.

Autoimmune Demyelination Alters Hypothalamic Transcriptome and Disrupts Lipid Metabolism in Endocrine Glands

Jonathan J. Carver, Kristy M. Lau, Bryce A. Pugh, Alexandra E. Puckett, Alessandro Didonna

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

Multiple Sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) causing focal demyelination, cognitive and affective changes, and long-term neurodegeneration. Disturbances in neuroendocrine signaling have also been consistently documented in MS patients and include hypercortisolemia, enlarged adrenal glands, and reduced ovarian reserve. These findings may underlie common disease symptoms including MS-associated fatigue and depression, which are frequently rated as the most debilitating symptoms of MS. To provide mechanistic insights into neuroendocrine disturbance in MS, we employed the MOG35-55/C57Bl6 experimental autoimmune encephalomyelitis (EAE) paradigm to characterize hypothalamic and endocrine phenotypes during autoimmune demyelination. Using unbiased RNA-seq technology, we found that EAE disrupted hypothalamic endocrine axes and altered expression levels of important neuropeptides during both pre-onset and acute phases of the disease. Notably, EAE drove higher expression of arginine-vasopressin (HPA-axis) and lower expression of kisspeptin (HPG-axis) during the acute phase of the disease. Additionally, serum levels of gonadotropic hormones were significantly lower in EAE mice. In the adrenals, EAE caused cortical hyperplasia and expansion of both zona glomerulosa and zona fasciculata cell layers. These structural changes were mainly associated with perturbation in genes mediating monocarboxylic acid metabolism as revealed by RNA-seq profiling. Conversely, EAE caused atrophy of the ovaries along with lower number of viable follicles. RNA-seq analysis of ovarian tissue found genetic signatures associated with cholesterol metabolism. Genes involved in extracellular matrix degradation were also dysregulated upon disease—a molecular event which may underlie the degenerative process. Interestingly, PPARγ signaling signatures were conserved between adrenal glands and ovaries, suggesting shared signaling pathways affecting both organs. Altogether, the current work establishes the hypothalamus and endocrine glands as sites prone to dysregulation during autoimmune demyelination.

Understanding 4-Aminopyridine's Effects on Glial Cell Bridging Post-Spinal Cord Injury in a Regenerative Model

Natalie Clark, Karen Mruk

Brody School of Medicine, Department of Pharmacology and Toxicology, East Carolina University, Greenville, NC

Every year there are more than 15,000 new spinal cord injuries in the United States.[1] A complete spinal cord transection, characterized by a lesion through both the motor and sensory tracts, is one of the most devastating injuries. During the subacute and chronic phases of injury, glial cells in vertebrae species accumulate at the lesion site to provide a protective barrier through scar formation.[4] Although the glial scar is imperative in protecting against additional tissue loss, it blocks axon regeneration, causing additional loss of function. A powerful model that lacks this glial scar formation is the zebrafish (*Danio rerio*). Its genetic commonalities to humans and larval translucency make it one of the more resourceful models when studying new pharmacological therapeutics for spinal cord injury.[2] 4-Aminopyridine (4-AP) is a therapeutic that is inhibitory to voltage-gated potassium channels (Kv) allowing for increasing action potentials across demyelinated axons.[3] It is essential to understand 4-AP's therapeutic effect on glial cells and the zebrafish model allows a window to discover its role in glial cell proliferation, migration, and remodeling.

A complete spinal cord injury was performed on an *Tg(gfap:EGFP) x Tg(elavl3:mcherry)* transgenic zebrafish line five days post fertilization. On one day post injury (dpi), continuous dosing of E2 recovery buffer supplemented with either DMSO or 4-AP was given to transected zebrafish and uninjured zebrafish. Utilizing the Leica Thunder System, Z stack images were taken to analyze pixel intensity of the glial cell bridging to ensure a complete transection and progress of bridging.

Continuous dosing of 4-AP increased glial cell proliferation at the rostral side of the lesion site. The 4-AP zebrafish had narrower injury sites by the fifth day post injury. The DMSO zebrafish showed higher proliferation at the caudal side of the lesion site.

In closing, it was found that continuous dosing of 4-AP one day post injury enhances glial cell bridging, promoting regeneration of the spinal cord in the zebrafish model. Varying the dosing schedules and monitoring locomotion behaviors are needed to advance the knowledge of 4-AP's effects on regeneration after spinal cord injury.

Social Regulation of the Parathyroid Type II Neuropeptide System in Zebrafish *(Danio rerio)*

Abigahill Simon, Perla Morales, Fadi A Issa

Department of Biology, East Carolina University, Greenville, NC

Social dominance is prevalent among social species. It allows group members to divide limited resources according to social rank. However, social dominance is often accompanied by social stress and anxiety as animals fight for social dominance. However, the neurobiological mechanisms underlying social anxiety remain poorly understood. This project examines the physiological consequences of social dominance on the thalamic parathyroid system using zebrafish as a model organism. Zebrafish are social animals and form stable dominance relationships consisting of dominant and submissive fish. As with other vertebrate species, the parathyroid hormone type II (PTH2) expressing nucleus is in the thalamus, and it is involved in modulating social activity, and it plays an anxiolytic role during social interactions. However, the neurobiological mechanisms examining the role of PTH2 in information processing and stress induced by social dominance remain poorly understood. Here we examine the morphological and functional effects of social dominance on the thalamic PTH2 nucleus during two weeks of social interactions. We show that PTH2 neurons innervate the retinal ganglion cells suggesting potential modulation of visual sensory processing. Secondly, our results show that social dominance influence the number of PTH2 expressing cells: After one-week of social interactions the number of PTH2 cells is higher in dominants compared to subordinates and communals (control), but this difference is abolished after two-weeks of interactions. Thirdly, we show that the cellular activity of PTH2 neurons is significantly enhanced in dominants compared to subordinates after one-week of social interactions. Our results suggest that social interactions influence the parathyroid system, and socially dominant zebrafish are likely better in managing social stress as indicated in elevated numbers of PTH2 cell number and likely higher PTH2 release to serve as an endogenously released anxiolytic mechanism to cope with stressful social interactions.

PASC-Induced Exacerbation of Alzheimer's Disease is Mitigated through Kinin B1 Receptor Blockade

Drew Theobald[1], Shaw M. Akula[2], Jeffrey B. Eells[3], and Srinivas Sriramula[1]

[1]Department of Pharmacology and Toxicology
[2]Department of Microbiology and Immunology
[3]Department of Anatomy and Cell Biology, Brody School of Medicine at East Carolina University, Greenville, NC, USA.

Post-acute sequalae of SARS-CoV-2 infection (PASC), characterized by persistent symptoms three months following SARS-CoV-2 infection, has been implicated in the exacerbation of neurodegenerative diseases, including Alzheimer's disease. Evidence suggests that inflammatory and immune responses triggered by PASC may accelerate Alzheimer's disease like pathology through mechanisms involving tau phosphorylation and microglial activation. We previously showed that transient SARS-CoV-2 viral infection can increase kinin B1 receptor (B1R) expression in brain regions critical for neurocognition, enhance neuroinflammation, and cause persistent behavioral changes. However, the role of B1R in SARS-CoV-2-induced exacerbation of Alzheimer's disease like pathology remains unknown. In this study, we investigated the hypothesis that B1R blockade will reduce microglial activation and subsequent tau phosphorylation in a long-COVID model. K18-hACE2 mice were infected intranasally with saline (mock) or SARS-CoV-2 and treated with a B1R antagonist or vehicle for 28 days. SARS-CoV-2 infection triggered pro-inflammatory microglial activation, but B1R antagonism shifted them toward an anti-inflammatory state. Additionally, SARS-CoV-2 infection increased tau phosphorylation whereas B1R selective antagonism was able to attenuate this response, suggesting its potential in mitigating neuroinflammation and reducing Alzheimer's disease like pathology in PASC patients. These findings highlight the critical role of B1R in the neuropathological processes triggered by SARS-CoV-2 and suggest that B1R antagonism may offer a promising therapeutic strategy to reduce Alzheimer's disease like symptoms in PASC patients.

Research Poster Abstracts

(listed by presenting author in alphabetical order)

Investigation of Corticol Activation Following Covid-19 Infection

America Alfaro, Brittany Trotter, Nicholas Murray

Department of Kinesiology, East Carolina University, Greenville, NC

Background: When COVID-19 was introduced in 2019, and declared as a pandemic in March 2020, it was mainly known to target the respiratory and gastrointestinal tract, which caused slight flu-like symptoms to fatal situations (headache, myalgia, sore throat, nausea, vomiting, etc.). The purpose of this research is to assess the theta brain activity, which is related to cognition and behavior, of COVID-19 infection participants with prolonged symptoms (for over 4 weeks) to determine if oculomotor control is impaired, versus participants who have experienced symptoms but recovered from the infection (less than 4 weeks), and no history of COVID-19 infection. Additional comparisons were made between long COVID-19 participants and those that experience mTBI's.
Methods: Participants were divided into 3 groups based on COVID-19 infection history- participants with no history of infection CONTROL (n=13), participants with prolong symptoms LONG (n=14), and participants with symptoms resolved in a brief period ACUTE (n=16). They were assigned to complete 6 eye-tracking tasks that were done in virtual reality, using the HTC VIVE headset with an embedded TOBII Pro infrared eye-tracking. Participants were fitted with a dry 32-channel g.NAutilus wireless EEG cap, using 10-20 configuration, and g.Recorder software to record neural activity at a sampling rate of 500 Hz.
Results: There was a significant difference in performance of circular smooth pursuit (CSP) task and horizontal smooth pursuit (HSP) task. LONG and CONTROL ($p<0.001$; $p<0.001$) and LONG and ACUTE ($p<0.05$; $p<0.05$).
Conclusions: Individuals that experience COVID-19 infection present an increase efficiency of performance for tasks than individuals that experience no history of infection. As theta brain neural activity may implicate in learning and memory.

Acute Artery of Percheron Infarction: A Case Report Highlighting Diagnostic Challenges and Management

Nathan Barefoot[1], Hayley Behm[1], Andrew R. Cunningham[1], Andrew W. Ju[2], Matthew S. Peach[2]

[1]Brody School of Medicine, East Carolina University, Greenville NC
[2]Department of Radiation Oncology, East Carolina University, Greenville NC

Background: The thalamus receives its vascular supply primarily from the posterior cerebral artery (PCA) and posterior communicating artery (PComA). The paramedian thalamic territory is typically supplied by multiple paramedian arteries originating from the PCA's P1 segment. However, in rare instances, a single Artery of Percheron (AOP) from one P1 segment can supply the bilateral paramedian thalamus and rostral midbrain. AOP infarcts, though rare (0.1% to 0.6% of all ischemic strokes), present with variable symptoms and pose challenges for early diagnosis due to limitations of conventional imaging.

Objective: To report a case of an AOP infarct in a patient presenting with acute encephalopathy and highlight the diagnostic and management challenges associated with this rare vascular anomaly.

Case: A 58-year-old male with a history of ischemic stroke and other comorbidities presented with unresponsiveness and a Glasgow Coma Scale (GCS) score of 8. The patient exhibited profound unresponsiveness and neurological deficits, with initial CT and CTA failing to identify an acute ischemic event. MRI performed on hospital day one revealed a bilateral median thalamic and left midbrain ischemic pattern consistent with an AOP infarct. Despite the delayed diagnosis precluding thrombolytic therapy, the patient showed gradual clinical improvement. On hospital day two, the patient's responsiveness and motor function began improving, but he subsequently developed right-sided weakness and ptosis. Repeat CT without contrast demonstrated no acute changes. The patient was discharged to a skilled nursing facility on hospital day 15. While his encephalopathy had improved, he had residual dysphagia, unintelligible speech, and required assistance with his activities of daily living.

Conclusion: This case underscores the diagnostic difficulty of AOP infarcts due to their atypical presentation and the limitations of early imaging modalities. The variability in clinical presentation necessitates a high index of suspicion and use of advanced imaging techniques for timely diagnosis. Early recognition and tailored management are crucial for optimizing patient outcomes in cases of rare cerebral vascular anomalies. OBJ

Sulforaphane Protects Developing Neural Networks from VPA-induced Synaptic Alterations

R. Bessetti[1], R. Lilley[1], N. Johnson[1], D. Perez[1], V. Koonce[1], M. Cobb[1], K. McCoy[2], K. Litwa[1];

[1]Anatomy and Cell Biology, East Carolina University, Greenville, NC
[2]Harbor Branch Oceanographic Institute, Florida Atlantic University, Fort Pierce, FL

Pregnant women frequently encounter chemical and environmental factors that can significantly impact brain development and increase the likelihood of neurodevelopmental disorders in their offspring. For example, fetal exposure to the anti-epileptic drug valproic acid (VPA) increases the risk of human offspring developing an autism spectrum disorder and similarly leads to autism-like behaviors in rodent models. At a cellular level, VPA increases oxidative stress, altering neural differentiation and synapse development. In our present study, we hypothesized that upregulation of cellular antioxidant defense mechanisms would prevent VPA-induced synaptic alterations in developing neural circuits. To address this hypothesis, we used phytochemical sulforaphane (SFN) to promote cellular antioxidant defenses. SFN potently induces NRF2-mediated transcription of cytoprotective and antioxidant genes. SFN binds to the ubiquitin ligase, KEAP1, preventing NRF2 proteasomal degradation and resulting in NRF2 nuclear translocation and transcriptional activity. Thus, we tested whether SFN-mediated increases in NRF2 activity could prevent VPA-induced oxidative stress and subsequent synaptic alterations. We exposed human neural progenitor cells, human cortical spheroids and primary mouse neurons to VPA alone, VPA with SFN, SFN alone, or a solvent control to investigate SFN's neuroprotective effects in a VPA-induced autism model. Our results demonstrate that SFN significantly enhances NRF2 nuclear translocation, leading to the upregulation of mRNAs associated with antioxidant pathways and synaptic structural integrity. Consistent with these gene expression changes, SFN prevents VPA-induced oxidative stress and protects developing synapses in both human cortical spheroids and primary mouse neurons. Our results reveal neural network maturity influences the susceptibility of developing neural networks to VPA, and SFN alleviates VPA-induced disruptions in neural activity in primary mouse neurons with synchronized network activity. Our study provides compelling evidence for SFN's ability to prevent early VPA-induced synaptic alterations. In conclusion, our results reveal molecular signatures of SFN-mediated neuroprotection that could be relevant for protecting the developing fetal brain from other chemical and environmental contaminants.

Autoimmune Demyelination Alters Hypothalamic Transcriptome and Disrupts Lipid Metabolism in Endocrine Glands

Jonathan J. Carver, Kristy M. Lau, Bryce A. Pugh, Alexandra E. Puckett, Alessandro Didonna

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

Multiple Sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) causing focal demyelination, cognitive and affective changes, and long-term neurodegeneration. Disturbances in neuroendocrine signaling have also been consistently documented in MS patients and include hypercortisolemia, enlarged adrenal glands, and reduced ovarian reserve. These findings may underlie common disease symptoms including MS-associated fatigue and depression, which are frequently rated as the most debilitating symptoms of MS. To provide mechanistic insights into neuroendocrine disturbance in MS, we employed the MOG35-55/C57Bl6 experimental autoimmune encephalomyelitis (EAE) paradigm to characterize hypothalamic and endocrine phenotypes during autoimmune demyelination. Using unbiased RNA-seq technology, we found that EAE disrupted hypothalamic endocrine axes and altered expression levels of important neuropeptides during both pre-onset and acute phases of the disease. Notably, EAE drove higher expression of arginine-vasopressin (HPA-axis) and lower expression of kisspeptin (HPG-axis) during the acute phase of the disease. Additionally, serum levels of gonadotropic hormones were significantly lower in EAE mice. In the adrenals, EAE caused cortical hyperplasia and expansion of both zona glomerulosa and zona fasciculata cell layers. These structural changes were mainly associated with perturbation in genes mediating monocarboxylic acid metabolism as revealed by RNA-seq profiling. Conversely, EAE caused atrophy of the ovaries along with lower number of viable follicles. RNA-seq analysis of ovarian tissue found genetic signatures associated with cholesterol metabolism. Genes involved in extracellular matrix degradation were also dysregulated upon disease—a molecular event which may underlie the degenerative process. Interestingly, PPARγ signaling signatures were conserved between adrenal glands and ovaries, suggesting shared signaling pathways affecting both organs. Altogether, the current work establishes the hypothalamus and endocrine glands as sites prone to dysregulation during autoimmune demyelination.

Understanding 4-Aminopyridine's Effects on Glial Cell Bridging Post-Spinal Cord Injury in a Regenerative Model

Natalie Clark, Karen Mruk

Brody School of Medicine, Department of Pharmacology and Toxicology, East Carolina University, Greenville, NC

Every year there are more than 15,000 new spinal cord injuries in the United States.[1] A complete spinal cord transection, characterized by a lesion through both the motor and sensory tracts, is one of the most devastating injuries. During the subacute and chronic phases of injury, glial cells in vertebrae species accumulate at the lesion site to provide a protective barrier through scar formation.[4] Although the glial scar is imperative in protecting against additional tissue loss, it blocks axon regeneration, causing additional loss of function. A powerful model that lacks this glial scar formation is the zebrafish (*Danio rerio*). Its genetic commonalities to humans and larval translucency make it one of the more resourceful models when studying new pharmacological therapeutics for spinal cord injury.[2] 4-Aminopyridine (4-AP) is a therapeutic that is inhibitory to voltage-gated potassium channels (Kv) allowing for increasing action potentials across demyelinated axons.[3] It is essential to understand 4-AP's therapeutic effect on glial cells and the zebrafish model allows a window to discover its role in glial cell proliferation, migration, and remodeling.

A complete spinal cord injury was performed on an *Tg(gfap:EGFP) x Tg(elavl3: mcherry)* transgenic zebrafish line five days post fertilization. On one day post injury (dpi), continuous dosing of E2 recovery buffer supplemented with either DMSO or 4-AP was given to transected zebrafish and uninjured zebrafish. Utilizing the Leica Thunder System, Z stack images were taken to analyze pixel intensity of the glial cell bridging to ensure a complete transection and progress of bridging.

Continuous dosing of 4-AP increased glial cell proliferation at the rostral side of the lesion site. The 4-AP zebrafish had narrower injury sites by the fifth day post injury. The DMSO zebrafish showed higher proliferation at the caudal side of the lesion site.

In closing, it was found that continuous dosing of 4-AP one day post injury enhances glial cell bridging, promoting regeneration of the spinal cord in the zebrafish model. Varying the dosing schedules and monitoring locomotion behaviors are needed to advance the knowledge of 4-AP's effects on regeneration after spinal cord injury.

Rearing Conditions Effect on Larval Zebrafish Thigmotaxis During the Visual Motor Response Test Assay

Lawson Cross, Karen Mruk

Department of Pharmacology and Toxicology, Brody School of Medicine, Greenville, NC

The visual motor response test (VMRT) has been used to induce thigmotaxis in larval zebrafish in past research. Thigmotaxis can be described as "wall hugging" where the larval zebrafish tends to stay on the outer wall of the well it is placed in. Thigmotaxis is used as an anxiety assay because larval zebrafish have been shown in past research to produce thigmotaxic behavior in times of stress. The VRMT induces anxiety and thigmotaxis due to the unexpected shift from complete light to complete darkness using the zebrafish behavioral box. This experiment tested whether rearing (housing) conditions affected the larval zebrafish thigmotaxic response to the VRMT. It was hypothesized that the individually housed larvae would have more thigmotaxis because zebrafish are social animals. I found that there was no significant difference between thigmotaxic behavior between individually housed versus group housed larval Zebrafish.

Modulating Social Perception: The Effects of tDCS on Sarcasm Interpretation in the Right Temporo-Parietal Junction

Peyton Disser[1,6], Essence Hopkins[2,6], Ke'Asia Craig [3], Anna Abernathy[1,6], Moritz Dannhauer[4,6], & Kathrin Rothermich[5,6]

[1]Department of Biology, East Carolina University, Greenville, NC
[2]Department of Multidisciplinary Studies, East Carolina University, Greenville, NC
[3]Department of Psychiatry, Virginia Commonwealth University, Richmond, VA
[4]Department of Computer Science, East Carolina University, Greenville, NC
[5]Department of Communication Sciences and Disorders, East Carolina University, Greenville, NC
[6]Center for Brain Stimulation, East Carolina University, Greenville, NC

We are currently investigating the relationship between the engagement of the right temporoparietal junction (rTPJ), and the ability to understand nonliteral language, such as sarcasm and teasing. The rTPJ has been shown to play a critical role for processes that underlie verbal irony perception, for example theory of mind (ToM) and cognitive empathy. Transcranial direct current stimulation (tDCS) has been used to explore the role of the rTPJ in social cognition, and results show that cathodal stimulation of the rTPJ leads to decreased accuracy in ToM and empathy tasks. However, the exact role of the rTPJ in social language processing is still being investigated. Previous studies have often used still images or written materials, ignoring the dynamic nature of face-to-face interaction. To accurately investigate the dynamic perception of interactions, we use 96 videos of people engaging in conversation, using forms of positive and negative verbal irony, sarcasm, and sincerity. The participants' task is to decide if somebody is being sarcastic, uses teasing, or is being literal (% accuracy as outcome measure). Cathodal stimulation is used in this study to slow activity of the rTPJ, therefore, we will also measure reaction time as an indicator of task efficiency. Before participants are performing the task, we inhibit brain activity in the rTPJ using cathodal tDCS (15 minutes of either 1.5 mA or sham). As the participants are watching the videos, we record eye tracking behavior to be able to better quantify how brain stimulation influences the processing of these complex social scenes. Participants also fill out questionnaires pertaining to certain aspects of their personality, anxiety, empathy, psychopathy, and sarcasm use. Current study results revealed that after receiving tDCS, reaction time is slower in videos that display blunt interactions [N=15] when compared to the sham condition. We are currently testing more participants [N=30] to shed light on the relationship between the rTPJ and the perspective of social aspects of language. In the future, we would also like to test clinical populations that exhibit social cognitive deficits, such as people with Autism Spectrum Disorders, Schizophrenia, or Parkinson's Disease.

STORMing the Synapse: A Developmental Timeline of Synapse Formation in Autism Spectrum Disorders

Kara DuBois[1], Riley Bessetti[2], Michelle Cobb[3], Dr. Karen Litwa[3]

[1]Department of Neuroscience, East Carolina University, Greenville, NC
[2]Brody School of Medicine Department of Anatomy and Cell Biology, East Carolina University, Greenville, NC
[3]Department of Anatomy & Cell Biology; East Carolina Diabetes and Obesity Institute, East Carolina University, Greenville, NC

Synapses mediate communication between neurons of the brain. This communication supports cognitive functions, such as learning and memory formation. Synaptic alterations contribute to numerous neurodevelopmental disorders, including autism spectrum disorders.

The Litwa Lab uses human brain models to research the molecular mechanisms of synapse formation. Using these human brain models, they can visualize the development and maturation of individual synapses. Closer association of pre- and post-synaptic compartments reflects synaptic strengthening; however, it is unknown whether initial events in synapse strengthening are altered in autism spectrum disorders.

In our present study, it is hypothesized that autism brain models will express weaker association between pre- and post-synaptic compartments as measured by proximity of pre- and post-synaptic compartments when compared with neurotypical models. Immunostaining and STORM super-resolution microscopy were used to visualize and analyze individual synapses between human neurons. Specifically, primary antibodies were used to detect pre-synaptic protein VGLUT1 and post-synaptic protein PSD95, followed by detection with fluorescently labeled secondary antibodies. STORM super-resolution imaging has allowed us to acquire the position of thousands of individual pre- and post-synaptic molecules and measure the proximity of the pre- and post-synaptic compartments at developing synapses after 25, 43, 71, and 98 days of differentiation of the human brain model. It will be assessed whether the distance between pre-synaptic and post-synaptic compartments differs from the developmental timeline established in control patient brain models, where we observed closer spatial proximity of pre- and post-synaptic compartments with longer developmental time.

These studies will address whether initial events in synapse formation are altered in developing neural circuits of autistic individuals, allowing us to assess whether interventions at specific periods can restore normal synapse formation and neural communication.

The Optimization of Golgi-Cox Staining in Parallel with Immunofluorescence to Colocalize the Adhesion Protein, N-Cadherin, to Developing Synapses

Victoria Frank[1], Karen Litwa[2]

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Golgi staining is an old methodology with relies on the interaction between Silver Nitrate, Potassium Chromate, and Potassium Dichromate to produce a black substance which binds to a limited number of neurons in brain tissue. It was developed in 1873 by Camillo Golgi and was modified in 1891 by W. H. Cox by adding Sodium Thiosulfate, Ammonia and Mercuric Chloride. In this new variant, a metallic salt is formed and theorized to bind to the neurons to visualize them. This new technique is more consistent and provides better visualization of the dendritic spines than the original technique. The actual mechanism of how this process occurs though is unknown. In this study our purpose is to combine this methodology in parallel with immunofluorescence to correlate adhesion proteins with the different dendritic spine morphologies. Dendritic spines are key to forming synapses and there are adhesion proteins that are implicated in their stabilization and maturation during synaptogenesis. It is our goal to see what morphologies SynCAM, Neuroligin-1, and N-Cadherin favor in developing mice. In this study we used E18.5 and P17 CD-1 mice. The gender was also determined at E18.5 using a novel technique that relies on phenotypic differences in genitals to differentiate the males and females. The brain tissue was harvested from the mice and not prefixed. The tissue was then transferred to a Golgi-Cox solution containing 5% Potassium Chromate, 5% Potassium Dichromate, and 5% Mercuric Chloride in deionized water for 2 weeks at 4°C. After impregnation the tissue was sliced at 100μm on a cryostat then developed with 10% Ammonia and 0.5% Sodium Thiosulfate. Gelatin coated slides were prepared and used for mounting, with the tissue being coverslipped with Fluromount gel. For the immunofluorescence pathway tissue blocks were immersed in cryoprotectant solution for at least 3 days after a 48hr prefix in 4% formaldehyde at 4°C. Tissue blocks were flash frozen in 2-methyl butane before sectioning. Tissue blocks were sectioned on a cryostat at 25μm and mounted onto superfrost slides. The tissue sections were first photobleached for 4hrs under a white LED light then blocked for 2hrs at room temp with 5% Goat Serum. Primary antibody incubation occurred at 4°C for 48 hours, was washed blocked a second time with a Mouse-on-Mouse lab kit to prevent non-specific staining with the mouse secondary antibodies. The secondary antibodies were incubated with the tissue sections for 2 hours at room temperature then coverslipped. An Olympus FV1000 microscope was used to image the immunofluorescence and a light microscope for the Golgi-Cox stain. The Neurolucida program was also utilized to analyze dendritic morphology as well as develop 3D models of the neurons. The current results were successful for the use of the Golgi-Cox stain and immunofluorescence. The optimized methodology can now be applied to future studies by the Litwa lab in investigating the effects ASD has on the brain throughout the human lifespan.

SK1 Is Upregulated Following Spinal Cord Injury in Zebrafish Affecting Recovery and Regeneration

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Spinal cord injury affects a large population of people annually, however, there has been little progress for patients for improving their recovery. Small conductance calcium-activated potassium channels (SK) are activated by an increase in cytosolic Ca^{2+} and determine the hyperpolarization following an action potential, in turn affecting the firing rate. They have been indicated to be involved in spinal cord injury and there has been progress with recent studies in zebrafish, but they are still understudied. Therefore, we sought to determine whether SK channels are involved in recovery and/or regeneration after spinal cord injury. Are SK channels differentially expressed after spinal cord injury, and if so, where? To answer these questions, we used whole mount in situ hybridization, RT-qPCR, and behavioral tracking. We found that expression of SK1 mRNA was upregulated following spinal cord injury and that administering a channel activator and inhibitor affected behavior differently.

Breaking Barriers: Innovating and Advocating for Inclusive Brain Health Research in North Carolina

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Background: Diverse representation in brain health research is essential to understand the effects of memory disorders in marginalized communities. It is imperative that researchers make efforts to include diverse populations, along with residents of rural areas and other underrepresented groups, in brain health research initiatives. Partners from the statewide NC Registry for Brain Health assessed Registry participant demographics stratified based on rural/urban classifications and participation levels in brain health research.
Methods: Data was collected across five NC sites. Rurality was determined by address or zip code. Descriptive characteristics are presented analyzed by rurality and ethno-racial groups.
Results: The NC Registry has 12,297 participants; 92% have residential data available. Of these, 17% (n=1,889) are from rural areas, and 83% (n=9,456) are from urban areas. Regardless of rurality, most (76%) participants are ≥60 years of age, 13% have a ≤12th grade education, and most participants are female (77% urban and 73% rural). Overall, the urban group had higher diversity (30% Black, 4% Hispanic) than the rural group (23% Black, 2% Hispanic). Most NC Registry participants were invited to participate in at least one research study (86% urban and 84% rural); however, only 4% urban and 3% rural participated.
Discussion: The NC Registry has majority urban, female, and senior membership, with some demographic differences appreciated between urban and rural members. Participation rates in Registry-affiliated studies were similar. Future efforts will focus on understanding who is participating in brain health research and exploring potential factors influencing research accessibility and engagement levels across the state.

The Perception, Judgement, and Justification of SSRI Usage

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Selective serotonin reuptake inhibitors (SSRIs) are a class of drugs utilized as antidepressants to manage symptoms of major depressive disorder, anxiety disorders, and other neurological disorders. Serotonin is the paramount "feel-good" neurotransmitter responsible for the regulation of emotion, sleep, appetite, memory, and even healing. Serotonin aids in effective communication and balance throughout the body. Serotonin is stored and released by vesicles into the synaptic cleft. After it has completed its communication upon its release, Serotonin is reabsorbed ("reuptake") by presynaptic vesicles. SSRIs work by increasing the extracellular levels of serotonin in the brain by limiting the reuptake process. This process allows for more serotonin to remain in the brain, thereby providing chemical balance to the system.

This study investigates college students' perception of SSRI usage. Undergraduate students 18+ were recruited from Psych 1000 course at ECU. To comprehensively assess the conditions of a 2x2 between subjects design, N=100 with the participants divided into two groups: control and manipulated.
The control group evaluates a scenario involving a veteran with post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI) treated solely with SSRIs, while the manipulated group assess a similar scenario with the addition of other treatments including psychotherapy, meditation, and focus groups. Both groups are provided with side effects and success of SSRIs. The aim is to determine whether students view SSRIs as a positive or negative solution, assess their perceived effectiveness based on provided data, and evaluate whether SSRIs should serve as a main or supplemental treatment option. Additionally, a proposed clinical experiment will investigate the impact of discontinuation of SSRI treatment and its neurological impact, focusing on serotonin production and brain activity alterations. This would determine whether organic serotonin production within the brain is adversely affected after cessation of SSRIs and determining the duration required for serotonin levels to return to pre-SSRI conditions.

This research addresses vital concerns of SSRI usage, considering the major increase of their usage among young adults following post-COVID mental wellness crisis. It ascertains the gap in population opinion-based surveys on SSRI usage, integrating results from memory studies, neurobiological mechanisms, and neuroanatomy.

Keywords: SSRIs, perception, judgment, PTSD, TBI, brain plasticity, neurobiological mechanisms, learning, memory, serotonin production, college students.

Angiotensin II-Induced Hypertension Triggers Pro-Inflammatory Microglial Activation and Morphological Alterations

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Microglia are the immune cells exclusive to the central nervous system and are crucial for maintaining brain homeostasis by responding to neuronal dysfunction, injury, and infection. Microglia undergoes functional and morphologic changes in the presence of a pathological stimulus. Upon activation, microglia can take on a pro-inflammatory phenotype and release reactive oxidative species (ROS) and inflammatory cytokines. Activation of inflammatory cytokines and ROS can exacerbate tissue damage in disease. In contrast, microglia can also undergo a phenotypic shift to an anti-inflammatory phenotype and elicit a neuroprotective response by releasing brain derived neurotrophic factor (BDNF). Although an acute inflammatory response is necessary, prolonged activation can lead to chronic inflammation and tissue damage, contributing to neurodegenerative processes and worsening disease states. Hypertension is an inflammatory condition characterized by peripheral immune activation that extends to the central nervous system. Therefore, we hypothesize that in a model of Angiotensin II-induced hypertension, microglia are activated and adopt a pro-inflammatory phenotype. In this study, we analyzed the morphological changes of microglia in the hypothalamic paraventricular nucleus (PVN), a brain region critical for cardiovascular control, using photomicrograph analysis techniques in ImageJ. Traditional ImageJ analysis techniques assess overall microglial activation, but they fail to capture detailed morphological alterations. Using ImageJ AnalyzeSkeleton (2D/3D) analysis techniques, we were able to quantify microglia morphology using soma area, end-point voxels, junction voxels, and slab voxels. In this study, we identified that in Angiotensin II-induced hypertension, microglia display a larger soma size, decreased branch length, and a reduction in the number of end point voxels compared to control, indicating microglial activation. This analysis technique offers insights into the role of microglia in the pathogenesis of hypertension and associated neuroinflammation.

Activity-Dependence of Synapse Stabilization in Developing Neural Circuits

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Synapses mediate information transfer in neural circuits of the brain and support cognitive functions, including learning and memory formation. Not surprisingly, synaptic alterations contribute to neurodevelopmental and neurodegenerative diseases. We are particularly interested in how synapses form and how this process is disrupted in neurodevelopmental disorders. Our current research focuses on the molecular mechanisms that enable post-synaptic spine precursors to initiate synapse formation with a pre-synaptic axon partner. Spine precursors are dynamic, actin-enriched membrane protrusions that form along the post- synaptic dendrite in a neuron. Spine precursors in the early developing brain will go on to mature into mushroom shaped dendritic spines in the adult brain. In our current research, we will address whether the presence of ionotropic glutamatergic receptors, NMDAR and AMPAR, within spine precursors increases the likelihood of synapse formation. We hypothesize that NMDARs, which are expressed early in development, promote synaptic stabilization and maturation in developing neural circuits. To test this hypothesis, we will use siRNA to reduce expression of *Grin1* (NMDARs) or *Gria1* (AMPARs) and assess the resulting expression of synaptic markers in both primary mouse hippocampal and cortical neurons. We will first examine whether spine precursors contain NMDAR and AMPAR through immunostaining for NMDAR or AMPAR together with doublecortin to identify neurons and Rhodamine Phalloidin to visualize actin-enriched spine precursors. I will analyze and quantify the percentage of actin-enriched spine precursors containing either AMPAR or NMDAR or both and determine whether these associations change throughout development. We will then assess whether siRNA-mediated knockdown of AMPAR or NMDAR impacts synapse formation by immunostaining for PSD-95 and synapsin. These studies will be instrumental in determining whether there is heterogeneity in the molecular composition of spine precursors. We will use these insights to inform future experiments where we will alter spine precursor composition and analyze the resulting impact to synapse formation and neuronal communication.

Live Imaging of the Inflammatory Response to Injury in Zebrafish

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Vertebrates vary widely in their regenerative capacity. Mammals have a more limited regenerative capacity, but other vertebrates possess a higher degree of regenerative capacity. While zebrafish on the other hand have this unique ability to regenerate after injury. To better understand the cause of these differences, we use the regenerative model zebrafish to study regeneration after injury. The purpose of this study was to begin to characterize the necessary inflammatory response to injury. As zebrafish can regenerate most of their body, two forms of injury were studied. The first type of injury studied was spinal cord injury (SCI). In SCI, zebrafish regenerate the spinal cord through glial bridging within 5 days post injury (dpi). For this portion of the study Tg(*gfap:egfp*) larvae were transected at 3 days post fertilization (dpf) and on the day of injury full transection of the spinal cord was confirmed. Each day after injury fish were imaged and collected for future analysis and a group of control, uninjured fish, were also imaged and collected in the same manner (n=5). The collected samples were used for qPCR analysis of the four different cytokines: *tgf-β1, tgf-β3, il-1β, and tnf-a,* in comparison to the housekeeping gene *gapdh.* Live imaging of the immune response in spinal cord injury is difficult due to the thickness of the tissue. To visualize the individual immune cell response to injury a different model of regeneration was used with a thinner tissue. This is the tail cut model; where the tail of Tg(*mpx:mCherry*) larvae at 2 dpf, (n=25) is cut off using a razor blade and 1 hour later imaged for neutrophil number compared to uninjured control fish (n=18). Interestingly, each cytokine was released at varying concentrations and times. This variation in response may be due to the progression of regeneration. The neutrophil number in the tail significantly increased after injury showing the importance and level of immune response needed for regeneration. Our study confirms that the immune response is beneficial for regeneration and that additional studies are needed to dissect out the pathways that promote a beneficial from harmful immune response after injury.

Arsenic Impairs Optic Vesicle Formation in a Cerebral Organoid Model

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Optic vesicle formation is a key step in the early eye development of embryos as it gives rise to the optic cup, which ultimately forms the retina. Signaling pathways that are vital to this process include Wnt/BMP, and IGF. Any disruption in this process of optic vesicle or optic cup formation can result in deficits in eye structure and eyesight. Modeling human eye development and function is challenging due to the complexity of the organ. However, brain organoids can be formed that mimic the early development of the eye, through a self-organization process, which forms an optic vesicle structure similar to what is seen in embryos. Arsenic is a metal that is present in water, soil, food, and air. Arsenic has been posited to impede the developmental process in embryos. Here we use a cerebral organoid kit to culture human induced pluripotent stem cells into cerebral organoids in 40 days to mimic early optic vesicle formation. This stage is vital due to it providing a prototype for vital anatomical eye structures. The 40-day organoid model was also ideal to mimic vital signaling pathways regulated during optic vesicle formation. In this study, organoids were treated with 0, 0.01, 0.1, and 1 μM sodium arsenite to determine its effect on optic vesicle formation and signaling pathway regulation. The 40-day organoids expressed optic vesicle marker proteins including VSX2 and PAX6. VSX2 plays a vital role in the production of retinal neurons. Increasing the level of arsenic exposure resulted in a comparable decrease in optic vesicle size. RNA sequencing analysis indicated a downregulation of genes vital to eye formation in the arsenic 0.1 μM exposure group compared to non-treated organoids. Genes that notably decreased include GAD2, DLX1, and DLX5. GAD2 is involved in regulating retinal cell signaling and metabolic processes. Both DLX1 and DLX5 are vital for craniofacial development and the development of GABAergic neurons. In summary, arsenic exposure is posited to impede the expression of vital transcription factors in eye development, which downregulates the associated genes and ultimately results in deficits in early eye formation.

*HLA-DRB1*04:01* has a Neuroprotective Role in a Mouse Model of Parkinson's Disease

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Background: Parkinson's Disease (PD) is the most common age-related motor neurodegenerative disease in North America. The pathological hallmarks of PD include death of dopaminergic neurons in the substantia nigra, mitochondrial dysfunction, neuroinflammation, and accumulation of abnormal α-synuclein (α-SYN) aggregates termed Lewy bodies. However, the underlying cause of PD remains elusive. A recent study sequencing the human leukocyte antigen (HLA) locus from 1,597 PD patients and 1,606 healthy controls found a strong genetic association between shared epitope (SE) containing *HLA-DRB1*04:01* allele and PD risk. The SE is a five amino-acid sequence (QKRAA) at position 70-74 in the beta chain of the HLA molecule that was previously identified as a risk factor for rheumatoid arthritis (RA). In the central nervous system, *HLA-DRB1* expression is restricted to the resident immune microglial cell population which has been implicated in PD pathology via α-SYN aggregate clearance.

Objective and Aim: The aim of this study was to investigate the genetic association between HLA alleles and PD protection using an *in vivo* animal model.

Methods: To better understand the mechanistic role of SE-HLA alleles in PD, we induced an acute model of PD pathology in transgenic mouse lines expressing *HLA-DRB1*04:01* and *HLA-DRB1*04:02* by injection of mouse α-SYN pre-formed fibrils. Mice were subjected to several tests to evaluate behavior changes, and their brains were later sectioned for immunohistologic analysis.

Results: The 04:01 mice had significantly less spread of α-SYN in the brain. The 04:01 mice had fewer total microglia yet higher levels of deramification leading to increased prevalence of amoeboid microglia, even in PBS injected animals. The behavior of the mice was found to be significantly different between 04:01 and 04:02 mice in a variety of tasks. Interestingly, this trend was still observed among the control PBS mice that had not been exposed to α-SYN.

Conclusion: Our results showed that the 04:01 allele causes increased microglial activation, neurocognitive changes in behavioral tasks, and protection against misfolded α-SYN spread. These findings provide us with an increased understanding of Parkinson's disease pathogenesis and lead us closer to improved options for prevention and treatment of PD.

Development of Novel Molecular Optogenetic Tools to Study Hirano Body Formation in Neurons

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Introduction and Objectives: Abnormal neuronal cytoskeleton dynamics is a common feature of neurodegenerative disorders including Alzheimer's disease (AD). Hirano bodies (composed of filamentous actin and actin-binding proteins) are neuronal inclusions associated with aging and universally present in the AD brain. This study focuses on understanding the involvement of actin-ATP interactions in cytoskeletal anomalies and their role in neuronal inclusion formation.

Materials and Methods: *DNA constructs:* Point mutations (G158L, S14V, K18A and D154A) were introduced into *Actin* in a pNic28 plasmid using site directed mutagenesis.
Primary neuron cultures and transfections: Dissociated cortical neurons were prepared from E18 mouse embryos (CD1) and cultured in 6-well plates with coverslips at 500K/ml density. Neurons were transfected with 5 μg plasmid/well on DIV5 using Lipofectamine LTX reagent.
Fixed neuron experiments: 48-72 hours post-transfection neuros were immunostained for MAP2 or tau.
Imaging: Confocal images were obtained on a Zeiss LSM 800 microscope with Airyscan.
Particle analysis: Images were analyzed using FIJI equipped with the BioFormats package.

Results: Distinct cytoskeletal phenotypes were associated with specific mutants. G158L and S14V lead to cofilin-actin rod phenotype with structural destabilization reminiscent of pathological actin-cofilin rods, while K18A and D154A exhibited large cluster phenotypes, similar to Hirano bodies. These results highlight the critical role of the actin-nucleotide binding pocket in regulating actin function.

Conclusions: This work provides insights into the role of actin-ATP interactions in cytoskeletal anomalies observed in neurodegenerative diseases and lays the groundwork for further biochemical characterization and potential therapeutic strategies targeting aberrant cytoskeletal dynamics.

Investigating the Role of Tuberous Sclerosis Complex in Synapse Formation

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Tuberous sclerosis (TS) is a genetic condition manifesting as non-cancerous tubers throughout the body, especially in the brain where they result in several neurodevelopmental disorders, including autism spectrum disorder (ASD). However, even when patient tubers are removed, neuropsychiatric symptoms do not fully recover. This is consistent with other research demonstrating neural autonomous effects resulting from loss of tuberous sclerosis complex (TSC) function. TS results from mutations in either the TSC1 or TSC2 gene, which form a complex to regulate mammalian target of rapamycin (mTOR), a major driver of cell growth and inhibitor of synaptic autophagy. However, early synaptic effects appear to be independent of mTOR activity, leading us to hypothesize that non canonical TSC pathways drive initial synaptic defects. To begin to address this hypothesis, we generated and characterized human induced pluripotent stem cells (hIPSCs) from a family with TS. To model the emergence of synaptic defects, we differentiated TS patient hIPSCs into human cortical brain spheroids (hCSs), which model fetal brain development and synapse formation. Our initial observations suggest that similar to idiopathic autism cases, TS-derived brain spheroids exhibit increased excitatory synapses. We used flow cytometry and real time reverse transcriptase-polymerase chain reactions (RT-PCR) to characterize cell populations in our hCSs. We observed decreased neural progenitor cell mRNA and protein, and increased expression of early neuronal markers, suggesting that accelerated neural differentiation may contribute to increased synapse formation. We have also optimized siRNA conditions to model TS in both human and mouse neurons to examine how loss of TSC siRNA specifically impacts synapse formation independent of neural differentiation. Our findings highlight novel TS-mediated defects in progenitor cell maintenance and a corresponding increase in neural differentiation. We have developed tools to examine how loss of TSC drives synaptic pathology at distinct stages in developing neural circuits.

Determining the Effects of Traumatic Brain Injury and Aging on Lipid Metabolism

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Traumatic brain injury (TBI) is a prominent health concern worldwide with varying recovery times depending on age. Although brain phospholipid (PL) content and aging significantly impact recovery, there has been no clear association between lipid metabolic control and aging in response to TBI. Dietary intake of the omega-3 fatty acid docosahexaenoic acid (DHA) promotes nervous system function and improves injury response and recovery. DHA is the most abundant polyunsaturated fatty acid (PUFA) in the brain, however, DHA content declines with aging, causing age-related cognitive and neuronal dysfunction. Reduced mRNA modulation in aged animals suggests that aging reduces the brain's ability to aggressively respond and repair following TBI. We discovered that in both young and aged mice, most lipid species changes occurred one month post TBI. DHA-containing PLs decreased during the month following injury while arachidonic acid-containing PLs increased, suggesting that dietary intake of DHA post injury may be a therapeutic target. We previously reported that long-chain acyl-CoA synthetase 6 (Acsl6) promotes membrane DHA enrichment in neurons across the life span. Furthermore, gene expression data confirmed that Acs enzymes were downregulated post injury. By analyzing genes critical for endogenous PUFA formation, we found that PUFA synthesis increased in both age groups, indicating that the conversion of precursor fatty acids into PUFAs is essential for restoring membrane lipid profiles after TBI at any age.

Investigating Microglial Abundance in Brains of Mice Exposed to Perfluorohexanoic Acid (PFHxA)

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Per- and polyfluoroalkyl substances (PFAS) are a large class of synthetic chemicals used in many industrial and consumer products. Their unique structure that provides chemical and thermal stability makes them highly desirable in products such as water- and stain-repellants, non-stick cookware, fire-fighting foams, and more. However, due to their widespread use, they have become environmental pollutants, including in the bodies of living organisms. In North Carolina, some of the PFAS that contaminate surface waters used as drinking water sources have not been studied for their toxicity. This is concerning as research on other PFAS has demonstrated that their exposure is linked to different types of toxicitites, including immunotoxicity and neurotoxicity. While the evidence of immunotoxicity in human populations and animal models is strong, data linking neurotoxicity is limited. Due to links between the immune and nervous systems, we hypothesized that microglia, resident immune cells of the central nervous system, would be modified by PFAS exposure at levels likely to impact other arms of the immune system. Adult male and female C57BL/6 mice were orally exposed to one of three doses of perfluorohexanoic acid (PFHxA) or a control for 30 days. One day after dosing ended, mice were humanely euthanized and brains were excised, weighed, and processed for embedding in paraffin. Brains were sliced at 10 μM on a rotary microtome starting with the pre-frontal/frontal cortices. Sections were stained immunohistochemically with anti-ionized calcium binding adaptor molecule (anti-Iba1) to identify microglia. Images of two regions of interest (ROIs)/slide were captured at 20X magnification. Relative staining intensity for all ROIs was determined with the Fuji plug-in for Image J and all microglia were counted in ROIs. Differences in numbers of microglia were observed in male brains, with males exposed to 0.5 mg/kg of PFHxA having more microglia than controls. Differences in staining intensity for microglia were observed in males across all doses, with 0.5 and 5 mg/kg of exposure having a higher staining intensity and 50 mg/kg of exposure having a lower staining intensity, relative to controls. These differences in microglial features suggest slightly higher microglial activity that may be linked to PFHxA-induced changes in the brain. Additional work to evaluate brains for inflammatory cytokines will help to clarify the functional impact of these changes.

A Novel Humanized TAU Mouse Model as a Tool to Develop Oligonucleotide Drugs for Alzheimer's Disease

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Introduction: TAU protein is known to play a crucial role in the progression of Alzheimer's disease. The accumulation of hyperphosphorylated tau proteins within cells forms neurofibrillary tangles that disrupt normal neuronal cell function and ultimately lead to Alzheimer's disease (AD).
Objectives: Given the pivotal role TAU protein plays in the pathophysiology of AD, there has been considerable interests in the development of TAU-targeting oligonucleotide drugs for treating AD. Therefore, it is essential to have scientifically appropriate mouse models for such research needs.
Results: We successfully developed a mouse model, B-hTAU, which expresses humanized TAU. We achieved this by editing the exons 2~10 of mouse Tau gene that encode the full-length protein and replaced them with human TAU exons 2~15. The 3'UTR region of the mouse gene is replaced by its human counterpart. The chimeric TAU expression is driven by endogenous mouse Tau promoter, while mouse Tau gene transcription and translation will be disrupted. Human TAU mRNA was detectable only in homozygous B-hTAU mice but not in wild-type littermates. In the B-hTAU mice, we detect all six isoforms (including both 3R and 4R forms) of human TAU gene present in human brain and confirmed by Sanger Sequencing. Human and mouse TAU protein expression was detectable in the brains of wild-type mice and homozygous B-hTAU mice due to cross-recognition of antibodies. Additionally, through collaboration we evaluate the inhibitory efficiency of nucleic acid drugs against human TAU in the B-hTAU mice. The human TAU-targeting nucleic acid drug or PBS were administered intracerebroventricularly to mice. And the mice were sacrificed after 7 days, the brains were collected for the detection of human TAU expression. Compared with control group, there is a significant decrease in both mRNA and protein levels of human TAU in the treatment group.
Conclusions: In summary, B-hTAU mice is a powerful preclinical model for in vivo evaluation of human TAU-targeting nucleic acid drugs.

Clinical Poster Abstracts

(listed by presenting author in alphabetical order)

X-Games Gone Wrong - the Nature and "Impact" of Acute and Repetitive Chronic Traumatic Brain Injury: Histopathologic Distinction between Diffuse Axonal Injury (DAI, Affecting White Matter) and Chronic Traumatic Encephalopathy (CTE, Affecting Cerebral Cortex)

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Background: Recognition of the adverse effects of traumatic brain injury, both immediate and long-term, has emerged during the past decade. We present the case of a young man with evidence of both acute and chronic traumatic brain injury at autopsy.

Methods and Materials: The clinical and neuropathologic autopsy findings seen in a young athlete are summarized. A literature review was performed using relevant key words.

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 diffuse axonal injury (DA() and (2) early-stage chronic traumatic encephalopathy (CTE).

Discussion: This highly informative case highlights and distinguishes between two related but anatomically and histopathologically distinct traumatic brain injuries and underscores the immediate and chronic effects of head trauma in a young athlete. DAI affects the white matter and results from axon damage, primarily within long white matter tracts, corpus callosum and ascending and descending brainstem axons. CTE affects the cerebral cortex and is now recognized as the long-term sequela of multiple traumatic head injuries, concussive and subconcussive, experienced over time. First recognized in boxers and football players, CTE has been demonstrated post-mortem in individuals who suffered repetitive traumatic injuries while playing hockey, soccer, and other sports. While severe cases of DAI can be recognized using radiologic imaging, definitive diagnosis of both subtle DAI and CTE can only be made at autopsy where histopathologic identification of damaged axons and abnormal accumulation of heat shock proteins (e.g. amyloid precursor protein) and phosphorylated tau protein within cortical neurons and axons and dendrites is noted, respectively.

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.

Metastatic Involvement of the Pituitary Gland: A Case Series

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Background: Pituitary metastasis (PM) from a systemic organ neoplasm is uncommon, representing less than 1% of intracranial metastases and 1% of pituitary neoplasms. Only a small proportion of cases are symptomatic with clinical manifestations including diabetes insipidus, visual deficits, cranial nerve deficits, hypopituitarism, and headache.

Methods: A 10-year retrospective review of our laboratory information system records for pituitary metastasis was undertaken. Patient medical records and pathology slides were concurrently reviewed. A literature review was undertaken.

Results: Seven PM cases were identified, 6 surgical resections, and 1 autopsy case, including 6 women and 1 man, with a median age of 66 years (range: 53 to 76). Four patients had a documented history of malignancy with lung primary most common (2 adenocarcinomas and 2 neuroendocrine carcinomas), followed by breast (1), kidney (1), and prostate (1). All lesions appeared to have metastasized to the anterior lobe of the pituitary. Radiologically, the lesions were described as "enlarged pituitary gland" or "sellar and suprasellar mass lesion" and pituitary adenoma was the favored clinical diagnosis. Notably, in the case of breast origin, the metastatic lobular carcinoma involved a pre-existing pituitary corticotroph adenoma.

Discussion: Distinction between PM and a pituitary adenoma, or PM to an adenoma, is not possible without histopathologic evaluation. Tumor-to-tumor metastasis is extremely rare in the pituitary, with fewer than 30 published cases, including 4 involving breast cancer. While metastasis is more common to the posterior lobe of the pituitary than the anterior lobe, all the neoplasms in this series appeared to have metastasized to the anterior lobe. When a patient presents with a pituitary mass and diabetes insipidus, PM should be considered in the differential diagnosis, especially in those with a history of malignancy. A better understanding of this uncommon metastatic site and high clinical awareness is necessary for a definitive diagnosis and appropriate treatment.

Brain Metastasis of Follicular Variant of Papillary Thyroid Carcinoma with Tall Cell Variant Features: Case Report and Literature Review

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Background: Thyroid carcinoma (TC) is the most prevalent endocrine malignancy and distantly metastasizes to the lung and bone. Histological subtypes of TC include papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), which are well-differentiated, and medullary thyroid carcinoma (MTC), a non-differentiated neuroendocrine tumor. PTC and FTC have prognoses that are more favorable than MTC. Metastasis of TC to the brain occurs in approximately 1% of patients, more likely in women. PTC is the most likely to metastasize to the brain; the median overall survival is 15.17 months after diagnostic findings of PTC with brain metastasis. Here, we present a patient with PTC of follicular variant (FV) with tall cell variant features (TCV) with brain metastases in two distinct regions.
Methods and Materials: The patient's clinical history, imaging studies, and laboratory testing were reviewed via the electronic medical record. A literature review was then conducted using the relevant key words.
Case Report: A 77-year-old woman with a past medical history of PTC of FV with TCV features underwent a thyroid resection on 12/3/2009 and was treated with radioactive iodine therapy (RIT). A recurrence in 2019 and subsequent neck dissection identified metastatic PTC of FV in 2/9 lymph nodes. After a second round of RIT, head imaging revealed two circumscribed, contrast-enhancing nodules. A 1.2 cm nodule with surrounding edema in the left middle frontal gyrus and a smaller (0.8cm) nodule in the left paramedian frontal lobe, which lacked surrounding edema, were found. CT Chest, Abdomen and Pelvis showed many small nodules, particularly in the inferior right middle lobe and central right lower lobe. A resection and histological analysis of the frontal lobe nodule diagnosed metastatic PTC of FV; immunohistochemical studies highlighted TCV features present in greater than 30% of the nodule and revealed a metastatic epithelioid neoplasm with a pushing border with gliotic neuroparenchyma and scant inflammatory cell infiltrates.
Discussion: Even though brain metastasis of PTC is rare, clinicians should not overlook the possibility of PTC brain metastasis, especially in women and PTC of FV with TVC features.

Dural Hemangioma Masquerading as Meningioma: Case Report and Literature Review

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Background: Intracranial hemangiomas are rare, benign vascular tumors (0.4-0.8% of general population; 5-13% of central nervous system vascular malformations) which can arise sporadically or by an autosomal dominant inheritance pattern. Intracranial hemangiomas typically arise within brain parenchyma. Only a small number of hemangiomas arising from dura and calvaria have been reported. We a dura-based hemangioma which was interpreted to be a meningioma on imaging evaluation.

Case Report: The patient is a 66-year-old man who presented with headaches of about a month duration, progressive bilateral lower extremity weakness with a shuffling gait, and staring spells. Imaging of his brain identified an anterior right temporal region lesion, 3.1 X 3.1 X 3.6 cm, with avid and heterogenous contrast enhancement. Radiologically, the findings were suggestive of a parenchymal lesion. A CT scan of the chest, abdomen, and pelvis was negative for a primary or metastatic disease process. Intraoperatively, a highly vascular extra-axial lesion was encountered, dura-based, with compression of the brain. A near-gross total resection was undertaken with a small portion of the lesion remaining near the sphenoid sinus. Histologic and immunohistochemical findings were diagnostic of a hemangioma with cavernous and capillary features and organizing hemorrhage. Subsequent imaging demonstrated recurrence of the lesion. Resection was again carried out six months after the original surgery with the diagnosis unchanged.

Discussion: A small number of case reports have described dura-based hemangiomas. Given the radiologic overlap of hemangiomas and meningiomas and the rarity of dura-based hemangiomas, the radiologic differential diagnosis typically favors meningoma. Several cases have been described in the middle cranial fossa, most often involving or arising from the cavernous sinus. They have also been described over the convexities of the cerebral hemispheres. Similar to meningiomas, dura-based hemangiomas usually are diagnosed in adults, although childhood presentation has been described. Optimal treatment has not been established but complete resection is recommended. While the role has not been established, several reports describe the use of radiation therapy or stereotactic radiosurgery.

Incidental Identification of Alzheimer Disease Changes in Neurosurgical Specimens: Clinical Significance an Optimal Reporting in Surgical Pathology Reports

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Background: Alzheimer disease (AD) changes are occasionally encountered incidentally in a neurosurgical resection specimen of a neoplasm or another lesion. We report the identification of AD changes in a patient with metastatic adenocarcinoma of the lung and a patient with an intracranial hemorrhage.

Case Reports:
Case A: A 75-year-old man presented with altered mental status and had recently been involved in a motor vehicle collision where he rear-ended a non-moving vehicle. Imaging of his brain identified a right parietooccipital region mass. Imaging of his chest identified a left lung apical and lingular nodules suspicious for bronchogenic carcinoma. Resection of the intracranial lesion was undertaken revealing a metastatic, poorly differentiated adenocarcinoma with immunohistochemical findings consistent with a lung primary. Sparse to moderate number of neuritic plaques were also identified.
Case B: A 63-year-old woman presented with chronic headaches. Her past medical history was significant for a previous stroke with no residual deficits. Imaging of her head revealed an acute right temporal intraparenchymal hemorrhage. The hematoma was evacuated, and a cortical biopsy was undertaken. Histologic evaluation revealed congophilic amyloid angiopathy and a sparse to moderate number of neuritic plaques. In both cases, the diagnosis "Alzheimer disease-type changes" was made with the statement that clinical correlation is necessary for optimal interpretation.

Discussion: Alzheimer disease can be definitively diagnosed only by postmortem neuropathologic examination which evaluates for the presence of specific Alzheimer-type changes including neuritic plaques and neurofibrillary tangles. Alzheimer-type changes are occasionally identified as an incidental finding in a neurosurgical specimen. In a large series of patients with suspected normal pressure hydrocephalus, cortical biopsy was carried out during placement of a ventricular shunt tube and AD changes were identified in a significant proportion of them and clinical follow-up revealed Alzheimer disease features in many of these patients. Given that the AD changes in our two patients were incidentally identified, the diagnosis "Alzheimer disease-type changes" was made with the qualifying statement that clinical correlation is necessary for optimal interpretation. While reversal of AD is not possible, two recently Food and Drug Administration-approved drugs may slow the progression in a proportion of patients.

Supratentorial Pilocytic Astrocytoma Presenting with Intracranial Hemorrhage: Case Report and Literature Review

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Background: Intracranial hemorrhage in childhood is uncommon and elicits a differential diagnosis including (1) a developmental disease, e.g. a vascular malformation, (2) a toxic-metabolic-nutritional disease process, e.g. a coagulopathy including hemophilia or thrombocytopenia, and (3) a neoplastic disease process. Neoplasms are identified in up to 10% of pediatric intracranial hemorrhages, most commonly in either high-grade neoplasms or metastatic neoplasms. We present a case of a hemorrhage in the brain of a 16-year-old boy in the context of an underlying pilocytic astrocytoma.

Case Report: A 16-year-old boy with no past medical history presented with headaches and a left-sided visual field defect. A head CT and CTA scan identified a right occipital intraparenchymal hemorrhage, 4.3 X 4.3 X 3.7 cm with adjacent vasogenic edema and a 0.2 to 0.3 cm right-to-lift shift across midline with normal flow voids identified in the major intracranial vessels and no evidence of an underlying vascular malformation. An MRI of the head confirmed the presence of a hemorrhage with findings worrisome for an underlying lesion. Resection was undertaken. Histologic evaluation revealed a glial / glioneuronal neoplasm. Molecular evaluation revealed an *FGFR1* mutation. Methylation analysis revealed findings consistent with a supratentorial pilocytic astrocytoma

Discussion: We describe the case of a 16-year-old boy with a supratentorial pilocytic astrocytoma which presented in the context of a hemorrhage. Similarity of this case with the literature includes intratumoral hemorrhage as a rare finding in PA, a *MAPK* signaling pathway abnormalities are seen in most pilocytic astrocytomas, *FGFR1* mutation as an uncommon but well-described abnormality in PA, ~6%, with a greater incidence in supratentorial rather than infratentorial neoplasms, an association between an *FGFR1* mutation and hemorrhage has been identified in pediatric and young adult low-grade gliomas, including PA. Differences of this case with the literature include that pediatric cases of PA with hemorrhage are more common in the infratentorial region rather than the supratentorial region. This case highlights (1) the need to consider the possibility of an underlying neoplasm in the setting of an intracranial hemorrhage in a child and (2) the essential role of histopathologic and molecular evaluation of the lesion.

Spectrum of Meningoencephaloceles Presentation: From Massive to Atretic - Case Reports and Literature Review

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Background: Meningoencephaloceles are neural tube defects which affect approximately 0.8-4 per 10,000 live births. They represent congenital malformations with protrusion of central nervous system structures through a cranial defect with associated arachnoid, cerebrospinal fluid, and dura. We report a case of a male infant with a prenatally diagnosed large occipital meningoencephalocele and female infant with an occult presentation.

Methods: Clinical features were summarized from the patient's medical record. A literature search was undertaken using relevant key words.

Case A: A large meningoencephalocele was identified in utero in a male fetus with elevated maternal alpha-fetoprotein levels. Following Caesarean section delivery, imaging revealed an occipital encephalocele, 10.5 x 9.4 x 4.5 cm, associated with a midline defect in the posterior calvarium. Resection was undertaken and macroscopic examination identified nodules of malformed cerebrum enclosed by cystically dilated meninges associated with skin. Microscopic evaluation identified neuroparenchyma with dystrophic lamination and calcifications. No evidence of cerebellar parenchyma or other hindbrain elements was identified.

Case B: A 7-year-old girl presented with a midline posterior parietal scalp mass at birth. During early childhood, the lesion would increase in size while crying and was noted to be pulsatile. Imaging revealed normal intra-axial structures with persistent falcine and emissary veins extending to what was interpreted as an extracranial venous malformation in the parasagittal parietal scalp. The radiologic diagnosis was sinus pericranii and the treatment was deferred. Tenderness and increased size, to 1.7 x 2.2 x 1.7 cm, lead to resection. Histologic evaluation revealed a minute nodule of dysplastic neuroparenchyma surrounded by arachnoid, dura, and skin.

Discussion: The prognosis for occipital and parietal encephaloceles is related to the size and location of the encephalocele, the presence or absence of cerebellum or other hindbrain contents within the herniated tissue, the occurrence of hydrocephalus, and the presence or absence of concurrent cerebral malformations.

Neurosarcoidosis: Multifarious Clinical Presentations and Imaging Characteristics with Pathological Correlations

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Background: Sarcoidosis is a multisystem granulomatous disease. A majority of patients with sarcoidosis are present with pulmonary manifestations. However, sarcoidosis may present with non-pulmonary symptoms. We report a patient with neurosarcoidposis and provide radiologic-histopathologic correlation.

Methods: Clinical course was summarized from the patient's medical record. Relevant images were exported without identifying data.

Results: A 27-year-old man presented with a months-long history of headaches with dizziness, ataxia, and blurred vision. Imaging of his head identified (1) communicating hydrocephalus, (2) subacute, bilateral cerebellar hemisphere infarcts, (3) chronic infarcts involving occipital lobes and basal ganglia, and (4) leukoencephalopathy. A thoracic CT scan identified mediastinal and axillary lymphadenopathy. Serum calcium was elevated. Patchy nodular opacities with consolidation predominantly in the right lower lobe but also present in the posterior segment of the right upper and right middle lobes. Taken together, imaging was suggestive of sarcoidosis with pulmonary and neurological pathology. Autopsy findings included diffuse arachnoid thickening over cerebral convexities. Multifocal, cavitated parieto-occipital infarcts were observed, thought to be secondary to vasculitis-associated injury. Bilateral basal ganglia appeared diffusely soft and discolored.

Discussion: Neurosarcoidosis may have variable clinical presentation and is rarely observed without systemic sarcoidosis. Vascular involvement in neurosarcoidosis frequently affects small arterial perforators, although larger vasculature may also be affected and result in ischemic changes. Meningeal involvement is present in 40% of neurosarcoidosis cases, often seen on contrast-enhanced T1-weighted imaging as thickening and enhancement. Hydrocephalus may occur in neurosarcoidosis, likely secondary to sarcoid granuloma obstruction of cerebrospinal fluid flow.

Journey to the Center of the Cranium: Developing 3D Craniotomy Models for Neurosurgery Resident Education

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Craniotomies are a fundamental aspect of neurosurgery and training neurosurgeons to perform these procedures has traditionally involved the use of cadaver skulls, scientific images, and direct surgical observation. Cadaver skulls are both limited and costly, leaving many surgeons-in-training without tangible practice. 3-Dimensional (3D) printers are being used to advance medical education, providing a cost-effective, lightweight, and easily distributable method of understanding and engaging with anatomy, including but not limited to neuroanatomy. While 3D printing has become more common in residency training, it has not yet been optimized and is far from standard practice. The goal of this project is to create an affordable, accessible, and standardized model of skull printing and practice for neurosurgical residents to use when learning to perform craniotomies. Residents at University of North Carolina at Chapel Hill were consulted to determine which aspects of craniotomy training they found the most challenging and how they would want 3D models built to address these challenges. We obtained an open-source skull model from the National Institute of Health's 3D model repository and edited it to include the locations for the three most common craniotomy approaches: pterional, orbitozygomatic, and retrosigmoid. A miniature model was printed and reviewed by neurosurgeons at ECU Health. The models were then revised and distributed to residents at UNC Chapel Hill, Atrium Health Carolinas Medical Center, and Duke. The models are currently being assessed for usability via standardized measure and likelihood of implementation via Technology Acceptance Model. A full-size craniotomy model was confirmed to be accurate to include the three craniotomy approaches mentioned above and is currently being reviewed by residents for usability and acceptance into training. 3D printed craniotomy models offer a cost-effective solution to address the limitations of cadaver skull use in neurosurgical training. Further research should be conducted to make materials for 3D printed skulls to resemble skull bone, as well as incorporating 3D printed soft tissue to replicate internal skull anatomy.

Primary Extramedullary Spindle Cell Neoplasms of the Spinal Cord: Algorithmic Approach to a Frozen Section Dilemma

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Background: Spinal cord lesions can be designated as either (1) intramedullary, located within the spinal cord, or (2) extramedullary, located outside of the spinal cord, with further craterization as intradural and extradural. Neoplasms with a spindle cell phenotype can be challenging to optimally classify at the time of frozen section with immunohistochemistry necessary for optimal classification. This study looks at a spectrum of spinal cord tumors with a significant spindle cell component and offers an algorithmic approach for intraoperative consultation.

Methods: A series of extramedullary spindle cell cases was compiled for comparison and contrast. A PubMed and Google literature search was undertaken.

Results: A total of 10 cases were compiled including meningioma with predominantly spindle cell features (WHO grade 1 and grade 2), solitary fibrous tumor, schwannoma lacking nuclear palisades and Verocay bodies, neurofibroma; malignant peripheral nerve sheath tumor, perineurioma, and spindle cell (tanycytic) ependymoma. During intraoperative consultation, touch preparations and frozen section features often overlapped. Radiologic localization of the neoplasm was essential to effective frozen section diagnosis as some lesions had a distinctly astrocytic phenotype. A general diagnosis was employed in most cases, specifically spindle cell neoplasm with or without high-grade features. A differential diagnosis was provided when characteristic features were identified, including whorls, psammoma bodies, and intranuclear cytoplasmic inclusions favoring meningioma; abundant collagen between cells raising the differential diagnosis of solitary fibrous tumor; nuclear palisades and Verocay bodies suggestive of Schwannoma; abundant extracellular matrix suggestive of neurofibroma; and perivascular pseudorosettes suggestive of extramedullary ependymoma variant.

Conclusions: This study provides a summary of extramedullary spinal region lesions that overlap with respect to imaging and frozen section characteristics. It emphasizes the need for clinical-radiologic-pathologic correlation on such lesions, the challenges in generating the differential diagnosis clinically prior to histologic evaluation, and the pragmatism to rendering a clinically relevant diagnosis of a spindle cell neoplasm with a differential diagnosis at frozen section with final diagnosis after immunohistochemical and as indicated, molecular evaluation.

Extradural Meningioma Invading Epidural Adipose Tissue: An Uncommon Location with Potential for Aggressive Behavior

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Background: Most meningiomas are located in the intradural extramedullary space. We report an unusual case of a meningioma arising in the extradural complicated by infiltration of epidural adipose.

Case Report: A 68-year-old woman presented with lower extremity weakness and numbness, subacute onset. Imaging of her spine identified a T3-T5 epidural mass with spinal cord compression. Resection was undertaken but given the association of the lesion with epidural adipose, a subtotal resection was undertaken. Histologic evaluation identified a meningioma with predominant meningothelial features and an admixed spindle cell component which diffusely invaded epidural adipose tissue. Atypical features including increased cellularity and sheeting were noted. Immunohistochemical evaluation identified expression of epithelial membrane antigen, E-cadherin, and S100 by neoplastic cells. Infiltrated adipocytes showed only S100 expression. The final diagnosis was meningioma, WHO grade 1. The infiltration of adipose was noted.

Discussion: Intradural meningiomas can in some cases extend into extradural space. The extradural location of a meningioma is uncommon and can invade soft tissues including epidural adipose. Compared to intradural meningiomas, extradural meningiomas are more likely to behave in an aggressive manner. When invasive, it may be impossible to perform a gross total excision of an extradural meningioma with residual neoplasm present postoperatively. This location poses challenges in formulating a differential diagnosis preoperatively. The differential diagnosis of an epidural lesion should include meningioma.

Squamous Cell Carcinoma Arising in an Epidermoid Cyst in the Sellar Region: Case Report and Literature Review

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Background: Epidermoid cysts are slow-growing, benign lesions that rarely undergo malignant transformation into squamous cell carcinoma. Sellar lesions commonly present with non-specific headaches and visual disturbances, and among these, epidermoid cysts, although rare, comprising about 1-2% of all brain tumors; most commonly located in cerebellopontine and parasellar locations. Herein, we present a case of a sellar-based squamous cell carcinoma arising in an epidermoid cyst.

Methods and Materials: A review of the patient's electronic medical record was undertaken, and radiologic and histologic findings were reviewed. A literature search was conducted using appropriate key words.

Case Report: The patient is a 50-year-old man with a history of chronic smoking, chronic obstructive pulmonary disease, and cirrhosis. He presented with left-side forehead headaches, left ear and eye pain, and peripheral vision deficits. Magnetic resonance imaging identified a sellar and suprasellar mass with compression of the optic chiasm and hypothalamus. The radiologic differential diagnosis included craniopharyngioma and pituitary macroadenoma with apoplexy. An endocrine evaluation revealed reduced LH, FSH, ACTH, and cortisol levels and an increased TSH level. CT scan of the chest, abdomen, and pelvis revealed emphysema but no primary or metastatic disease process. The otolaryngology examination was negative. Subtotal transsphenoidal resection through the left nostril identified an epidermoid cyst with high-grade dysplasia and Rathke cleft cyst elements. Molecular evaluation identified numerous abnormalities. He presented again two months later with left eye pain and rapid left eye vision loss. Imaging revealed suspected recurrence. Repeat subtotal resection of the lesion by transsphenoidal approach through the right nostril revealed invasive squamous cell carcinoma along with epidermoid and Rathke cleft cyst elements. Radiation therapy and cisplatin chemotherapy were initiated. The patient became progressively less responsive and *Enterobacter cloacae* meningitis and bacteremia were diagnosed. The patient died a month after the second resection.

Conclusions: Squamous cell carcinoma arising rarely arises in an intracranial epidermoid cyst, with only 54 cases reported in a 2021 review. They arise during development and present after persistent growth; reactive inflammation and dysplastic features can develop in large lesions. The presence of multiple molecular abnormalities suggests a contribution of smoking to this patient's neoplasm.

Recurrent Symptoms Status-Post Percutaneous Intervertebral Disc Decompression: Case Report and Review of the Literature

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Various pathologic processes affect intervertebral discs including both degenerative disease and traumatic disruption which can manifest with symptoms associated with impingement on nerve roots or on the spinal cord. Treatment options include (1) conservative measures and (2) surgical removal of the disc with decompression of areas of impingement. Percutaneous disc decompression offers a "minimally invasive treatment" which employes various modalities (cannulation and extraction of disc material versus laser or plasma disruption without extraction) producing reduced intra-disc pressure and, ideally, reduction in symptoms. In this study we report clinical, imaging, intraoperative, and surgical pathology findings for a patient who underwent (1) Stryker "Disc Dekompressor" cannulation and partial disc extraction and (2) subsequent surgical excision of the affected disc. A 51-year-old man presented with a multiple-year history of both (1) low back pain and (2) subsequent buttock and left leg pain. Imaging studies identified a left L4-L5 paracentral and subarticular disc herniation abutting the left L5 nerve root. Conservative therapy was not successful, and he underwent percutaneous decompression. While he experienced pain relief for approximately two weeks, the pain was subsequently recurrent, and he ultimately underwent surgical disc excision nearly 7 months after the percutaneous procedure. Evaluation of pre- and post-procedure imaging studies did not reveal discernable differences. Intraoperatively, upon incision of the annulus fibrosis, soft and paste-like disk material exuded under pressure. Histologically, the disc showed moderate to severe degenerative and regenerative changes, similar to those seen in a consecutive group of 20 control cases. However, unlike in the controls, the cannulated specimen was markedly disrupted and fragmented and showed multifocal aggregates of variably fine, granular material. No evidence of thermal damage to the tissue was identified. In contrast, in the control discs, the disc material was largely intact and only very focal granular degenerative areas were noted. There was no evidence of an inflammatory infiltrate in either the cannulated or the non-cannulated specimens. A detailed description of findings, including histopathologic changes, following a percutaneous procedure has not been reported to date. Reporting of this data is important for quality control purposes with respect to the percutaneous procedure.

Bihemispheric IDH-Wildtype Glioblastoma with Unilateral FGFR3-TACC3 Fusion in Patient with Breast Cancer History: A Case Report and Literature Review

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Adult IDH-wild type glioblastomas comprise a histopathologically heterogeneous spectrum of neoplasms, characterized by poor prognosis and frequent resistance to the conventional chemoradiotherapy regimes. For optimal WHO integrated diagnosis classification and to establish possible treatment options, molecular analysis is necessary. Herein, we present a case of molecularly confirmed glioblastoma, IDH-wildtype, with involvement of both cerebral hemispheres and an uncharacteristic in-frame fusion limited to one hemisphere.

The patient is a 52-year-old woman with past medical history of metastatic breast cancer status-post chemoradiotherapy who presented with headache and worsening facial pain. Brain magnetic resonance imaging brain demonstrated a right frontal lobe lesion with significant vasogenic edema. The patient was initially treated with Gamma Knife radiosurgery. Scans revealed enlargement and a new left frontal lobe lesion. Bihemispheric tumor resection and GammaTile placement was undertaken.

Histologically, the tumors were composed of hypercellular astrocytes, some with elongated nuclei, with mitotic activity, microvascular proliferation, and necrosis with no evidence of metastatic disease. By immunohistochemistry, neoplastic cells showed glial fibrillary acidic protein expression elevated Ki-67 proliferation index. Molecular examination revealed in the right hemisphere lesion status-post radiation 5 months earlier (1) *FGFR3::TACC3 (*exon 17::exon 11) fusion and (2) *TERT* promoter clinically relevant variant while the left hemisphere lesion which did not receive radiation showed clinically relevant variants in (1) *TERT* promoter, (2) *TP53*, (3) *NF1*, and (3) *PIK3CA* without identification of a fusion. An integrated diagnosis of glioblastoma, IDH-wildtype, CNS WHO grade 4 was established bilaterally.

The *fibroblast growth factor receptor 3 (FGFR3) - transforming acidic coiled-coil 3 (TACC3)* gene fusion (F3T3) is identified as a rare molecular feature in glioblastomas with an estimated prevalence of 4% (range: 1-12%). Recent clinical trials suggest that patients with F3T3-positive tumors have a better prognosis than those who do not harbor the translocation. The identification of the oncogenic *FGFR3:: TACC3* fusion highlights the possibility of identifying patients potentially responsive to targeted therapy with *FGFR* kinase inhibitors for clinical trial enrollment. Molecular differences between the right and left hemisphere lesions could represent (1) independent (multifocal) neoplasms or (2) genetic heterogeneity of a single neoplasm with occult spread not recognized by imaging.

Spurious Extramedullary Appearance of a Cystic Spinal Cord Lesion on Imaging Studies: Unusual Presentation of Hydromyelia

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Background: Cystic lesions involving the spinal cord include hydromelia, syringomyelia, arachnoid cyst, endodermal cysts, and cystic neoplasms in or adjacent to the spinal cord. These lesions are present clinically due to compression of or damage to adjacent axons, neurons, and nerve roots. Imaging studies are usually able to discern the intramedullary vs. extramedullary location of a lesion allowing for generation of a differential diagnosis. We present a case of a cystic spinal cord lesion which challenged radiologic localization and then the generation of an accurate differential diagnosis.

Methods: The patient's clinical record was reviewed and summarized. A literature search was conducted using Pubmed.gov and GoogleScholar.com with key words including hydromyelia and syringomyelia.

Case Report: A 64-year-old woman presented with years-long history of slowly progressive back pain and then weakness greater than sensory deficits in the bilateral lower extremities including left-sided greater than right-sided footdrop. She had status-post thyroidectomy 30 years previously for papillary thyroid carcinoma. Computer Tomography (CT) and magnetic resonance imaging (MRI) scans identified a large cystic structure, non-enhancing, extending from T11 to L1, with posterior displacement and moderate flattening of the conus. An extramedullary location was favored, but a myelogram suggested it was intramedullary, confirmed intraoperatively. Myelotomy released clear, straw-colored fluid under pressure. Endoscopic evaluation revealed a smooth walled, yellowish cyst cavity with no nodular excrescences and biopsy was not undertaken. Histologic evaluation of the cyst fluid identified acellular, proteinaceous material. Literature search identified no other cases where a hydromelia or syringomyelia was challenging to classify radiologically as either intramedullary or extramedullary. MRI scans between 4 months and 6 years post-operative showed no residual cyst(s), subsequent slight enlargement of cyst, and then stable features. By 7 months post-operative, footdrop had essentially resolved while some degree of weakness and sensory deficit remained and were static over the next 6 years of follow up.

Conclusions: Based on location, radiologic and intraoperative features, and clinical improvement after surgery, this patient's spinal cord lesion is best classified as a hydromyelia rather than syringomyelia. The term "syringohydromyelia" has been used in the literature to describe cases with combined pathophysiology of syringomyelia and hydromyelia.

Massive Maxillary Ameloblastoma with Orbital and Anterior Cranial Fossa Invasion: Diagnostic and Treatment Challenges

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Background: Ameloblastomas are rare tumors of the jaw that arise from odontogenic epithelium. We describe a rare case of maxillary ameloblastoma.

Case Report: 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 was previously seen in another hospital and diagnosed with a nasopharyngeal tumor years ago. He was scheduled for surgery, but his surgery was cancelled for unknown reasons and the patient was subsequently 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 in the right nostril. The patient underwent pre-surgical vascular embolization to debulk the tumor. Bicoronal frontal craniotomy was performed with removal of ameloblastoma from both frontal regions and 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. Unfortunately, following the surgery the patient was again lost to follow-up.

Discussion: Ameloblastomas are the second most common tumor arising from odontogenic epithelium, after odontomas. Tumor behavior is generally benign with slow grow, but neoplasms can be locally aggressive. With respect to location, 80% occur in the mandible while 20% occur in the maxilla. Initial presentation is usually with painless swelling of the jaw or as an incidental finding on dental imaging. They are generally considered benign but, as in this case, are locally aggressive when untreated. Maxillary ameloblastomas require early diagnosis and prompt treatment, as they may act more clinically aggressive 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. Local invasion into the orbital region or skull base are very rare but pose serious lethal potential.