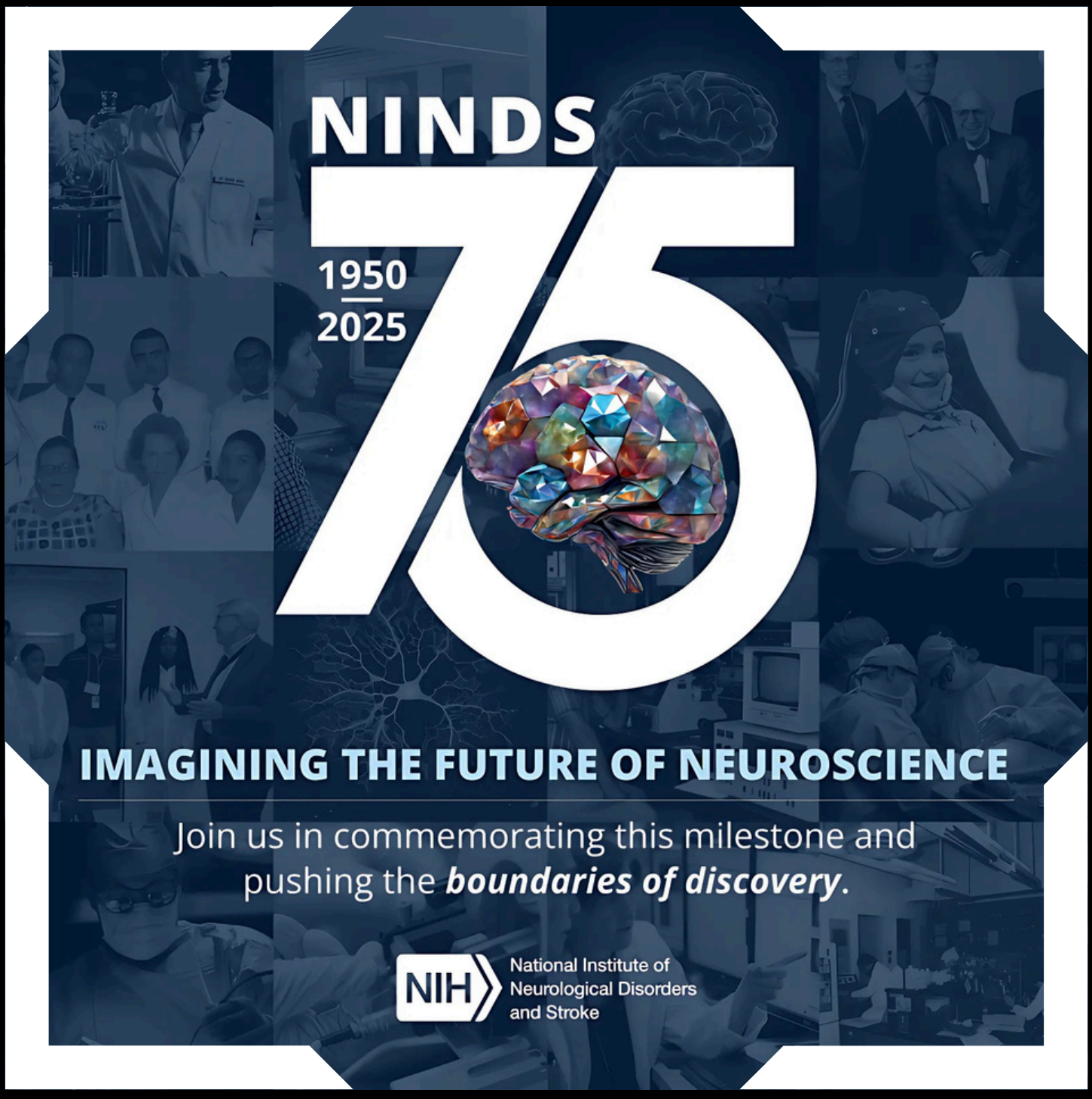
AMERICAN NEUROLOGICAL ASSOCIATION®
150 YEARS
THE HOME FOR ACADEMIC NEUROLOGY



ANA-NINDS Career Development Symposium

Friday, September 12 & Saturday, September 13
Baltimore, MD

TABLE OF CONTENTS

Page

Page Course Sponsorship Information 3

Course Agenda 4

SPEAKER/MENTOR INFORMATION

Faculty Listing 6

Faculty Biographies 7

Common Mistakes in NIH Grant Applications & NIH Websites 20

K-AWARDEE ATTENDEES

K-Awardee Attendee Listing 23

Awardee Abstracts by Category 26

Awardee Abstracts Author Index 59

NETWORKING & BREAKOUT ASSIGNMENTS

Friday Networking Tables 60

Saturday Breakout #1 62

Saturday Breakout #2 63

Saturday Poster Tour 64

ANA-NINDS Career Development Symposium

September 12-13, 2025
Baltimore Marriott Waterfront
Baltimore, MD

SPONSORED BY:

The American Neurological Association

921 Pleasant Valley Avenue,
#495
Mount Laurel, NJ 08054
(609) 596-2223
Email: info@myana.org
Website: www.myana.org

M. Elizabeth Ross, MD, PhD, FANA
President
Alexandra Nelson, MD, PhD
Chair

National Institute of Neurological Disorders and Stroke

Building 31, Room 8A07
31 Center Dr., MSC 2540
Bethesda, MD 20892-2540
(800) 352-9424
Website: www.ninds.nih.gov

Letitia (Tish) Weigand, PhD
Director
Elizabeth Sypek, PhD
Director

COURSE GOALS

The ANA-NINDS Career Development Symposium is designed to provide you with the essential tools to enhance your ability to write successful grant proposals, to obtain grant funding from NIH and other institutions and build an impactful academic career. This course is held in conjunction with the ANA2025 Annual Meeting.

This symposium, now in its twentieth year, is designed for K08, K12 and K23 recipients and will be chaired by senior neurologists and neuroscientists who have proven success in career building and navigation, scientific grant writing, networking, and balancing clinical and research efforts. In addition, senior staff from NINDS will provide advice concerning the mechanisms involved in grant submission and evaluation.

COURSE EVALUATION

Participants are asked to complete the evaluation by **Friday, November 14, 2025**. We sincerely appreciate your constructive feedback and comments and ask that you please take a few moments to complete the evaluation.

2025 ANA-NINDS Career Development Symposium Agenda

All times are listed in Eastern Daylight Time (EDT)

Grand Ballrooms 7 – 8

(All Session Located on the Third Floor)

Friday, September 12, 2025

2:00 PM - 2:30 PM **Registration (Grand Ballrooms 7 – 8 Foyer)**

2:30 PM - 2:45 PM **Welcome and Goals for the Meeting**
Chair: *Alexandra Nelson, MD, PhD, University of California, San Francisco*

2:45 PM - 3:15 PM **View of NINDS Leadership 2025**
Speaker: *Walter Koroshetz, MD, FANA, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)*

3:15 PM - 4:00 PM **Setting Yourself up for Success**
Speakers: Letitia (*Tish) Weigand, PhD, National Institutes of Health*
Annapurna Poduri, MD, MPH, Boston Children's Hospital

4:00 PM - 4:45 PM **Meet Your Peers and Colleagues Networking Sessions**
Table Assignments by Research Focus (20 min) and Clinical vs Lab (20 min). Please find your table assignments on the back of your name badge.

4:45 PM - 5:00 PM **ANA Presidential Address**
Speaker: *M. Elizabeth Ross, MD, PhD, FANA, Weill Cornell Medicine*

5:00 PM - 6:00 PM **K to Independence Panel – How I Did It**
Moderator: *Mercedes Paredes, MD, PhD, University of California San Francisco*
Panelists:
Nicole Coufal, MD, PhD, University of California, San Diego
Kristin Guilliams, MD, Washington University School of Medicine St. Louis
Eric Landsness, MD, PhD, Washington University in St. Louis

6:00 PM - 6:30 PM **Leadership: Lessons from Academia and Life**
Speaker: *Pooja Khatri, MD, MSc, Yale University*

6:30 PM - 7:15 PM **Opening Buffet Dinner**

7:15 PM – 8:45 PM **Chairs View Panel**
Moderator: *Alexandra Nelson, MD, PhD, University of California, San Francisco*
Panelists:
Dimitric Krainc, MD, PhD, FANA, Northwestern University
S. Andrew Josephson, MD, FANA, University of California, San Francisco
Jin-Moo Lee, MD, PhD, FANA, Washington University in St. Louis

Saturday, September 13, 2025

7:00 AM - 8:00 AM	**Breakfast**
7:30 AM – 8:00 AM	**Poster Set-Up (Poster Set-up in Grand Ballrooms 9 – 10)**
8:00 AM - 9:00 AM	**Building Your Portfolio Outside the NIH** **Moderator:** *Catherine Chu, MD, MMSc, Johns Hopkins University* **Panelists:** *Audrey Brumback, MD, PhD, UT Health Austin* *Justin McArthur, MBBS, MPH, FANA, Johns Hopkins University* *Kevin Sheth, MD, Yale School of Medicine*
9:00 AM - 9:15 AM	**Coffee Break and Head to Breakout Sessions** *Please find your breakout assignment on the back of your name badge.*
9:15 AM - 11:30 AM	**Breakout Session 1** *1st – 2nd Year Awardees – Abstract for First Major Paper Discussion* *3rd – 5th Year Awardees – Aims Page for R01 Discussion*
11:30 AM - 12:30 PM	**Why Be a Clinician-Scientist in 2025?** **Moderator:** *Lauren Sansing, MD, MS, FANA, Yale University School of Medicine* **Panelists:** *Karunesh Ganguly, MD, PhD, FANA, University of California, San Francisco* *Frances Jensen, MD, FACP, FANA, University of Pennsylvania* *Henry L. Paulson, MD, PhD, FANA, University of Michigan*
12:30 PM - 1:15 PM	**Lunch**
1:15 PM - 2:15 PM	**Building Collaborations and Sustaining Productive Relationships** **Moderator***: Eric Landsness, MD, PhD, Washington University in St. Louis* **Panelists:** *Romergryko Geocadin, MD, FANA, Johns Hopkins University* *David Greer, MD, MA, FANA, Boston University* *Anli Liu, MD, MA, New York University Langone Health*
2:15 PM - 2:30 PM	**Coffee Break and Head to Breakout Sessions** Please find your breakout assignments on the back of your name badge.
2:30 PM - 4:15 PM	**Breakout Session 2** *"What Are the Biggest Challenges You Are Facing and How Can We Help Each Other?"*
4:15 PM - 5:45 PM	**Moderated Poster Tours (Grand Ballrooms 9 - 10)** ***Please find your poster group assignment on the back of your name badge.***

Faculty List				
NAME	**LAST**	**CREDENTIALS**	**INSTITUTION**	**ROLE**
Audrey	Brumback	MD, PhD	UT Health Austin	Panelist, Mentor
Catherine	Chu	MD, MMSc	Johns Hopkins University	Moderator, Mentor
Nicole	Coufal	MD, PhD	University of California, San Diego	Panelist, Mentor
Karunesh	Ganguly	MD, PhD, FANA	University of California, San Francisco	Panelist, Mentor
Romergryko	Geocadin	MD, FANA	Johns Hopkins University	Panelist, Mentor
David	Greer	MD, MA, FANA	Boston University	Panelist, Mentor
Kristin	Guilliams	MD	Massachusetts General Research Institute	Panelist, Mentor
Frances	Jensen	MD, FACP, FANA	University of Pennsylvania	Panelist, Mentor
S. Andrew	Josephson	MD, FANA	University of California, San Francisco	Panelist, Mentor
Pooja	Khatri	MD, MSc	Yale University	Speaker, Mentor
Walter	Koroshetz	MD, FANA	National Institute of Neurological Disorders and Stroke; National Institutes of Health	Speaker
Dimitri	Krainc	MD, PhD, FANA	Northwestern University	Panelist
Eric	Landsness	MD, PhD	Washington University in St. Louis	Moderator, Panelist, Mentor
Jin-Moo	Lee	MD, PhD, FANA	Washington University in St. Louis	Panelist, Mentor
Anli	Liu	MD, MA	New York University Langone Health	Panelist, Mentor
Justin	McArthur	MBBS, MPH, FANA	Johns Hopkins University	Panelist, Mentor
Alexandra	Nelson	MD, PhD	University of California, San Francisco	Chair, Moderator, Mentor
Mercedes	Paredes	MD, PhD	University of California, San Francisco	Moderator, Mentor
Henry	Paulson	MD, PhD, FANA	University of Michigan	Panelist, Mentor
Annapurna	Poduri	MD, MPH	Boston Children’s Hospital	Speaker, Mentor
Elizabeth	Ross	MD, PhD, FANA	Weill Cornell Medicine	Speaker, Mentor
Lauren	Sansing	MD, MS, FANA	Yale University School of Medicine	Moderator, Mentor
Kevin	Sheth	MD	Yale School of Medicine	Panelist, Mentor
Elizabeth	Sypek	PhD	National Institute of Neurological Disorders and Stroke	Mentor
Letitia	Weigand	PhD	National Institute of Neurological Disorders and Stroke	Speaker, Mentor

PROGRAM CHAIRS

Alexandra Nelson, MD, PhD
University of California, San Francisco
Alexandra.Nelson@ucsf.edu

Alexandra Nelson MD, PhD is the Richard and Shirley Cahill Endowed Chair in Parkinson's Disease Research at UC San Francisco. Dr Nelson received her MD/PhD training at UC San Diego, completed her residency and fellowship training at UCSF, and joined the faculty in 2014. In the lab, her research group investigates the cellular and circuit basis of movement disorders, using electrophysiology, optogenetics, and other optical methods in mouse models of disease. In the clinic, she focuses on the care of patients and families with Huntington's Disease, atypical parkinsonian disorders, and Spinocerebellar Ataxias.

Elizabeth Sypek, PhD
National Institute of Neurological Disorders and Stroke
elizabeth.sypek@nih.gov

Elizabeth is a Program Manager for HEAL (The Helping End Addiction Long-term Initiative) and NINDS in the NINDS Office of Training and Workforce Development. She manages HEAL and pain-related training and early career funding opportunities. Prior to joining NINDS, Elizabeth completed her Ph.D. in Neuroscience at Stanford University with Dr. Gregory Scherrer studying microglial transcriptional responses to chronic opioid exposure and neuropathic pain. She then completed a postdoctoral fellowship at Johns Hopkins University further studying neuro-immune interactions in pain and itch.

Letitia (Tish) Weigand, PhD
National Institutes of Health
letitia.weigand@nih.gov

Tish Weigand, Ph.D. is the Acting Director of the Office of Training and Workforce Development at NINDS. Dr. Weigand's career in science has hit the trifecta of academia, government, and industry. She began at the lab bench conducting research at the intersection of neuroscience, physiology and immunology, after which she entered government service at NINDS as a program analyst and manager in the Training Office. There she oversaw institutional training programs and many other initiatives for a number of years before moving on to work in the pharmaceutical industry as a Medical Science Liaison for UCB, serving as a regional expert on the science underlying the company's epilepsy portfolio. She recently made her return to NINDS to create and lead programs that support research training and career development for graduate students, postdocs, and early career physician scientists. Dr. Weigand holds a PhD from John Hopkins University and completed a postdoctoral training in neuroscience at George Washington University. She is passionate about preparing and equipping the next generation of scientists and professionals for success. Throughout her career she has served as a speaker and mentor throughout the biomedical and neuroscience communities.

SPEAKERS

Audrey Brumback, MD, PhD
UT Health Austin
audrey.brumback@austin.utexas.edu

Dr. Audrey Brumback is a board-certified physician-scientist specializing in child neurology at UT Health Austin Pediatric Neurosciences at Dell Children's. She specializes in the care of patients with neurodevelopmental disorders, such as autism. Her research focuses on developing novel therapies for brain dysfunction based on modulation of neurophysiology. Her goal is to develop brain-circuit-based therapies for the developmental neuropsychiatric disorders seen in her clinical practice. Additionally, she is an assistant professor in both the Dell Medical School Department of Neurology and the Dell Medical School Department of Pediatrics.

Dr. Brumback earned a bachelor's degree in biochemistry at The University of Texas at Austin and then obtained her medical degree and doctorate in neuroscience at the University of Colorado under the mentorship of Kevin Staley. During this time, she helped establish the scientific basis for a novel treatment for neonatal seizures. She completed a pediatric neurology residency through the Neuroscience Pathway at the University of California, San Francisco. Under the mentorship of Vikaas Sohal, she built upon her strong medical and neurophysiology background to study and treat autism spectrum disorder. In her postdoctoral work, Dr. Brumback discovered that three mouse models of autism share a common defect in the prefrontal cortex in a particular class of neurons. Using in vivo calcium imaging, she observed that this population of neurons does not activate appropriately during social behavior in autism model mice.

As a result of this training, she is a nationally recognized expert in the clinical assessment and management of autism spectrum disorders and related conditions such as Rett syndrome. Dr. Brumback joined the faculty at Dell Medical School in 2017. She is also a member of the Department of Neuroscience at UT Austin and a member of the Center for Learning and Memory and the Institute for Neuroscience at UT Austin.

Her work is supported externally by a K08 career development award from the NINDS/NIH and the Philip R. Dodge Young Investigator Award from the Child Neurology Society. Previously, she held an NIH R25 award, an NIH K12 award, a Pilot Award for Junior Investigators in Basic and Clinical/Translational Sciences from UCSF, and the Pediatric Epilepsy Research Foundation Scientific Research Grant from the Child Neurology Foundation. She was also selected for the Autism Speaks Translational Postdoctoral Fellowship in 2013.

Dr. Brumback is a prolific writer and researcher. At Dell Children's Medical Center, she leads a team of researchers who work to understand how changes in the brain's electrical activity cause the symptoms experienced by many people with these disorders. Her long-term research goal is to develop therapies for the clinical features of neurodevelopmental conditions that cause disability. Working toward this goal, her current laboratory work focuses on functionally mapping the thalamocortical network involved in autism.

Catherine Chu, MD, MA
Johns Hopkins University
cjchu@jhu.edu

Dr. Catherine Chu is the Director of Child Neurology and Pediatric Epilepsy at Johns Hopkins University and Vice President of Neurology at Kennedy Krieger Institute. She is board-certified in Neurology (with special qualifications in Child Neurology), Epilepsy, and Neurophysiology. Dr. Chu cares for patients with refractory epilepsy and abnormal neurophysiology, specializing in developmental neurophysiology, neurosurgical planning, and responsive neuromodulation. Dr. Chu's laboratory identifies biomarkers and critical oscillations in neurodevelopmental disorders, memory and cognition, and epilepsy.

Nicole Coufal, MD, PhD
University of California, San Diego
ncoufal@health.ucsd.edu

Dr. Nicole Coufal is a physician scientist with training in pediatric critical care and research interests in neuroimmunology. The goal of her lab is to understand the contribution of innate immunity to neurodevelopmental and pediatric neurodegenerative diseases. By understanding the interaction between the brain environment and cellular ontogeny on macrophage function, the lab strives to understand the molecular and cellular mechanisms underlying innate immune dysfunction to ultimately identify novel therapeutic targets in untreatable pediatric diseases. Her lab utilizes a combination of translational, patient-specific pluripotent stem cell and genome-wide approaches to identify cellular mechanisms in common neurodevelopmental and rare pediatric neurodegenerative disorders.

Romergryko G. Geocadin, MD, FANA
Johns Hopkins University School of Medicine
rgeocad1@jhmi.edu

Dr. Romergryko (Romer) G. Geocadin is a professor of neurology, of neurosurgery and of anesthesiology and critical care medicine at the Johns Hopkins University School of Medicine. He holds a joint appointment in medicine. He completed his undergraduate education at the University of the Philippines, medical education at UERM School of Medicine in the Philippines, neurology residency at New York University and neurocritical care fellowship at Johns Hopkins. He is presently specializing in neurocritical care medicine at the Johns Hopkins Medical Institutions. His research focusing on translational studies and clinical trials in brain injury after cardiac arrest resuscitation is funded by the NIH. He has led or contributed to the development of many practice guidelines, scientific statements and reports from the American Academy of Neurology, American Heart Association, The Joint Commission and the Institutes of Medicine. He was Past President of the Neurocritical Care Society and the Vice President of the American Neurological Association from 2022 to 2024.

David Greer, MD, MA, FANA
Boston University
dgreer@bu.edu

Dr. David Greer is Professor and Chair of the Department of Neurology at Boston University School of Medicine and the Richard B. Slifka Chief of Neurology at Boston Medical Center. He has been a neurointensivist since 2001, having trained at Massachusetts General Hospital, where he began his career. He was then Vice Chair at Yale from 2010-17, before joining Boston University and Boston Medical Center in 2017. Dr. Greer has been editor-in-chief of Seminars in Neurology since 2013, and was the inaugural editor-in-chief for Neurocritical Care on Call. He has authored more than 400 peer-reviewed manuscripts, reviews, chapters, guidelines and books. He is the Chair of the AAN Academic Neurology Committee and is the current Vice President for the Neurocritical Care Society, due to be President in 2025. His research interests include predicting recovery from coma after cardiac arrest, brain death, and multiple stroke-related topics, including acute stroke treatment, temperature modulation and stroke prevention. He was the co-PI for the international INTREPID study, evaluating fever prevention for acute vascular brain injury, and is a multiple R01-funded investigator focusing on neuroprognosis after cardiac arrest. He was the lead author for the World Brain Death Project published in *JAMA* in 2020, and for the 2023 AAN Guidelines in Brain Death. Dr. Greer's greatest passion is in education and mentorship. In 2022, he received the prestigious A.B. Baker Lifetime Achievement Award for Neurological Education from the American Academy of Neurology. He has mentored innumerable students, residents, fellows and faculty, and considers himself a "lifelong mentor" for anyone and everyone he takes under his wing.

Karunesh Ganguly, MD, PhD, FANA
University of California, San Diego
karunesh.ganguly@ucsf.edu

Dr. Karunesh Ganguly MD, PhD is a clinical neurologist and a research scientist at the University of California, San Francisco and the San Francisco VA Medical Center. He graduated from Stanford University and then completed his MD/PhD degrees through the Medical Scientist Training Program at the University of California, San Diego. He subsequently completed his internal medicine and neurology residency at the University of California, San Francisco. Concurrent with his residency, he conducted research into the development of 'Brain-Machine Interfaces' in the Department of Electrical Engineering & Computer Science at UC Berkeley. His clinical expertise is on the neurological rehabilitation of patients with stroke and brain injury. He is also the Director of the Neural Engineering & Plasticity Lab. The laboratory's basic and translational research program focuses on the development of neural interfaces for patients with motor disability. Such implantable technology can eventually help disabled patients to directly control assistive devices. His research is funded by grants from the National Institutes of Health (NIH) and the Department of Veterans Affairs. He has been awarded the Presidential Early Career Award for Scientists and Engineers (PECASE Award) and was selected for a New Innovator Award by the NIH Office of the Director. He was also recent awarded the Outstanding Neurorehabilitation Clinical Scientist Award by the American Society of Neurorehabilitation (ASNR)

Kristin Guilliams, MD
Massachusetts General Research Institute
kristinguilliams@wustl.edu

Dr. Kristin Guilliams is a pediatric neurologist and intensivist specializing in pediatric cerebrovascular diseases and pediatric neurocritical care. She completed her pediatric neurology residency and pediatric critical care fellowship at Washington University in St. Louis. Kristin is an Associate Professor in Neurology, Pediatrics, and Radiology. She is Section Head of Pediatric Neurocritical Care in the Department of Neurology at Washington University and directs the Pediatric Stroke and Cerebrovascular Program. Her translational imaging lab investigates changes in cerebral blood flow and metabolism throughout childhood to understand mechanisms of stroke and cognitive impairment in vulnerable populations.

Frances E. Jensen, MD, FACP, FANA
The University of Pennsylvania
Frances.Jensen@pennmedicine.upenn.edu

Dr. Jensen is Professor of Neurology and Chairman of Neurology at the Perelman School of Medicine, University of Pennsylvania, and Co-Director of Penn Translational Neuroscience Center. She was formerly Professor of Neurology at Harvard Medical School, Director of Translational Neuroscience, and senior neurologist at Boston Children's Hospital and Brigham and Women's Hospital. After receiving her AB from Smith College and her MD from Cornell Medical College, she completed her neurology residency training at the Harvard Longwood Neurology Residency Program. Her research focuses on mechanisms of epilepsy and stroke, and the mechanistic interaction of epilepsy with other disorders such as autism and dementia, with specific emphasis on elucidating new therapies for clinical trials development. She received the 2007 Director's Pioneer Award from the NIH to explore the interaction between epileptogenesis and cognitive dysfunction and was elected a member of the National Academy of Medicine in 2015. She has authored over 150 manuscripts related to her research, has been continuously funded by NIH since 1987, and received an NIH-NINDS Javits Award in 2020.

Dr. Jensen has trained numerous clinical and basic research fellows who now hold independent faculty positions nationally and internationally. She served as President of the American Neurological Association (2020–2022) and as President of the American Epilepsy Society in 2012, and has participated on multiple leadership boards including the Society for Neuroscience and NIH. She is also a Trustee of the Franklin Institute in Philadelphia and engages in community outreach for brain research and education. Additionally, she advocates for awareness of adolescent brain development, its unique strengths and vulnerabilities, and their impact on medical, social, and educational issues affecting teenagers and young adults. She is the author of *The Teenage Brain*, released by HarperCollins in 2015/16 and translated into over 25 languages worldwide.

S. Andrew Josephson, MD, FANA
University of California, San Francisco
andrew.josephson@ucsf.edu

Dr. S. Andrew Josephson specializes in neurovascular and other neurologic disorders, caring for general neurology and stroke patients in the hospital as well as in clinic. He is the founder of UCSF's Neurohospitalist Program and specializes in difficult to diagnose inpatient neurologic conditions. He serves as Chair of the Department of Neurology and is the Carmen Castro Franceschi and Gladyne K. Mitchell Neurohospitalist Distinguished Professor. After graduating from Stanford University, Dr. Josephson earned his medical degree at Washington University in Saint Louis. He completed an internship in internal medicine and a residency in neurology at UCSF, where he was chief resident. He also completed fellowships in neurovascular neurology (stroke) and behavioral neurology at UCSF and is board certified in both vascular neurology and neurocritical care. Dr. Josephson is known nationally for his pioneering work launching the neurohospitalist model of care and his leadership of its society. His research interests include improving models of inpatient neurologic care delivery, quality and safety in hospitalized patients, neurologic education, delirium, and the contribution of stroke to dementia. He serves as the Editor-In-Chief of *JAMA Neurology*, a leading journal in the field. Dr. Josephson has won numerous teaching awards from medical students and residents at UCSF including being selected to present the keynote address for the School of Medicine Commencement; the Henry J. Kaiser Award for Excellence in Teaching; the Academic Senate Distinction in Teaching Award, and the Robert Layzer Golden Toe Award for resident teaching.

Pooja Khatri, MD, MSc
Yale University
khatrip@UCMAIL.UC.EDU

Dr. Pooja Khatri is the Albert E Kent Professor and Chair of Neurology at Yale University. She co-directs the National Coordinating Center of NIH StrokeNet, the primary infrastructure for developing and implementing multicenter trials of stroke funded by NIH and training the next generation. With 20 years of sustained NIH funding, in addition to industry funding, she has broad experience in therapeutic development from conception to post-marketing phases including translational, study design, regulatory, safety, and ethical aspects. Her scientific expertise and contributions span acute stroke therapy, prevention of early stroke recurrence, biomarkers of stroke recovery, and population-level epidemiology of stroke and brain health.

Dimitri Krainc, MD, PhD, FANA
Northwestern University
krainc@northwestern.edu

Dr. Dimitri Krainc is the Ward Professor and Chairman of the Department of Neurology and Director of the Feinberg Neuroscience Institute at Northwestern. Previously, Krainc spent two decades at the Massachusetts General Hospital and Harvard Medical School, where he completed his research and clinical training and served on faculty. His research group has uncovered key mechanisms of neurodegeneration that have led to the development of targeted therapies. Krainc received the Javits Neuroscience Investigator Award, Outstanding Investigator award from NIH, and was elected to the Association of American Physicians, National Academy of Medicine, and the National Academy of Inventors. He serves as President-elect of the American Neurological Association.

Walter Koroshetz, MD, FANA
National Institute of Neurological Disorders and Stroke, National Institutes of Health
koroshetzw@ninds.nih.gov

Walter Koroshetz is the Director of the National Institute of Neurological Disorders and Stroke (NINDS). He works to advance the mission of the Institute, to improve fundamental knowledge about the brain and the nervous system, and to use that knowledge to reduce the burden of neurological disorders. He joined NINDS as the Deputy Director in 2007. Before coming to NIH, Dr. Koroshetz was a Harvard Professor of Neurology, Vice Chair of Neurology at the Massachusetts General Hospital, director of Stroke and Neurointensive Care, and a member of the MGH Movement Disorders clinic. His research activities spanned basic neurobiology to clinical trials. He directed Neurology training at MGH for 16 years. A graduate of Georgetown University and University of Chicago Medical School, Dr. Koroshetz specialized in Internal Medicine and Neurology.

Eric Landsness, MD, PhD
University of Washington in St. Louis
landsness@wustl.edu

Dr. Eric Landsness Is a physician-scientist with 20 years of expertise in stroke and neuroplasticity research. He obtained his MD PhD training at the University of Wisconsin focusing on understanding the underlying mechanisms of sleep and brain plasticity and their impact on disease. After completing clinical training in neurology and sleep medicine he joined the faculty at Washington University where his lab studies the bidirectional role of sleep and stroke. He has been involved in the ANA since residency and is passionate about introducing junior and early career neurologists to the ANA.

Jin--Moo Lee, MD, PhD, FANA
Washington University School of Medicine
leejm@wustl.edu

Jin--Moo Lee, MD, PhD, is the Andrew B. & Gretchen P. Jones Professor, Chair of the Department of Neurology at Washington University School of Medicine, and Neurologist-in-Chief at Barnes-Jewish Hospital. Dr. Lee is a physician-scientist and vascular neurologist, who has dedicated his career towards understanding mechanisms underlying brain injury after stroke and repair of damaged circuits resulting in recovery. He has published more than 250 research articles, chapters, reviews and editorials. A major focus of Dr. Lee's academic career has been research mentoring—he has mentored more than a dozen K-awardees—and has received several awards for mentorship, including the Sven Eliasson Award for Teaching Excellence and the Washington University Distinguish Faculty Mentorship Award.

Dr. Lee graduated from Yale College with a degree in Molecular Biophysics and Biochemistry, then attended Weill Cornell Medical College, earning an MD and PhD in neuroscience. After completing residency training at the University of Pennsylvania, he completed a neurovascular fellowship at Washington University, where he subsequently joined the faculty in the Department of Neurology.

Anli Liu, MD, MA
New York University Langone Health
anli.liu@nyulangone.org

Dr. Anli Liu is an Associate Professor of Neurology at NYU Langone, Principal Investigator of the NYU Memory and Neuromodulation Laboratory, and an Investigator at the NYU Neuroscience Institute. Dr. Liu earned her BA from Stanford University, MA from UC Berkeley, and MD from UCSF. She completed her neurology residency at NYP-Weill Cornell, followed by fellowships in clinical neurophysiology and cognitive neurology at Harvard at Beth Israel Deaconess Medical Center. In the clinic, she cares for adult patients with epilepsy and memory disorders. Her lab works to: (1) develop naturalistic tasks to measure human episodic memory behavior; and (2) clarify the neurophysiological mechanisms of memory by using single unit, micro-, and macro-LFP invasive recordings in epilepsy surgical patients.

Justin McArthur, MBBS, MPH, FANA
Johns Hopkins University
jm@jhmi.edu

Dr. Justin McArthur is nationally and internationally recognized for his work in studying the natural history, development and treatment of HIV infection, multiple sclerosis and other neurological infections and immune-mediated neurological disorders. Dr. McArthur has also developed a technique to use cutaneous nerves to study sensory neuropathies, including those associated with chemotherapy, HIV and diabetes. This has been incorporated into clinical practice on a world-wide basis. Dr. McArthur is the founding director of the Johns Hopkins/National Institute of Mental Health Research Center for Novel Therapeutics of HIV-associated Cognitive Disorders. The Center is comprised of an experienced interdisciplinary research team who have pooled their talents to study the nature of HIV-associated cognitive disorders. Their aim is to translate discoveries of the pathophysiological mechanisms into novel therapeutics for HIV-associated dementia (HIV-D). Dr. McArthur received his medical degree from Guys Hospital Medical School in London, UK. He then completed an internship and residency in internal medicine at The Johns Hopkins Hospital in Baltimore, MD. Dr. McArthur stayed with Johns Hopkins to complete a residency in neurology and achieve his Master's in public health. He is the current Director of the Johns Hopkins Department of Neurology and holds the John W. Griffin Professorship in neurology which was established in 2015 by Jeffrey and Harriet Legum. Dr. McArthur is a Professor of Neurology, Epidemiology, Medicine and Pathology at the Johns Hopkins School of Medicine and the Neurologist-in-Chief of the Johns Hopkins Hospital. In 2017, Dr. McArthur was elected to the Association of American Physicians, and in 2020 to the National Academy of Medicine.

Mercedes Paredes, MD, PhD, FANA
University of California, San Francisco
Mercedes.Paredes@ucsf.edu

Mercedes Paredes is associate professor in the Department of Neurology and Neuroscience, Developmental and Stem Cell Biology, and Biomedical Sciences graduate programs at UCSF. She received her undergraduate degree from Harvard University and then joined the UCSF MSTP (Medical Scientist Training Program). She subsequently did residency in neurology at UCSF postdoctoral training with the Broad Center for Regenerative Medicine and Stem Cell Research. Her lab focuses on identifying features of neuronal progenitor proliferation and migration that are unique to the gyrated brain, such as in humans, with an emphasis on the perinatal period. She is a practicing neurologist who serves epilepsy patients with neurodevelopmental conditions, is an associate director for the UCSF MSTP, and holds a passion for mentoring UIM (or underrepresented in medicine) in careers in medicine, STEM, and neurology.

Henry Paulson, MD, PhD, FANA
University of Michigan
henryp@umich.edu

Henry L. Paulson, MD, PhD, is the Lucile Groff Professor of Neurology and director of the Michigan Alzheimer's Disease Center at the University of Michigan. Dr. Paulson received his MD and PhD in Cell Biology from Yale University in 1990, and then completed neurology residency and neurogenetics/movement disorders fellowships at the University of Pennsylvania. He's served on the Neurology faculty at the University of Iowa for ten years before moving to the University of Michigan in 2007. Dr. Paulson's research and clinical interests concern the causes and treatment of age-related neurodegenerative diseases, with an emphasis on polyglutamine diseases, Alzheimer's disease and frontotemporal dementia. Nationally, Dr. Paulson has served on the advisory boards of numerous disease-related national organizations and is currently a member of the National Advisory Council for Neurological Disorders and Stroke Council at the National Institutes of Health. Among his awards, Dr. Paulson was recipient of an Ellison Medical Foundation New Scholar in Aging Award, the Paul Beeson Physician Faculty Scholar in Aging Award, and the NINDS Landis Award for Outstanding Mentorship. He is an elected Fellow in the American Association for the Advancement of Science and a member of the National Academy of Medicine.

Annapurna Poduri, MD, MPH, FANA
Boston Children's Hospital
annapurna.poduri@childrens.harvard.edu

Professor Ann Poduri is Director of the Epilepsy Genetics and Neurogenetics Programs, Associate Chief for Academic Development in the Department of Neurology, and the Diamond Blackfan Chair of Neuroscience Research at Boston Children's Hospital. Through her multi-disciplinary program that spans from the clinic to the laboratory, she has launched studies of that continue to reveal many genetic causes for epilepsy and other neurodevelopmental disorders, including novel discovery in the area of somatic mutation in pediatric brain disease. At BCH, she is a member of the steering committees of the Children's Rare Disease Cohorts Initiative and the Sandra L. Fenwick Pediatric Health Equity Institute. Beyond BCH, Ann serves as an elected member of the Board of the American Epilepsy Society and has served as an invited member of the Genomics Commission of the International League Against Epilepsy, Chair of the American Epilepsy Society/National Institute of Neurological Disorders and Stroke Benchmarks Stewards Committee, member of the NINDS NST1 study section, and on scientific advisory boards for companies and foundations devoted to developing precision medicine for patients with epilepsy. Her collaborative research and mentorship contributions have been recognized through numerous honors, including the American Neurological Association's Derek Denny-Brown Young Neurological Scholar Award, the American Academy of Neurology's Dreifuss-Penry Epilepsy Award, and the Harvard Club of Boston's Most Influential Women designation.

M. Elizabeth Ross, MD, PhD, FANA
Weill Cornell Medicine
mer2005@med.cornell.edu

Dr. Ross is the Nathan Cummings Professor of Neurology and Neuroscience and Director of the Center for Neurognetics in the Brain and Mind Research Institute at Weill Cornell Medicine. She received her MD and PhD from Cornell University Medical College her Neurology residency at Massachusetts General Hospital and molecular genetic fellowships at MGH and Rockefeller University. She built her laboratory at University of Minnesota before returning to Weill Cornell Medicine as a tenured Professor. She is a physician scientist who leads the Laboratory of Neurogenetics and Development. Common threads in her work have been discovery of gene mutations causing neurological disorders as a window on the drivers of brain development and function. In addition to human genetics, her studies use cell biological tools, genetically engineered mice and patient derived stem cells to investigate the molecular mechanisms leading to disease. In 2015, she founded the Center for Neurogenetics at WCM. The Center has both basic science and clinical arms, and operates a patient DNA and cell biobank that supports translational research across the neurological community. Dr. Ross has devoted much of her career to medical and neuroscience education. While at the University of Minnesota, she directed the NIH funded MD-PhD training program. At Weill Cornell Medicine she is Chair of the Neuroscience Graduate Program and is the founding Chair of the forming Master of Science in Genetic Counseling. Her current national service includes as an editorial board member of *Annals of Neurology* and *Neurology Genetics*, Chair of the NIH-CHHD-C study section, and President of the American Neurological Association.

Lauren Sansing, MD, MS, FANA
Yale University School of Medicine
lauren.sansing@yale.edu

Dr. Sansing completed her residency in Neurology in 2006 followed by a Vascular Neurology fellowship from 2006-2008, both at the Hospital of the University of Pennsylvania. Her clinical interests include acute ischemic stroke and intracerebral hemorrhage as well as other complex neurovascular diseases. Following clinical training, she completed a Master of Science in Translational Research at Penn studying immune mechanisms of injury after intracerebral hemorrhage. She then joined the faculty at the University of Connecticut and Hartford Hospital in 2010, where she was active in the Departments of Neurology, Neuroscience, Neurosurgery, and Immunology. She leads an NIH-funded laboratory identifying immunological treatment targets for intracerebral hemorrhage and stroke. Her laboratory moved to Yale in the summer of 2014, where she continues her work in stroke immunology through basic and translational studies. She has received numerous national and international awards for her research and is the Academic Chief of the Division of Stroke and Vascular Neurology and the Associate Vice Chair of Faculty Development for the Department of Neurology.

Kevin Sheth, MD, FANA
Yale University School of Medicine
kevin.sheth@yale.edu

Dr. Kevin Sheth is the Vice Chair for Clinical & Translational Research in Neurology & Neurosurgery and a founding Director of the Yale Center for Brain & Mind Health. He is recognized for his leadership in prevention, acute treatment, and recovery stroke research and has led highly innovative programs in drug development, translation, and medical devices. His team at Yale has served as a national model for academic neurology units. Dr. Sheth has served as PI or co-PI for eight multicenter clinical trials in stroke and has chaired clinical endpoint and data safety monitoring committees for several pivotal studies. He is a winner of the prestigious Robert Siekert Award from the American Heart Association (AHA), the Derek Denny Brown Award from the American Neurological Association, and an elected member of the American Society for Clinical Investigation (ASCI). He has mentored dozens of investigators and received the Stroke Mentorship Award from the AHA. His research has been funded by the NIH, American Academy of Neurology, AHA, and the US Army. He is the author of over 300 publications and has served on study sections for the NIH, AHA, FDA, and NASA. He is an Associate Editor at *Stroke* and a former member of the American Neurological Association and Neurocritical Care Society Board of Directors. His work has been showcased in *The Washington Post*, *Wall Street Journal*, NPR, CNN, BBC, and *Scientific American*. Dr. Sheth has also formed partnerships with entrepreneurs, pharmaceutical companies, and medical device start-ups to bring forward highly innovative solutions. He holds several patents and is a co-founder of early-stage companies. These efforts have resulted in extensive knowledge of FDA pathways, development of phase I–III drug programs, and implementation of new technology into the clinical workspace. A foremost example is the successful translation of glyburide from laboratory to multiple phase II studies, which was acquired from Remedy Pharmaceuticals by Biogen at the phase III stage. Similarly, he led efforts to acquire proof-of-concept data leading to FDA clearance for the world's first clinically relevant portable MRI system. Overall, the principal theme of his work is collaboration and advancing understanding of neurological disease.

Common Mistakes in NIH Grant Applications

The five review criteria for most NIH grant applications are Significance, Approach, Innovation, Investigator(s), and Environment. Innovation is not necessary, but the results should have compelling significance.

Problems with Significance:

Not significant nor exciting nor new research Lack of compelling rationale Incremental and low impact research

Problems with Specific Aims:

Too ambitious, too much work proposed Unfocused aims, unclear goals Limited aims and uncertain future directions

Problems with Experimental Approach:

Inappropriate level of experimental detail Feasibility of each aim not shown Little or no expertise with approach
Lack of appropriate controls

Not directly testing hypothesis Correlative or descriptive data
Experiments not directed towards mechanisms
No discussion of alternative models or hypotheses
No discussion of potential pitfalls

No discussion of interpretation of data
Inadequate description of statistical approach/analyses

Problems with Investigator(s):

No demonstration of expertise or publications in approaches Low productivity, few recent papers
Collaborators needed but none recruited, or no letters from collaborators Inadequate funding

Problems with Environment:

Inadequate institutional support

NIH Websites

FUNDING COMPONENTS OF THE NIH

The NIH Homepage:
https://www.nih.gov

Homepages of the NIH Institutes, Centers & Offices:
http://www.nih.gov/icd/

NIH GUIDE FOR GRANTS AND CONTRACTS
Program Announcements (PAs) and
Request for Applications (RFAs):
http://www.nih.gov/grants/guide/index.html

NIH Grants Policy Statement:
http://grants.nih.gov/grants/policy/

APPLICATION PROCESS
NIH Grant Application Instructions, Guidelines and Forms:
https://grants.nih.gov

SF424 (R&R) Application and Electronic Submission Information (including information on new biosketch formats):
http://grants.nih.gov/grants/funding/424/index.htm

NIH Modular Research Grant Applications:
https://grants.nih.gov/grants/how-to-apply-application-guide/format-and-write/develop-your-budget/modular.htm

Standard Due Dates for Competing Applications:
https://grants.nih.gov/grants/how-to-apply-application-guide/due-dates-and-submission-policies/due-dates.htm

Center for Scientific Review:
http://www.csr.nih.gov/

NCI's Quick Guide to the Preparation of
NIH Grant Applications:
https://deainfo.nci.nih.gov/extra/extdocs/gntapp.pdf

NIAID Samples of grant applications & more:
https://www.niaid.nih.gov/grants-contracts/sample-applications

NCCIH Tips for New NIH Research Grant Applicants:
https://www.nccih.nih.gov/grants/tips-for-new-nih-research-grant-applicants

REVIEW PROCESS

Review Criteria for Evaluation of Research Applications:
https://www.niaid.nih.gov/research/review-criteria

Descriptions of Initial Review Groups at the Center for Scientific Review:
http://www.csr.nih.gov/review/irgdesc.htm

NIH Center for Scientific Review Study Section Rosters:
http://www.csr.nih.gov/committees/rosterindex.asp

DATA ON ACTIVE GRANTS

Research Portfolio Online Reporting Tool (RePORT):
http://report.nih.gov/

NIH eRA Commons:
https://commons.era.nih.gov/commons/

SPECIAL PROGRAMS AT THE NIH

The K Awards:
https://www.niaid.nih.gov/grants-contracts/career-development-awards

Ruth L. Kirschstein National Research Service Awards Institutional Research Training Grants Individual Fellowships: https://grants.nih.gov/grants/guide/pa-files/PA-23-048.html

R03/Small Grant Program:
https://grants.nih.gov/grants/funding/r03.htm

AREA or R15 for Non-Research-Intensive Colleges and Universities:
http://www.nih.gov/grants/funding/area.html

SBIR/STTR Homepage:
https://sbir.nih.gov/

K - Awardee Attendee List

FIRST	LAST	CREDENTIALS	INSTITUTION	CITY	STATE
Scott	Adney	MD, PhD	Northwestern University	Chicago	IL
Shannon	Agner	MD, PhD	Washington University in St. Louis	St. Louis	MO
Asher	Albertson	MD, PHD	Washington University School of Medicine	St. Louis	MO
Ayham	Alkhachroum	MD. MSc	University of Miami	Miami	FL
Bhooma	Aravamuthan	MD DPhil	Washington University School of Medicine	St. Louis City	MO
Scott	Barbuto	MD PhD	Columbia University Medical Center	New York	NY
Jacob	Basak	MD, PHD	University of Colorado Anschutz Medical Campus	Aurora	CO
Ania	Busza	MD, PhD	University of Rochester	Rochester	NY
Cathryn	Cadwell	MD, PhD	University of California, San Francisco	San Francisco	CA
Philip	Campbell	MD, PhD	University of Pennsylvania	Philadelphia	PA
Nathan	Cohen	MD	Children’s National Hospital; George Washington University	Washington	DC
Erin	Conrad	MD	University of Pennsylvania	Philadelphia	PA
Daniel	Corwin	MD, MSCE	Children's Hospital of Philadelphia	Philadelphia	PA
Ana	Cristancho	MD, PhD	Children's Hospital of Philadelphia; University of Pennsylvania	Philadelphia	PA
Marian	Dale	MD, MCR	Oregon Health & Science University	Portland	OR
Alissa	D'Gama	MD, PhD	Boston Children's Hospital / Harvard Medical School	Boston	MA
Frank	Diaz	MD, PHD	Cedars-Sinai Medical Center	Los Angeles	CA
Matthew	Elrick	MD, PhD	Kennedy Krieger Institute	Baltimore	MD
David	Fischer	MD	University of Pennsylvania	Philadelphia	PA
Taha	Gholipour	MD	University of California, San Diego	La Jolla	CA
Maya	Graham	MD PhD	University of California, San Francisco	San Francisco	CA
Nicholas	Gregg	MD	Mayo Clinic	Rochester	MN
Aaron	Gusdon	MD	University of Texas Health Science Center	Houston	TX

K - Awardee Attendee List

FIRST	LAST	CREDENTIALS	INSTITUTION	CITY	STATE
Christopher	Hemond	MD	University of Massachusetts Chan Medical School	Worcester	MA
Lenora	Higginbotham	MD	Emory University School of Medicine	Atlanta	GA
Patrick	Hullett	MD, PhD	University of California, San Francisco	San Francisco	CA
Saef	Izzy	MD, FNCS, FAAN	Mass General Brigham, Harvard Medical School	Boston	MA
George	Kannarkat	MD, PhD	University of Pennsylvania	Philadelphia	PA
Benjamin	Kay	MD, PhD	Washington University in St. Louis	St. Louis	MO
Wesley	Kerr	MD, PhD	University of Pittsburgh	Pittsburgh	PA
Sattar	Khoshkhoo	MD	Brigham and Women's Hospital	Boston	MA
Minjee	Kim	MD	Northwestern University Feinberg School of Medicine	Chicago	IL
Matthew	Kirschen	MD, PhD, MSCE	Children's Hospital of Philadelphia, University of Pennsylvania	Philadelphia	PA
Youssef	Kousa	DO, PhD	Children’s National Hospital	Washington	DC
Mariel	Kozberg	MD, PhD	Massachusetts General Hospital	Boston	MA
Yi	Li	MD, PhD	Stanford University	Palo Alto	CA
Baijayanta	Maiti	MD, PhD	Washington University in St. Louis	St. Louis	MO
Eric	Mallack	MD, MBE, MS	Kennedy Krieger Institute	Baltimore	MD
Joanna	Mattis	MD, PhD	University of Michigan	Ann Arbor	MI
Katherine	McDonell	MD, MSCI	Vanderbilt University Medical Center	Nashville	TN
Divakar	Mithal	MD, PhD	Ann and Robert H. Lurie Children's Hospital	Chicago	IL
Evan	Noch	MD, PhD	University of Texas Southwestern Medical Center	Dallas	TX
Carlyn	Patterson Gentile	MD, PhD	Children's Hospital of Philadelphia	Philadelphia	PA
Davut	Pehlivan	MD	Baylor College of Medicine	Houston	TX

K - Awardee Attendee List

FIRST	LAST	CREDENTIALS	INSTITUTION	CITY	STATE
Bridget	Perry	PhD, CCC-SLP	MGH Institute of Health Professions	Boston	MA
John	Pluvinage	MD, PhD	University of California, San Francisco	San Francisco	CA
Araya	Puwanant	MD, MS	Wake Forest University School of Medicine	Winston-Salem	NC
Biswarathan	Ramani	MD, PhD	University of California, San Francisco	San Francisco	CA
Paul	Sampognaro	MD	University of California, San Francisco	San Francisco	CA
Andrea	Schneider	MD PhD	University of Pennsylvania	Philadelphia	PA
Laura	Scorr	MD, MSCR	Emory University	Atlanta	GA
Diane	Shao	MD, PhD	Boston Children's Hospital	Boston	MA
Richa	Sharma	MD, MPH	Yale School of Medicine	New Haven	CT
Sharan	Srinivasan	MD, PhD	University of Michigan	Ann Arbor	MI
Clare	Timbie	MD, PhD	University of California, San Francisco	San Francisco	CA
Douglas	Wilcox	MD, PhD	Brigham and Women's Hospital, Harvard Medical School	Boston	MA
Ifrah	Zawar	MD, MS-CR	University of Virginia	Charlottesville	VA

2025 ANA-NINDS K-Awardee Abstracts

Autoimmune Neurology and MS

Multiple Sclerosis and Neuroinflammation Is Associated with Hypertrophy of the Parasagittal Dura and MRI Pathology
Presenting Author: ***Christopher Hemond, MD, University of Massachusetts Chan Medical School***
Background: The parasagittal dura (PSD) is a likely neuro-immune interface in which dysfunction is hypothesized to contribute to chronic neuroinflammation, potentially from congestion and reduced clearance of central nervous system macromolecules.
Objectives: To develop a general automated method for segmentation of the PSD on 3D FLAIR images and determine clinical and MRI associations with this structure volume. The hypothesis was that PSD volume would be increased in MS compared to other non-inflammatory neurological disease (NIND) and healthy controls (HC), and that enlargement of this structure would show pathological clinical and MRI associations.
Methods: Two datasets were retrospectively examined including a prospective, observational cohort of patients at a large neuroimmunology clinic (COHORT 1), as well as a public MRI dataset (Fiscone et al., 2024) of persons with MS and HC (COHORT 2). 3D T1-weighted MRI scans were preprocessed and segmented using the CAT12 tool to determine whole brain volumes (WBV) and cortical thickness (CT), with additional FLAIR lesion segmentation performed using LST-AI. 3D FLAIR images were N4 bias corrected and then intensity normalized using Z-scores to the mean intensity of the (1) whole brain, (2) the lateral ventricles, and (3) the normal-appearing white matter (NAWM); (4) WhiteStripe (WS) normalization was also performed. The borders of the meningeal space were defined as the pial surface (inner) and dural-osteal junction (outer) using the mri_synthstrip tool in Freesurfer, followed by intensity thresholding, region-growing, and median filtering — all constrained by masking applied from standard space superior to the torcula. A range of intensity thresholds were tested empirically given a lack of gold standard, with a single threshold ultimately chosen for each normalization method that most closely aligned with PSD volumes reported in prior literature (~10mL) along with visual quality inspection. Resulting PSD volumes were log-transformed and clinical/MRI associations modeled with multivariable linear regression in R.
Results: COHORT 1 consisted of 360 patients with relapsing MS (RMS, age 45±12), 96 with progressive MS (PMS, age 58±9), and 89 with OIND (N=41, age 50 ±12) or NIND (N=48, age 49±11). COHORT 2 included 100 patients with RMS (age 57±17) and 50 HC (age 48±11). Z-score normalization methods were found to be biased, due to lower mean NAWM, whole brain, and ventricular CSF intensities in MS groups compared to HC, NIND and OIND (all $p<0.05$). In COHORT 2, this bias was able to be corrected though exclusion of 7 outlying participants, allowing for equalization of average NAWM and whole brain intensities between MS and HC groups. Average ventricular CSF intensity correlated strongly with multiple clinical and MRI parameters and was subsequently excluded as a method due to these intractable biases. Across both cohorts, PSD volumes obtained by different normalization methods agreed moderately to very strongly (r~0.4-0.9). More lenient intensity thresholding (leading to larger PSD volumes) was generally associated with stronger clinical and MRI correlations. In both cohorts and across all normalization methods, larger PSD volumes correlated with older age ($r=0.1$-0.5, $p<0.001$) and greater intracranial volume (ICV; $r=0.2$-0.4, $p<0.001$). If given, contrast administration in COHORT 1 prior to the FLAIR correlated with larger PSD ($r=0.1$-0.2, $p<0.01$). In multivariable models adjusting for age, sex and ICV (and contrast in COHORT 1), PSD volumes were ~40% larger in RMS vs HC (COHORT 2), and ~25% larger in RMS vs NIND ($p<0.001$) and ~60% larger in PMS vs NIND; but not RMS/PMS vs OIND ($p>0.05$; from COHORT 1). In COHORT 2, higher PSD volumes were associated with lower WBV and CT; this was only seen in MS and not in HC (as interaction terms: CT x type $p<0.001$; WBV x type $p<0.001$). In COHORT 1, all methods except WS showed significant pathological associations with higher PSD and lower WBV, and decreased CT (all $p<0.01$), but this was regardless of diagnosis and an interaction between these terms was not significant ($p>0.05$). Inconsistent findings were observed between normalization methods in association with lesion volumes, paramagnetic rim lesion number, and disability scores, with only Z-brain showing consistent associations ($p<0.01$) with all three. The strength or class of disease-modifying therapy was not associated with PSD volumes ($p<0.05$) by any method.
Discussion: PSD is 25-40% enlarged in RMS compared to NIND or HC brains, respectively, but not significantly different than OIND. This finding supports the hypothesis of the PSD as a neuro-immune interface that is hypertrophied in association with CNS inflammation. This hypertrophy of the PSD was also associated with greater cortical and whole brain atrophy in MS but not HC (COHORT 2), suggestive of a disease-specific effect; however, this same interaction was not observed in COHORT 1, in which PSD enlargement correlated with lower CT and WBV but did not statistically interact with NIND or OIND diagnoses. Regardless, for any intensity-based segmentation, normalization methods must be carefully considered due to bias. The unexpectedly lower mean NAWM and whole brain intensities in the MS group compared to HC/NIND/OIND may speculatively be due to the diffuse accumulation of (hypointense) iron in the white matter as part of MS pathology. A future research direction is to determine and validate an unbiased normalization method between disease states prior to segmentation. In general, more aggressive segmentations that included lower-intensity PSD tissue (and therefore higher PSD volumes) yielded stronger clinical correlations; this observation may guide future approaches to manualized “gold standard” segmentations of the PSD, a lack of which otherwise remains a significant limitation in the development of automated PSD segmentation methods.

Autoimmune Vitamin B12 Central Deficiency Underlying Idiopathic Myelopathy

Presenting Author: ***John Pluvinage, MD, PhD, University of California, San Francisco***

Co-Authors: *Sukhman Sidhu, BS, University of California, San Francisco, Kelsey Zorn, MS, University of California, San Francisco, Sravani Kondapavulur, MD, PhD, University of California, San Francisco, Carson Moseley, MD, PhD, University of California, San Francisco, Leah Zuroff, MD, PhD, University of California, San Francisco, Josiah Gerdts, MD, PhD, University of California, San Francisco, Iyas Daghlas, MD, University of California, San Francisco, Leena Suleiman, MD, University of California, San Francisco, Max Liu, MD, PhD, University of California, San Francisco, Todd Nguyen, MD, University of California, San Francisco, Benjamin Meyer, MD, University of California, San Francisco, Yair Mina, MD, NINDS, NIH, Min Kang, MD, University of California, San Francisco, Felicia Chow, MD, University of California, San Francisco, Maulik Shah, MD, University of California, San Francisco, Megan Richie, MD, University of California, San Francisco, Elan Guterman, MD, University of California, San Francisco, Vanja Douglas, MD, University of California, San Francisco, Joanne Guo, MD, University of California, San Francisco, Brian Scott, MD, Stanford University School of Medicine, Katherine Kvam, MD, Stanford University School of Medicine, Ahmed Abdelhak, MD, University of California, San Francisco, Tom Martin, MD, University of California, San Francisco, Jenny Linnoila, MD, PhD, University of Pittsburg, Sonam Mohan, MD, Kaiser Permanente, Madina Tugizova, MD, University of California, San Francisco, John Engstrom, MD, University of California, San Francisco, Alexis García Sarreón, Unit of Neuroimmunology and multiple sclerosis of Girona (UNIEMTG) of the University Hospital Dr. Josep Trueta, Ariadna Gifreu,Unit of Neuroimmunology and multiple sclerosis of Girona (UNIEMTG) of the University Hospital Dr. Josep Trueta, Mary Karalius, MD, University of California, San Francisco, Martineau Louine, MD, University of California, San Francisco, Bruce Cree, MD, PhD, University of California, San Francisco, Stephen Hauser, MD, University of California, San Francisco, Joseph DeRisi, PhD, University of California, San Francisco, Samuel Pleasure, MD, PhD, University of California, San Francisco, Ari Green, MD, University of California, San Francisco, Ralph Green, MD, PhD, University of California, Davis, Jeffrey Gelfand, MD, University of California, San Francisco, Gary Álvarez Bravo, MD, Unit of Neuroimmunology and multiple sclerosis of Girona (UNIEMTG) of the University Hospital Dr. Josep Trueta, Michael R. Wilson, MD, University of California, San Francisco*

Background: Disorders affecting the spinal cord (myelopathies) can cause severe disability. Despite diagnostic advances, approximately 12-18% of myelopathy cases continue to elude an etiological diagnosis, hampering effective treatment.

Methods: We retrospectively screened 584 patients enrolled in a neuroinflammatory disease research study for a diagnosis of idiopathic myelopathy. We performed programmable phage display to discover novel autoantibodies in the cerebrospinal fluid (CSF) of these patients. Orthogonal immunoassays were used to confirm candidate autoantibodies.

Results: 37 patients (6.3%) were diagnosed with myelopathy. 18 patients (48.6%) were eventually diagnosed with known causes, leaving 19 patients (51.4%) with the diagnosis of idiopathic myelopathy. 7 additional patients with idiopathic myelopathy were enrolled after the initial screen, comprising a total of 26 patients. Autoantibodies targeting the transcobalamin receptor (CD320) were identified in 16 patients (61.5%). Active vitamin B12 concentration was decreased in the CSF of anti-CD320 positive patients (P=0.0347), indicative of autoimmune B12 central deficiency (ABCD). Seropositive patients demonstrated a high frequency dorsolateral cord abnormalities on magnetic resonance imaging (MRI) (63%), normal CSF profile (69%), and antecedent viral illness (50%). Three patients received B12 supplementation and clinically improved.

Conclusions: ABCD underlies a substantial proportion of idiopathic myelopathy. B12 supplementation may be an effective treatment, but prospective studies will be necessary to assess causality and therapeutic efficacy.

Neuro-Immune Communication Across the Blood-Brain Barrier: A Critical Role for Astrocyte-T Cell Interactions in the Pathogenesis of Viral Encephalitis

Neuro-immune Communication Across the Blood-Brain Barrier: A Critical Role for Astrocyte-T Cell Interactions in the Pathogenesis of Viral Encephalitis

Presenting Author: ***Douglas Wilcox MD, PhD, Brigham and Women's Hospital, Harvard Medical School***

Co-Authors: *Adalia Zhou, BS, Harvard Medical School, Erin Mathieu, BS, Harvard Medical School, Chenghua Gu, PhD, Harvard Medical School*

Abstract: During inflammation of the central nervous system, immune signals from the brain must be relayed across the blood-brain barrier (BBB) to professional immune cells in the circulation. This critical relay of information is a fundamental process shared across neuroinflammatory conditions including multiple sclerosis, viral infection, and autoimmune encephalitis. Despite emerging recognition of the importance of this process, how professional immune cells enter the brain in response to parenchymal inflammation to modulate neural immune responses remains a mystery. The cascade of events that ultimately lead to end-stage pathology have been well-studied, but the root mechanisms of the earliest and causal neuro-immune interactions remain elusive, largely limited by the models used to study them. To address these earliest mechanisms of neuro-immune communication across the BBB, I developed a novel paradigm of neuroinflammation. In this model, viral infection of the brain and subsequent neuroinflammation is established without disruption of the BBB. Importantly, the focal infection in this model system allows for the temporal and spatial resolution required to understand the cellular responses that result in precise targeting of immune cells to the brain. I have optimized the dose and viral serotype to generate a transient viral replication in the brain with natural disease resolution and greater than 80% survival. Following characterization of this model, I found that astrocytes generate immune cell chemotactic cytokines and interact with T cells immediately after viral entry into the CNS. Both CD8 and CD4 T cells infiltrate the

brain early to interact with the perivascular microenvironment. Using cell-specific acute ablation and adoptive cell transfer, we demonstrate that CD4 T cells alone are both necessary and sufficient for survival during viral encephalitis. Surprisingly, CD4 T cells were found to modulate the astrocyte antiviral program, leading to control of viral replication and improved overall survival. Future work will focus on T cell- astrocyte interactions as a potential therapeutic target to improve outcomes in viral encephalitis, a disease with limited treatment options.

Behavioral Neurology and Dementia

Multiplex Proteomic Analysis of Lewy Body Dementia Reveals Cerebrospinal Fluid Biomarkers of Disease Pathophysiology and Progression

Presenting Author: ***Lenora Higginbotham, MD, Emory University School of Medicine***
Co-Authors: *Anantharaman Shantaraman, MS, Emory University School of Medicine, Qi Guo, MS, Emory University School of Medicine, Edward J. Fox, PhD, Emory University School of Medicine, Pritha Bagchi, PhD, Emory University School of Medicine, Fang Wu, PhD, Emory University School of Medicine, James J. Lah, MD PhD, Emory University School of Medicine, Allan I. Levey, MD PhD, Emory University School of Medicine, Nicholas T. Seyfried, PhD, Emory University School of Medicine*
Background: Lewy Body dementia (LBD), which comprises Parkinson's disease dementia (PDD) and Dementia with Lewy bodies (DLB), lacks established biofluid markers reflecting its complex molecular pathophysiology. The NULISAseq central nervous system (CNS) disease panel is a recently released commercial multiplexed proteomic assay that uses enhanced proximity ligation technology to measure 120 pre-selected analytes associated with a variety of neurodegenerative mechanisms. We evaluated the performance of this panel in a large multi-center cohort of individuals with LBD.
Methods: We applied the NULISAseq CNS disease panel to 685 CSF samples from 476 unique individuals with clinical diagnoses of control, PD without cognitive impairment, PD with cognitive impairment, and DLB. A subset of individuals had alpha-synuclein seed amplification assay (αSyn-SAA) results and/or paired longitudinal CSF samples. Differential expression, correlation analyses, and machine learning were used to identify markers highly associated with disease diagnosis, SAA positivity, and cognitive progression. We also compared LBD abundance trends to those observed in a separate NULISAseq analysis of Alzheimer's disease (AD) CSF samples.
Results: Of the 120 panel markers, nearly half (n=53) were significantly altered across one or more Lewy body diseases. DLB featured the most robust differential expression of the three disease groups compared to controls. Alpha-synuclein (SNCA) was not altered across disease, though it was among the 17 proteins significantly altered between SAA+ and SAA- DLB. Longitudinal analysis revealed five proteins (NEFL, NRGN, CCL26, CRH, PGF) featuring baseline levels that distinguished cases with stable versus declining cognition over the next two years. Machine learning identified a series of 10-analyte panels capable of discriminating Lewy body diagnoses and SAA pomallack sitivity with high accuracy (AUC > 0.9). Synaptic dysfunction (NRGN, SNAP25, NPTX2), inflammation (CCL17, CCL3, CCL26), and cell metabolism (ENO2, KLK6, UCHL1) were highly represented in these diagnostic panels. Several of these markers were also among the 12 proteins that featured divergent abundance trends in DLB and AD.
Conclusion: Our results highlight the utility of NULISAseq multiplex proteomic analysis in the identification of diagnostic and prognostic CSF biomarkers of LBD that reflect its diverse molecular pathophysiology.

Stimulant Medications Affect Arousal and Reward, Not Attention

Presenting Author: ***Benjamin Kay MD, PhD, Washington University in St. Louis***
Co-Authors: *Muriah D. Wheelock, PhD, Washington University in St. Louis, Joshua S. Siegel, NYU Langone, MD, PhD, Ryan Raut, PhD, Washington University in St. Louis, , Eric Feczko, PhD, Washington University in St. Louis, Timothy O. Laumann, Washington University in St. Louis, PhD, Scott A. Marek, PhD, Washington University in St. Louis, Evan M. Gordon, PhD, Washington University in St. Louis, Marcus E. Raichle, MD, Washington University in St. Louis, Deanna M. Barch, PhD, Washington University in St. Louis, Damien A. Fair, PhD, University of Minnesota, Nico U. F. Dosenbach, MD, PhD , Washington University in St. Louis*
Abstract: Prescription stimulants such as methylphenidate are being used by an increasing portion of the population (6.1\%), primarily children. These potent norepinephrine and dopamine reuptake inhibitors promote wakefulness, suppress appetite, enhance physical performance, and are purported to increase attentional abilities. Prior functional magnetic resonance imaging (fMRI) studies have yielded conflicting results about the effects of stimulants on the brain's attention, action/motor, and salience regions that are difficult to reconcile with their proposed attentional effects. Here, we utilized resting-state fMRI (rs-fMRI) data from the large Adolescent Brain Cognitive Development (ABCD) Study to understand the effects of stimulants on brain functional connectivity (FC) in children ({n} = 11,875; 8-11 years old) using network level analysis (NLA). We validated these brain-wide association study (BWAS) findings in a controlled, precision imaging drug trial (PIDT) with highly sampled (165-210 minutes) healthy adults receiving high-dose methylphenidate (Ritalin, 40 mg). In both studies, stimulants were associated with altered FC in action and motor regions, matching patterns of norepinephrine transporter expression. Connectivity was also changed in the salience (SAL) and parietal memory networks (PMN), which are important for reward-motivated learning and closely linked to dopamine, but not the brain's attention systems (e.g. dorsal attention network, DAN). The effect of getting adequate sleep closely matched the pattern of stimulant-related differences in action and motor cortex, and it was concordant with EEG- and respiration-derived brain maps of

arousal. Taking stimulants rescued the effects of sleep deprivation on brain connectivity and school grades. The combined noradrenergic and dopaminergic effects of stimulants may drive brain organization towards a more wakeful and rewarded configuration, explaining improved task effort and persistence without direct effects on attention networks.

Psychiatric and Behavioral Symptoms in Youth at Risk for Huntington Disease
Presenting Author: ***Katherine McDonell MD, MSCI, Vanderbilt University Medical Center***
Co-Authors: *Elizabeth M. Key, BS, Vanderbilt University Medical Center, Louis DeLuna, BS, BA, Vanderbilt University, Shuhei Shiino, BS, Vanderbilt University Medical Center, Kelly H. Watson, PhD, Vanderbilt University Medical Center, Bruce E. Compas, PhD, Vanderbilt University, Daniel O. Claassen, MD, Vanderbilt University Medical Center*
Background: Children growing up in families impacted by Huntington disease (HD) are subject to a wide range of psychosocial challenges and adverse childhood experiences, placing them at high risk of psychiatric problems. However, limited evidence is currently available regarding the prevalence and types of psychiatric symptoms experienced by young people from HD families compared to their peers.
Objective: To assess psychiatric and behavioral symptoms in children and adolescents at risk for HD compared to community controls using self-report and parent-report measures from the Achenbach System of Empirically Based Assessment.
Methods: The sample included a total of 97 youth ages 10-18, 42 of whom had a parent or grandparent with HD and 55 of whom were community controls. Young people completed the Youth Self-Report and parents completed the Child Behavior Checklist about their child.
Results: On self-report, youth at risk for HD reported significantly higher ratings on the attention problems [$t(94) = 2.58$, $p = .01$] and total problems [$t(94) = 2.16$, $p = .03$] subscales as compared to controls. Parents of at-risk children reported significantly higher scores on the anxious/depressed [$t(95) = 2.10$, $p = .047$], somatic complaints [$t(95) = 2.59$, $p = .01$], social problems [$t(95)= 3.27$, $p = .002$], internalizing problems [$t(95) = 2.24$, $p = .03$], and total problems [$t(95) = 2.25$, $p = .03$] subscales. On parent report, significantly more at-risk youth scored above the clinical cutoffs for somatic complaints, [17% of at-risk vs. 0% of controls, $\chi2$ (1, n = 97) = 9.64, $p = .002$], social problems [7% vs. 0%, $\chi2$ (1, n = 97) = 3.96, $p = .047$], internalizing problems [24% vs. 7%, $\chi2$ (1, n = 97) = 5.04, $p = .03$], externalizing problems, [7% vs. 0%, $\chi2$ (1, n = 97) = 3.96, $p = .047$] and total problems [19% vs. 4%, $\chi2$ (1, n = 97) = 5.90, $p = .02$].
Conclusions: Young people from HD-affected families experience significantly greater psychiatric and behavioral problems as compared to their peers, based on both self-report and parent report. A substantial proportion of parents also reported clinically elevated scores on multiple subscales for at-risk children, indicating clinically significant symptoms that warrant follow-up. Clinicians should be aware of the increased risk for psychiatric symptoms in children from HD families and implement proactive screening procedures to reduce the risk of psychological distress in this vulnerable population.

Enhancing Lysosomal Protease Activity Reduces TDP-43 Levels and Improves Neuronal Resilience in Human iPSC-Derived Neurons
Presenting Author: ***Paul Sampognaro MD, University of California, San Francisco***
Co-Authors: *Zoe Liau, BS, University of California San Francisco, Tara Antee, BS, University of California San Francisco, Aimee Kao, MD, PhD, University of California San Francisco*
Background: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are devastating neurodegenerative diseases characterized by the pathological accumulation of TDP-43 in neurons. Growing evidence implicates lysosomal dysfunction in ALS/FTD pathogenesis, impairing the clearance of toxic protein aggregates like TDP-43. Consequently, enhancing the activity of specific lysosomal proteases involved in TDP-43 degradation presents a promising therapeutic strategy.
Objective: To investigate the impact of modulating the activity of specific lysosomal proteases on TDP-43 levels and neuronal survival in human iPSC-derived cortical neurons (iNeurons) and motor neurons (iMNs), thereby evaluating a potential therapeutic avenue for ALS/FTD.
Methods: To identify promising candidates for targeting TDP-43 pathology, we first conducted an initial siRNA screen targeting a panel of lysosomal proteases, including cathepsins B, D, E, F, L, and asparaginyl endopeptidase (AEP), in iNeurons and iMNs. To further validate our findings, we next employed CRISPR activation (CRISPRa) and CRISPR interference (CRISPRi) technologies to specifically upregulate or downregulate the endogenous expression of these proteases. TDP-43 levels were assessed via Western Blot, and neuronal resilience was measured using AlamarBlue assays.
Results: Preliminary data show that siRNA-mediated knockdown of CTSB, CTSD, and AEP individually led to significantly increased steady-state TDP-43 levels in iNeurons, with similar trends observed in iMNs. CRISPRi-mediated knockdown of these proteases confirmed this relationship, causing increased TDP-43 levels. Conversely, CRISPRa-mediated upregulation of endogenous CTSB, CTSD, and AEP resulted in decreased steady-state TDP-43 levels. Correspondingly, protease activation enhanced neuronal resilience (particularly CTSB and CTSD in iNeurons and AEP in iMNs), while knockdown of these enzymes diminished resilience.
Conclusions: These preliminary findings support the hypothesis that enhancing the activity of specific lysosomal proteases (CTSB, CTSD, AEP) effectively reduces steady-state TDP-43 levels and improves neuronal resilience in relevant human neuronal subtypes. Modulating endogenous protease activity via CRISPRa offers a targeted approach to restore TDP-43 homeostasis. This strategy, leveraging the cell's intrinsic degradative machinery, holds therapeutic potential for a broad spectrum of ALS and FTD cases

characterized by TDP-43 pathology. Future studies will explore these mechanisms in more complex 3D models and assess downstream effects on neuronal viability.

Circuits from the Amygdala to Reticular Thalamus in Thalamic Networks and Behavior
Presenting Author: ***Clare Timbie, MD, PhD, University of California, San Francsico, San Francisco, CA***
Co-Authors: *Isaac Chang, BS, Gladstone Institute of Neurological Disease, Jeanne Paz, PhD, Gladstone Institute of Neurological Disease*
Background: The amygdala is at the core of the brain's emotional network, responding to stimuli with emotional valence and activating cortical and subcortical areas to influence attention, decision-making, and behavior. In primates, the network underpinning emotional attention includes connections between the amygdala, thalamus, and prefrontal cortex. A key component of this network is the GABAergic nucleus reticularis thalami (nRT), which forms an inhibitory shell around the thalamus. The nRT is reciprocally connected with thalamocortical relay nuclei, receives projections from the cortex, and is thought to gate signals in the thalamus from reaching conscious awareness in the cortex. Recent work has shown that in rodents, nRT also receives input from the amygdala. However, the function of this pathway in thalamocortical circuits and behavior is unknown.
Methods: To selectively activate amygdala-nRT pathways, I injected virus conferring expression of channelrhodopsin in projection neurons in the amygdala, under the Ca2+/calmodulin-dependent protein kinase II alpha (CamKIIα) promotor. After allowing time for expression, acute slices were prepared and responses in nRT neurons were recorded using whole cell patch clamp, while optically stimulating amygdala axons (n = 6 neurons from 4 mice). In a separate cohort of mice, optical fibers were implanted in the bilateral nRT for in vivo stimulation of amygdala-nRT pathways during the open field task to test the impact of activating this pathway on anxiety-like behaviors. Control animals underwent the same surgical procedures and behavioral testing, except with injection of CamKIIα AAV without channelrhodopsin (n = 6 controls and 9 opsin).
Results: Low amplitude excitatory, slowly decaying post-synaptic currents were recorded in nRT neurons using whole cell patch clamp, when optically activating amygdala axons. Bilateral optical activation of amygdala-nRT pathways in freely behaving mice led to increased velocity of the mouse. Moreover, after stimulation, mice spent more time in the center area of the open field. These behaviors suggest rodent anxiolysis. Stimulation did not affect behavior in controlled animals, which received the same surgical procedures and laser stimulation, but with injection of virus that did not contain channelrhodopsin.
Conclusions: Cellular electrophysiology combined with optogenetic stimulation in brain slices demonstrated the synaptic properties of the pathway connecting the amygdala with the nRT in mice. This pathway has features seen in modulatory inputs. Further, in vivo stimulation of this pathway suggests that this circuit's activation can decrease anxiety behaviors.
Funding: JTP is supported by the National Institutes of Health grants R01NS121287; R01MH121446, and the Gladstone Institutes; IC is supported by the Croucher Scholarship; CT is supported by grants from the National Institutes of Health (5R25NS070680-13) and the American Epilepsy Society (A143737).

Cerebrovascular Disease

Normal Aging in Mice is Associated with Diminished Behavioral Recovery and Prolonged Disruption of Somatomotor Networks after Experimental Stroke
Presenting Author: ***Asher Albertson MD, PHD, Washington University School of Medicine***
Co-Authors: *Ryan C. Bowen, PhD, Washington University School of Medicine, Kyrillos Ayoub, BS, Washington University School of Medicine, Roman Pati, BS, Washington University School of Medicine, Brendon Wang, BS, Washington University School of Medicine, Rose A Leon-Albvarado, BS, Washington University School of Medicine, Adam Q Bauer, PhD, Washington University School of Medicine, Jin-Moo Lee, MD PhD, Washington University School of Medicine*
Abstract: Stroke incidence is greatest in elderly individuals, and increasing age is a significant predictor of mortality and disability following stroke. Despite this, the underlying drivers of impaired stroke recovery in aged individuals remain poorly understood. Network dysfunction represents one potential mechanism contributing to age-related differences in stroke recovery. Normal aging is characterized by progressive deterioration in spontaneous network-level activity and disruptions of functionally connected networks. Stroke also disrupts network function, and stroke recovery is correlated with the restoration of these networks. We therefore hypothesized that aged mice subjected to experimental stroke would exhibit impaired behavioral recovery, greater disruption of network function, and reduced restoration of network activity compared to younger mice.
To test this hypothesis, we evaluated equal cohorts of aged (18 months, n=20, 50% male) and young (3 months, n=20, 50% male) Thy1-GCaMP6f mice before stroke (baseline) and at 1, 4, and 7 weeks after stroke or sham surgery (aged sham n=20, young sham n=20). Strokes were induced via Rose Bengal injection (200 µL, 10 g/L) and exposure of the forepaw somatosensory cortex to a laser (10 min, 23 mW). At each time point, somatomotor behavior was assessed using cylinder and grid-walking tests. Widefield calcium imaging was performed (454 nm LED excitation, 15 min acquisition, 16.8 Hz framerate, through a plexiglass extracranial window) to measure spontaneous neuronal activity (spectral power) and functional connectivity (seed-based correlations, node degree), as well as stimulus-evoked activation (forepaw stimulation at 3 Hz). Power spectral analysis of spontaneous GCaMP fluorescence was

computed via fast Fourier transform. Functional connectivity maps were generated by correlating the fluorescence time series within regions of interest against those of all pixels. Node degree was calculated by counting the number of pixels correlated above a defined threshold ($z > 0.4$). All mice were euthanized at study completion, and infarct sizes were measured.
Behavioral recovery was significantly impaired in aged mice at 7 weeks post-stroke (forelimb asymmetry aged: 5.1%; young: 6.82%). Despite differences in recovery, infarct sizes were not significantly different between aged and young cohorts. Both groups exhibited disrupted ipsilateral and contralateral somatosensory and motor network connectivity following stroke. However, bilateral somatosensory and somatomotor network connectivity recovered by 7 weeks in young but not aged mice. Stimulus-evoked responses, measured as peak GCaMP activity and power at 3 Hz stimulation, were diminished at baseline in aged mice and failed to improve post-stroke. These data demonstrate that reduced stroke recovery in aging is associated with both impaired reconnection of functional networks and diminished baseline network activity.

Microglia Interact with Dendritic Spines and Regulate Spine Numbers After Brain Injury Following Resuscitation from A Cardiac Arrest

Presenting Author: ***Jacob Basak MD, PhD, University of Colorado Anschutz Medical Campus***
Co-Authors: *Macy Falk, BS, University of Colorado Anschutz School of Medicine, Andra L. Dingman, MD, Children's Hospital Colorado, University of Colorado Anschutz School of Medicine, Annabelle Moore, BS, University of Colorado Anschutz School of Medicine, Erika Tiemeier, BS, University of Colorado Anschutz School of Medicine, Nidia Quillinan PhD, University of Colorado Anschutz School of Medicine*

Background: Cognitive dysfunction is common after a global cerebral ischemic injury caused by cardiac arrest and is likely due in part to changes in synaptic function. Increasing evidence suggests microglial cells regulate synapse architecture and activity in various pathophysiologic conditions. However, the role of microglia in mediating synaptic injury after global cerebral ischemia has not been addressed. In this study, we use a mouse model of cardiac arrest and cardiopulmonary resuscitation (CA/CPR) to evaluate changes that occur in the numbers and morphology of both dendritic spines and microglia in the hippocampus after global cerebral ischemia. We also directly evaluate the interaction between dendritic spines and microglia after CA/CPR and assess how altering microglial numbers after the injury affects spine numbers.
Methods: A murine cardiac arrest with cardiopulmonary resuscitation (CA/CPR) model was utilized to induce global cerebral ischemia in Thy1-GFP adult mice (age 8-12 weeks). Brain tissue was collected at 72 hours and 7 days post procedure and stained for Iba1 (marker of microglia cells) and CD68 (marker of phagocytosis). Dendritic spine density, microglia reactivity, and microglia-spine co-localization were measured and compared to sham animals. To determine if microglia cells impact spine numbers after a CA/CPR injury, microglia levels in the brain were depleted with twice daily injections of the colony-stimulating factor 1 inhibitor PLX5622 beginning 72 hours post procedure and continuing until 6 days post procedure. Brain tissue was then collected for immunohistochemistry and dendritic spine density and microglia proliferation were measured and compared to sham animals.
Results: Global cerebral ischemia in the setting of a CA/CPR injury resulted in a significant decrease in hippocampal secondary apical dendritic spine density 72 hours (1.7 versus 2.6 spines/µm, $p=0.006$) and 7 days (1.6 versus 2.0 spines/µm, $p=0.013$) post-injury in the hippocampus compared to sham animals. Additionally, microglia-spine interactions are increased in CA/CPR animals with significantly higher levels of spines showing >70% engulfment (6.6% versus 2.9%, $p=0.0013$). CD68 expression, a marker of cellular phagocytosis, is also significantly increased in the microglia of CA/CPR animals at 72 hours (13.6% versus 2.9% of microglia surface, $p<0.0001$). PLX5622 treatment increased hippocampal dendritic spine numbers in mice that survived a CA/CPR injury (1.44 versus 2.0 spines/µm in vehicle versus PLX5622 treated animals, $p=0.04$), while no change was observed with PLX5622 in the number of spines in mice that underwent a sham procedure.
Conclusion: Our results demonstrate an effect of global cerebral ischemia on decreasing spine density at delayed time points post CA/CPR Injury, suggesting a decrease in post synaptic spine numbers may play a role in the long-term cognitive deficits experienced after ischemic brain injury. Additionally, the increase in spine density in mice with a CA/CPR injury treated with PLX5622 highlights that modulating microglia numbers impacts spine density. Collectively, these results emphasize the important role microglia exhibit in regulating synapse numbers in the setting of a CA/CPR injury and suggest targeting microglia-synapse interactions may improve cognitive outcomes following global ischemic brain injury.

Longitudinal Changes in Wrist Muscle Activity Following Stroke: Preliminary Findings

Presenting Author: ***Ania Busza MD, PhD, University of Rochester***
Co-Authors: *Aaron Huynh, BS, University of Rochester, Adarsh Mavathaveedu, BS, University of Rochester, Paige Hepple, BS, University of Rochester*

Abstract: Despite current acute stroke therapies, many individuals are left with upper extremity (UE) disability after stroke. In the chronic stage, some individuals with post-stroke hemiparesis exhibit one or more impairments of motor control, including: (1) decreased maximal muscle activation, (2) delayed muscle activation, (3) motor fatigability, and (4) abnormal co-activation of antagonistic muscle groups. However, it is still unclear what factors predict the emergence of these motor control abnormalities in some but not all stroke survivors. To better understand the mechanism underlying specific motor control abnormalities, we have developed an electromyographic (EMG)-computer interface to collect EMG signals from participants performing repetitive muscle

activations. Our EMG-computer interface uses surface EMG signals from the wrist flexor and extensor muscle groups to control a simple computer game. Successful gameplay requires multiple isometric muscle contractions at precise time points, each lasting three seconds. We are using this system to collect EMG data from participants with hemiparesis due to stroke at one week, one month, three months, and six months post-stroke. We are collecting additional baseline information from each subject including baseline neuroanatomy via neuroimaging; and early post-stroke motor function via bedside motor testing and the ability to obtain motor evoked potentials via transcranial magnetic stimulation. Together, these data will be examined to identify potential biomarkers in the early stages after stroke that best predict specific motor control abnormalities in the chronic phase after stroke. Thus far, we have enrolled over 40 subjects. Preliminary analysis looking at grip strength and EMG amplitude one-month post-stroke has found both to be larger in the ipsilesional (unaffected) side, as would be expected. Furthermore, participants with higher Fugl-Meyer values (a score for measuring arm impairment) at one-month post-stroke have higher maximum EMG values and a longer time-to-peak EMG latency as compared to those with lower Fugl-Meyer values. Further analysis will include additional time points (including 3- and 6- months post-stroke) and analysis of co-activation of antagonist muscle groups. This data will be used to assess the prevalence and individual trajectory of each motor impairment over the first six months post-stroke. Ultimately, we hope to use the information gained in this longitudinal study to develop personalized, impairment-specific interventions for motor recovery.

Secondary Ischemia From (Convexity) Subarachnoid Hemorrhage in A Mouse Model of Cerebral Amyloid Angiopathy
Presenting Author: ***Mariel Kozberg, MD, PhD, Massachusetts General Hospital***
Co-Authors: *S. Eugene Kim, BS, Massachusetts General Hospital, Lee Hanlin, BS, Massachusetts General Hospital, Ajay George, BS, Northeastern University, Damilola Adetunla, BS, Massachusetts General Hospital, S. Soumya Vytla, BS, Massachusetts General Hospital, Susanne van Veluw, PhD, Massachusetts General Hospital*
Background: Cerebral amyloid angiopathy (CAA) is a small vessel disease that leads to intracerebral hemorrhage (ICH) and cognitive impairment. CAA-related cortical superficial siderosis (cSS), the chronic form of convexity subarachnoid hemorrhage (cSAH), is an important risk factor for ICH and cognitive decline; however, the mechanisms linking cSS to these clinical manifestations are incompletely understood. We hypothesize that damage to cortical blood vessels from chronic blood products worsens vascular function in CAA, leading to ischemic injury and/or recurrent hemorrhage.
Aim: To establish a model of cSAH progressing to cSS in mice with advanced CAA, enabling assessments of vascular function (in-vivo) and secondary cortical injury (ex-vivo).
Methods: Cranial windows with custom-made silicone ports were implanted in 11-month-old APP23 transgenic (Tg) mice – a mouse model of amyloidosis – and wildtype (WT) littermates. One-month post-surgery, mice were injected with 10μL of arterial blood vs sterile PBS through the port and above the cortex (n=6 Tg-blood, 7 WT-blood, 5 Tg-PBS, 7 WT-PBS). Using in-vivo widefield-microscopy, pial vascular structure and vascular transit time were assessed at baseline and one-day, one-week, and one-month post-injection. Vascular transit time was assessed by determining the amount of time needed for a bolus of contrast to travel from the arterial to venous circulation. After perfusion, brains were sectioned and stained for H&E and iron ex-vivo; infarcts and iron deposits were quantified using machine-learning assisted quantitative histopathology.
Results: Iron deposits were observed in the cortex ex-vivo, resembling cSS in human tissue. We observed a trend towards higher infarct volumes in blood-injected vs PBS-injected mice (p=0.14, two-way ANOVA). Comparing iron deposition to infarcts in sections from blood-injected mice revealed a genotype-iron interaction: sections from Tg mice had higher infarct volumes for a given amount of iron (p=0.018, linear mixed-effects model).
To analyze our in-vivo data, we developed a technique for automated vascular segmentation, distinguishing between arteries and veins. We observed a trend towards an increase in vascular transit time one-week post-blood injection in the WT-blood group (suggesting vasoconstriction), which returned to baseline at 1-month (p = 0.077, linear-mixed effects model). No change in vascular transit time was observed throughout this imaging period in the Tg-blood group (p = 0.86, linear mixed-effects model). Ongoing work assessing structural changes in the pial vasculature will also be presented.
Conclusions: Our findings in histopathological tissue suggest ischemic injury occurs secondary to cSAH/cSS, exacerbated by CAA pathology. Intriguingly, our in-vivo imaging findings in the same mice demonstrated an increase in vascular transit time in WT but not Tg blood-injected animals, suggesting less vasoconstriction in Tg animals in response to subarachnoid blood. Therefore, the relative increase in infarcts in Tg mice may not be due to vasoconstriction alone. Ongoing work is focused on delineating alternative pathways which may lead to susceptibility to hemorrhage-related infarction in CAA, including baseline microvascular dysfunction and perivascular inflammation.

Plasma Proteomic Signatures Associated with Ischemic Stroke Etiologies
Presenting Author: ***Richa Sharma MD, MPH, Yale School of Medicine***
Co-Authors: *Ho-Joon Lee, PhD, Yale School of Medicine, Lauren Sansing, MD, MS, Yale School of Medicine, Srikant Rangaraju, MBBS, MS, Yale School of Medicine, Ohm Parikh, BS, Yale School of Medicine*
Background: Nearly one-quarter of acute ischemic strokes (AIS) are recurrent strokes. Another stroke can lead to death or further disability. The causative mechanism or etiology of an AIS can be heterogeneous including large artery atherosclerosis (TOAST 1), cardio embolism (TOAST 2), small vessel disease (TOAST 3), and other rare, determined etiologies (TOAST 4). Once a stroke etiology

diagnosis is determined, there are proven, guideline-recommended therapies that can be implemented to target the pathology. Despite their availability, evidence-based secondary stroke prevention therapies such as carotid revascularization for strokes due to symptomatic carotid disease, dual antiplatelet therapies for intracranial atherosclerosis-related strokes, and anticoagulation for hypercoagulability of malignancy-related strokes, are underutilized worldwide. Diagnostic uncertainty about stroke etiology may contribute to the differential rates of targeted secondary stroke prevention therapy use.

Objective: We aim to derive plasma proteomic signatures associated with ischemic stroke etiologies during the acute phase.

Methods: This was an observational study of all adult patients admitted to Yale-New Haven Hospital with an AIS diagnosis between 2015-2020 and plasma sample collected and stored in the Yale Acute Stroke Biorepository. Samples were analyzed using the SomaScan 11K Assay platform by SomaLogic Laboratory (CO, USA) to derive calibrated quantitative measurements of 11,083 unique human protein analytes using Slow Off-rate Modified Aptamer reagents, which are single stranded DNA-based protein affinity reagents with unique nucleotide sequences. The outcome was the ischemic stroke etiology adjudicated by agreement of at least 2 board-certified vascular neurologists. Using samples from non-cryptogenic strokes, univariate analyses were performed using Student T-tests and Wilcoxon Rank Sum tests to identify protein that are significantly different between each etiology versus the rest at a false detection rate adjusted p-value threshold of <0.15 to reduce dimensionality. We then built random forest models to predict each etiology versus the rest using these proteins and performed 5-fold cross-validation for each model.

Results: The cohort was comprised of 71 samples from eligible patients (median age: 69 years [IQR 58-76], 60.6% male, time from last known well to sample collection: median 28 hours [IQR 22-68], TOAST 1: n=17; TOAST 2: n=24; TOAST 3: n=6; TOAST 4: n=9; TOAST 5: n=15). The number of proteins differentiating each non-cryptogenic etiology versus the rest were: 660 (TOAST 1), 20 (TOAST 2), 8 (TOAST 3), and 160 (TOAST 4). The top 5 proteins distinguishing each etiology are presented in the Table. Compared with vascular neurologists' diagnoses, the mean cross-validated area under the curve (AUC) and accuracies of the proteomic-based classifiers were 0.81 and 0.75, respectively. The AUC for each etiology versus not depicted in the Figure were: 0.78 (TOAST 1), 0.78 (TOAST 2), 0.76 (TOAST 3), and 0.94 (TOAST 4). The accuracy rates for each versus not were: 0.68 (TOAST 1), 0.58 (TOAST 2), 0.92 (TOAST 3), and 0.82 (TOAST 4).

Conclusion: Using cross-validated proteomics-based classifiers derived from plasma samples collected in the acute phase after an AIS, we distinguished between non-cryptogenic ischemic stroke etiologies in a single-center cohort comparably to board-certified vascular neurologists. Future studies are necessary to evaluate the generalizability of these findings.

Table. Top 5 proteins distinguishing each non-cryptogenic ischemic stroke etiology versus the rest ranked by the smallest FDR-adjusted p-values.

Large artery atherosclerosis (TOAST 1)
1. Zinc finger CCCH domain-containing protein 15
2. Histone deacetylase 3
3. Developmentally regulated GTP-binding protein 1
4. Ras-related C3 botulinum toxin substrate 2
5. Copine-2

Cardio embolism (TOAST 2)
1. Lithostathine-1-beta
2. Myostatin-Propeptide
3. SH3 domain-binding protein 5
4. Oxytocin-neurophysin 1
5. Protein kinase C iota type

Small Vessel Disease (TOAST 3)
1. SH2 domain-containing adapter protein D
2. Receptor expression-enhancing protein 2
3. Ras-related protein Rab-26
4. Retinal dehydrogenase 2
5. ER membrane protein complex subunit 1

Other rare, determined etiologies (TOAST 4)
1. Histo-blood group ABO system transferase
2. Lithostathine-1-beta
3. Lithostathine-1-alpha
4. Growth/differentiation factor 15
5. Interleukin-8

Figure. Receiver operating curves depicting the cross-validated test characteristics of the proteomics-based random forest classifiers for each etiology (Class 1-4 map to TOAST 1-4, respectively) versus the rest among patients with non-cryptogenic ischemic strokes.

Epilepsy

Excitatory Neuron Dysfunction and Pharmacologic Rescue in an SCN2A Gain-of-Function Variant Associated with Early-Onset Epilepsy

Authors: ***Scott Adney MD, PhD, Northwestern University***
Co-Authors: *Sashmita Panda, PhD, Northwestern University, Luis Williams, PhD, Quiver Bioscience, Diana Jazmin Ixmatlahua Ribera, PhD, Northwestern University, Steve Ryan, PhD, Quiver Bioscience, Chinwendu Obi Obasi, BS, Northwestern University, Owen McManus, PhD, Quiver Bioscience, Graham Dempsey, PhD, Quiver Bioscience, Alfred L. George, Jr., MD, Northwestern University*
Abstract: Variants in the gene SCN2A, which encodes for the Nav1.2 voltage-gated sodium channel, are linked to monogenic causes of variable onset epilepsy, autism spectrum disorder, and epileptic encephalopathies. While the mechanism for SCN2A haploinsufficiency and concomitant loss of function has been explored in detail, the impact of missense SCN2A variants is less clear due to a paucity of studies looking at neuronal function. To address this roadblock, we applied high-throughput all-optical electrophysiology to patient-derived neurons with the p.M1879T variant compared to CRIPSR-corrected isogenic lines. We complemented the findings in these 'Optopatch' experiments with conventional patch-clamp electrophysiology. The p.M1879T variant neurons had significantly increased firing rates compared to isogenic controls at higher and longer optical stimuli, indicating increased firing reserve. These neurons tended to fire later into the pulse as well, demonstrating resistance to depolarization block. Machine learning-based classification was able to differentiate the neuron genotype with high accuracy (>95%) based on these evoked firing parameters. We further applied high-throughput optical electrophysiology to characterize the effect of different clinically available sodium channel blocking agents on evoked neuronal firing: carbamazepine, phenytoin, lacosamide, and cenobamate. Compared to DMSO-treated controls, all anti-seizure medications resulted in a dose-dependent reduction of evoked firing. Select concentrations of drugs were able to partially rescue the variant firing close to isogenic levels, demonstrating translational application of our in vitro findings. These results provide the first application of high-throughput iPSC-derived neuron electrophysiology and pharmacology in SCN2A-related disorders, demonstrating proof that this platform can be readily applied to a variety of monogenic models of epilepsy.

Clinical, Radiological, And Pathological Associations of Executive Dysfunction in Children with Focal Cortical Dysplasia-Related Epilepsy

Presenting Author: ***Nathan Cohen, MD, Children's National Hospital, The George Washington University School of Medicine, Washington, DC***
Co-Authors: *Hua Xie, PhD, Children's National Hospital, The George Washington University School of Medicine, Washington, DC, Venkata Sita Priyanka Illapani, MS, Children's National Hospital, The George Washington University School of Medicine, Washington, DC, Sonya M. Leikin, BS, Children's National Hospital, The George Washington University School of Medicine, Washington, DC, Xiaotong Li, BS, Children's National Hospital, The George Washington University School of Medicine, Washington, DC, Ana Moreno Chaza, BS, Children's National Hospital, The George Washington University School of Medicine, Washington, DC, Chloe Hooker, BS, Children's National Hospital, The George Washington University School of Medicine, Washington, DC, L. Gilbert Vezina, MD, Children's National Hospital, The George Washington University School of Medicine, Washington, DC, Hayley J. Loblein, PhD, Children's National Hospital, The George Washington University School of Medicine, Washington, DC, William D. Gaillard, MD, Children's National Hospital, The George Washington University School of Medicine, Washington, DC, Leigh N. Sepeta, PhD, Children's National Hospital, The George Washington University School of Medicine, Washington, DC, Madison M. Berl, PhD, Children's National Hospital, The George Washington University School of Medicine, Washington, DC*
Background: Executive dysfunction (ExD) occurs as a common comorbidity of focal epilepsy. Focal cortical dysplasia (FCD) is the most frequent etiology of surgically treatable epilepsy in children. The purpose of this study was to investigate clinical, etiologic (pathology), and anatomic versus functional network associations with ExD in FCD-related epilepsy. FCD cortical location is not consistently associated with ExD- lesions from different lobes may or may not cause ExD. Recent evidence implicates FCD lesion-network interactions as a mechanism underlying ExD. FCD Type I pathology has been reported to be associated with worse intellectual function. We hypothesized that FCDs with co-localization to Frontoparietal Control or Attentional networks are associated with ExD; and separately, that FCD Type I pathology is associated with ExD.
Methods: FCD patients were selected from surgical/radiological databases if they had preoperative neuropsychological testing. Behavior Rating Inventory of Executive Function (BRIEF) Global Executive Composite (GEC) scores and contributing indices/subscales were collected. FCD co-localization to the Yeo 7-network atlas was determined. Clinical, radiological, and pathological factors were evaluated for associations with ExD.
Results: Preoperative BRIEF-GEC T-scores were available for 93 FCD patients. Control network co-localization (OR 3.6, $p<0.05$) and FCD Type I (OR 4.45, $p=0.009$) were associated with ExD (BRIEF-GEC T-score≥65). Control network co-localization was associated with: Cognitive-Regulation-Index ($p=0.03$) and its contributing Plan/Organize subscale ($p=0.028$). FCD Type I associated with: BRIEF-GEC T-score ($p=0.007$), CRI ($p=0.019$), Working Memory ($p=0.021$), Plan/Organize ($p=0.042$), Shift ($p=0.015$), and Emotional Control

(p=0.006) subscales. These findings were unrelated to Full Scale IQ. FCD co-localization to attentional network (Dorsal or Ventral), lobar location, or age seizure onset were not associated with ExD.
Discussion: These data show the importance of lesion-network interaction in neuropsychological comorbidity (ExD) in focal epilepsy. The findings are independent of lesion size or cortical lobar location. Control network co-localization network is associated with ExD in this heterogeneous cohort of FCD-related epilepsy. There is a potential network-level structure-function correlation suggested as the most affected processes of cognitive regulation (e.g. planning/organization) are domains regulated by this network. These findings lend toward a more unified theory of focal epilepsy, by beginning to link common neuropsychological deficits seen across the epilepsies by cortical lesion-network interaction, regardless of lobar location.
Funding: NTC is supported by the American Academy of Neurology Career Development Award and the Hess Foundation. While this work was funded by the American Academy of Neurology, the findings and conclusions in this work are those of the authors and do not necessarily represent the official position of the American Academy of Neurology. LNS is supported by NIH NINDS K23NS093152. This work was also supported by DC-IDDRC NICHD NIH P50 HD105328. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

The Effect of Low-frequency Stimulation on Interictal Spike Rates
Presenting Author: ***Erin Conrad, MD, University of Pennsylvania***
Co-Authors: *Carlos A. Aguila, BS, University of Pennsylvania, Sarah Lavelle, MS, University of Pennsylvania, William Ojemann, BS, University of Pennsylvania, Zican Zhou, ME, University of Pennsylvania*
Background: Electrical brain stimulation has been variably described to either increase or reduce interictal spikes in patients with epilepsy. Stimulation-induced changes in spike rates are important both because sites with stimulation-induced spike increases may localize the epileptogenic zone [1], and because a stimulation-induced reduction in spikes is associated with subsequent seizure reduction in chronic implanted neurostimulation devices [2]. The effect of stimulation location on spike rates remains unclear, which limits our understanding of both how to use stimulation-induced spikes as a biomarker in surgical planning, as well as the optimal stimulation paradigms for seizure reduction.
Methods: We performed a retrospective analysis of intracranial EEG recordings of 32 patients with drug-resistant epilepsy who underwent low frequency brain stimulation as part of a standard clinical protocol (3 mA, 1 Hz, 500 us pulse width, 30 s train duration). We measured interictal spike rates using a previously validated automated detection algorithm [3,4] at 10,000 random segments throughout the intracranial recording to estimate the baseline distribution of spike rates. We compared the spike rates during stimulation to this baseline distribution and compared the change in spike rates across stimulation locations.
Results: Overall, spike rates were lower during stimulation (median (IQR) 0.15 (0.05-0.35) spikes/min) than at baseline (0.36 (0.24-0.47) spikes/min) (sign rank test: $W = 67$, $p < 0.001$). Stimulating in the seizure onset zone had a similar effect on spike rates as stimulating outside the seizure onset zone ($W = 151$, $p = 0.24$)
Conclusions: Low-frequency stimulation tends to reduce interictal spike rates, independent of whether stimulation is performed within or outside the seizure onset zone. These results suggest that spike suppression may reflect a broad network-level effect rather than a site-specific response. Future directions include testing the effect of the anatomical location of stimulation on spike rates and testing the effect of different stimulation parameters.
References:
1. Valentín, A. et al. Single pulse electrical stimulation for identification of structural abnormalities and prediction of seizure outcome after epilepsy surgery: a prospective study. Lancet Neurol. 4, 718–726 (2005).
2. Lundstrom, B. N. et al. Chronic subthreshold cortical stimulation to treat focal epilepsy. JAMA Neurol. 73, 1370–1372 (2016).
3. Brown, M. W., 3rd et al. Comparison of novel computer detectors and human performance for spike detection in intracranial EEG. Clin. Neurophysiol. 118, 1744–1752 (2007).
4. Conrad, E. C. et al. Spatial distribution of interictal spikes fluctuates over time and localizes seizure onset. Brain 143, 554–569 (2020)."

Molecular Genetic Mechanisms of Neonatal and Infantile Epilepsies
Presenting Author: ***Alissa D'Gama MD, PhD, Boston Children's Hospital/Harvard Medical School***
Co-Authors: *Wanqing Shao, PhD, Boston Children's Hospital, Lacey Smith, MS, CGC, Boston Children's Hospital, Maya Davis, BA, Boston Children's Hospital, Anna Dong, BA, Boston Children's Hospital, Julia Koh, BS, Boston Children's Hospital, Lili Mihajlovits, BS, BA, Boston Children's Hospital, 617-355-5254, Brandon Oby, BS, Boston Children's Hospital, Gillian Prinzing, MS, CGC, Boston Children's Hospital, Katelyn Stone, BS, Boston Children's Hospital, Cesar Urzua, BS, Boston Children's Hospital, Rosalia Valentine, MS, CGC, Boston Children's Hospital, Shira Rockowitz, PhD, Boston Children's Hospital, Beth R. Sheidley, MS, CGC, Boston Children's Hospital, Annapurna Poduri, MD, MPH, Boston Children's Hospital, National Institute of Neurological Disorders and Stroke, National Institutes of Health*
Background: Neonatal and infantile epilepsies are collectively common, associated with substantial burden of disease, and most have presumed molecular genetic etiologies. Early identification of these etiologies is urgently needed to enable development of

effective precision therapies and ultimately improve outcomes. In preliminary work, we enrolled a cohort of 100 infants with unexplained new-onset epilepsy over one year through a multi-center collaboration (34 enrolled locally) and identified genetics etiologies for 43% using rapid genome sequencing (rGS). Most cases remain unsolved, suggesting that molecular genetic etiologies of neonatal and infantile epilepsies remain to be discovered with comprehensive analyses.
Methods: We have continued local enrollment of infants presenting to Boston Children's Hospital (BCH) with unexplained epilepsy. We include and phenotype infants with seizure onset at <12 months recruited within 6 weeks of presentation. We exclude infants with simple febrile seizures, acute provoked seizures, or known genetic or acquired cause. Families are consented to the study and rGS, blood or buccal samples are collected from the infant and available biological parents, rGS is performed at a clinically accredited laboratory, and results are returned to families and treating clinicians. For infants who remain genetically unsolved after rGS, we perform comprehensive reanalysis of the short read GS data as well as long read sequencing and deep sequencing to identify additional genetic etiologies. This study was approved by the BCH IRB.
Results: From September 2021– April 2025, parents of 91% of eligible infants consented and we enrolled 135 infants with unexplained epilepsy. Clinically accredited rapid GS and analysis for coding single nucleotide variants (SNVs), short insertions-deletions (indels), copy number variants (CNVs), and mitochondrial variants identified genetic diagnoses for 55/135 infants (41%). For the initially unsolved cases, we are performing ongoing reanalysis of the short-read GS data for the variant types initially analyzed as well as for structural variants, mobile element insertions, short tandem repeat expansions, and non-coding variants. Thus far, reanalysis has identified an additional 5 diagnoses, including 3 variants not reported by the clinical laboratory (SNV and 2 small CNVs) and 2 previously reported variants of uncertain significance with new evidence (SNV and indel). In addition, ongoing long read sequencing and deep sequencing have identified novel diagnoses (short tandem repeat expansion and 3 mosaic SNVs, respectively). Thus far, advanced genomic sequencing and analyses have identified genetic diagnoses for 9/80 (11%) of the initially unsolved cases, bringing the total diagnostic yield to 47% (64/135). This includes 49 different genes/genomic regions, with more than one infant identified with variants in DEPDC5, KCNQ2, PAFAH1B1, PRRT2, SCN1A, SCN2A, SCN8A, and SMC1A. We expect additional diagnoses from ongoing analyses of unsolved cases.
Conclusion: Our findings support implementation of rGS in the clinical care of neonates and infants with unexplained epilepsy, providing a paradigm for additional rare diseases, and demonstrate the importance of comprehensive sequencing and analyses approaches to discover additional molecular genetic mechanisms underlying epilepsy pathogenesis. Future research is needed to understand the clinical, personal, and long-term utility of early genetic diagnosis in this population."

Divergent Changes in Functional Connectivity in Left- and Right-Onset Temporal Lobe Epilepsy: An Analysis of the Epilepsy Connectome Project
Presenting Author: ***Taha Gholipour, MD, UC San Diego***
Co-Authors: *Carrie McDonald, PhD, University of California San Diego, William D Gaillard, MD, Children's National Hospital, Washington DC, Victoria Morgan, PhD, Vanderbilt University*
Background: Temporal lobe epilepsy (TLE) is associated with distributed brain network dysfunction. Prior work has suggested specific aberrations in the default mode network (DMN) and limbic regions. In this study, we leveraged the Epilepsy Connectome Project (ECP) dataset to delineate lateralized and network-specific functional connectivity (FC) disruptions in TLE.
Methods: We processed 1,557 resting-state fMRI runs from 87 TLE patients (66 with left TLE [LTLE], 21 with right TLE [RTLE]) and 77 healthy controls. Timeseries were extracted from 432 cortical and subcortical regions of interest (ROIs). A 432×432 FC matrix thresholded at the 90th percentile was used to compute two measures per run: mean FC (average value) and FC degree (number of above-threshold connections). Group comparisons (LTLE vs. controls; RTLE vs. controls). False discovery rate correction was applied, and effect sizes were estimated using Cohen's d. To evaluate network-specific changes, we ranked significant ROIs by effect size and grouped the top 20 and bottom 20 ROIs by network affiliation. Additionally, multiple regression within TLE patients were conducted, controlling for laterality, presence of hippocampal sclerosis, age, sex, and epilepsy duration.
Results: In LTLE compared to controls, widespread FC disruptions were observed. Over half of the 432 ROIs showed significant alterations in FC degree and/or mean FC after correction. Limbic regions showed robust increases in FC degree (8 of the top 20 increased ROIs; Cohen's d = 0.35–0.43, $p < 10^{-7}$), primarily in the left hemisphere, without significant changes in mean FC. DMN regions demonstrated prominent decreases in FC degree (6 among the 20 most decreased; Cohen's d = –0.35 to –0.42, $p < 10^{-8}$), yet consistently showed increased mean FC. In the somatomotor network, decreased FC degree co-occurred with significant reductions in mean FC (16 regions). In RTLE, similar patterns were observed, but with more robust and bilateral limbic increases in FC degree (13 regions increased; Cohen's d = 0.57–1.04, $p < 10^{-7}$). The DMN also showed widespread reductions in FC degree (9 regions; Cohen's d = –0.54 to –0.75, $p < 10^{-7}$) and increased mean FC in several regions. Unlike LTLE, the somatomotor network in RTLE displayed divergent changes in degree and mean FC. Regression analyses controlling for covariates revealed that seizure lateralization and presence of hippocampal sclerosis were associated with increased FC degree in sensorimotor and control networks (β_tleside > 12.7), but with decreased FC degree in DMN regions (β_tleside < –6, $p < 0.001$). Sex primarily influenced FC in control networks. Longer epilepsy duration and older age were independently associated with increased FC degree in control network hubs (e.g., left cingulate), but with decreased mean FC with longer duration.
Conclusions: Our findings reveal extensive, lateralized, and network-specific FC alterations in TLE, with particularly divergent

patterns in limbic and DMN regions. LTLE-related limbic changes were predominantly unilateral, while RTLE showed more bilateral disruptions. Multiple regression analysis identified a decrease in DMN coupling with seizure lateralization, and strong associations between sensorimotor/control network FC and clinical variables. These FC signatures and their clinical correlations in the large, high-quality ECP dataset underscore the potential utility of resting-state fMRI for lateralizing epileptogenic foci and informing targeted interventions.

Thalamic Stimulation Induced Modulation of Network Excitability in Epilepsy During Stereotactic-EEG
Presenting Author: ***Nicholas Gregg, MD, Mayo Clinic, MN***
Co-Authors: *Gabriela Ojeda Valencia, BA, Mayo Clinic, MN, Tereza Pridalova, BS, Mayo Clinic, MN, Harvey Huang, BS, Mayo Clinic, MN, Vaclav Kremen, PhD, Mayo Clinic, MN, Brian Lundstrom, MD PhD, Mayo Clinic, MN, Jamie Van Gompel, MD, Mayo Clinic, MN, Kai Miller, MD PhD, Mayo Clinic, MN, Gregory Worrell, MD PhD, Mayo Clinic, MN, Dora Hermes, PhD, Mayo Clinic, MN*
Background: Deep brain stimulation (DBS) of the thalamus is an approved therapy for drug resistant epilepsy, however, the latency to response is long, and seizure freedom is rare. Seizure networks are heterogeneous across individuals, and the clinical read-out—patient reported seizure diaries—is slow and often unreliable. Brain stimulation evoked potentials (BSEPs) offer a rapid, quantitative read out of effective connectivity and excitability. We hypothesized that combining single pulse stimulation–derived BSEPs with short trials of high frequency (145 Hz) thalamic DBS during stereo-EEG (sEEG) could map seizure network (SN) engagement and track stimulation induced network modulation.
Methods: Ten patients with drug resistant epilepsy undergoing clinical sEEG including a thalamus electrode were enrolled in this retrospective cohort study. Participants completed a trial of high-frequency (HF) (145 Hz) thalamic stimulation, and BSEPs were collected at baseline and following HF stimulation to map connectivity and assess change in network excitability. Interictal epileptiform discharges in SN contacts were quantified using an automated classifier. Thalamic electrode contacts were localized relative to the Krauth/Morel atlas.
Results: Baseline BSEPs delineated nucleus specific connectivity. Stimulation fields engaging both the anterior nucleus of the thalamus and ventral anterior nucleus elicited the broadest frontotemporal engagement. DBS reliably suppressed thalamocortical BSEP amplitude when the active HF stimulation time exceeded 1.5 h, and the magnitude of suppression scaled with baseline connectivity strength ($P < 0.01$). Shorter trials produced no change or augmentation of BSEPs. IED rates fell immediately during DBS on phases; the extent of suppression was significantly increased in SN with strong thalamocortical connectivity ($P<1e-10$).
Conclusions: BSEPs and HF thalamic stimulation during sEEG provide novel network biomarkers to efficiently assess seizure network engagement, modulate network activity, and track excitability. This work advances biomarker informed neuromodulation for epilepsy.

Medial-excitatory and Lateral-Inhibitory Networks in the Human Brain Control Emotion-Related Sympathetic Outflow
Presenting Author: ***Patrick Hullett, MD, PhD, University of California, San Francsico***
Co-Authors: *Quinn Greicius, BS, University of California, San Francisco, CA, Aria Lin, BS, University of California, San Francisco, CA, Jacqueline Geyfen, BS, University of California, San Francisco, CA, Nathaniel Morris, BS, University of California, San Francisco, CA, Edward F. Chang, MD, University of California, San Francisco, CA, Virginia E. Sturm, PhD, University of California, San Francisco, CA*
Abstract: The neural mechanisms underlying changes in sympathetic nervous system outflow during emotions are not well understood. While human neuroimaging studies have advanced neural network models that produce autonomic outflow, non-invasive brain recordings have limited temporal resolution. Here, we use high temporal resolution intracranial recordings from nine participants to investigate the functional organization of the sympathetic control network subserving human emotion. In this work, participants watched a series of emotion-eliciting video clips chosen to evoke amusement, disgust, awe, fear, sadness, or nurturant love (mean video-clip number = 132 ± 91 SD) while skin conductance, a sympathetic measure, was monitored. We used fronto-temporo-insular activity to generate network-level models that predicted continuous skin conductance on the millisecond timescale with high accuracy ($p < 0.05$, permutation test). The network model weights show medial nodes exhibit excitatory control, while lateral nodes exhibit inhibitory control of skin conductance. Additionally, electrical stimulation mapping in five participants shows medial node stimulation generates skin conductance while lateral node stimulation suppresses skin conductance. Overall, these findings show a medially distributed excitatory network.

Quantifying the Impact of Computer-aided Diagnostic Score on the Clinical Diagnosis of Functional Seizures
Presenting Author: ***Wesley Kerr, MD, PhD, University of Pittsburgh***
Co-Authors: *Katherine N. McFarlane, MS, University of Pittsburgh, Markus Reuber, MD, University of Sheffield, Meagan Watson, MBA, University of Colorado, Anto Bagic, MD, PhD, University of Pittsburgh, Nicholas J. Beimer, MD, University of Michigan, Danielle R. Carns, PsyD, University of Pittsburgh, Alex Israel, MD, University of Pittsburgh, Yanshan Wang, PhD, University of Pittsburgh, Laura A. Strom, MD, University of Colorado, Page B. Pennell, MD, University of Pittsburgh, John M. Stern, MD, University of California, Los Angeles, Lubomir Hadjiyski, PhD, University of Michigan, William C. Stacey, MD, PhD, University of Michigan*
Objective: The diagnosis of functional seizures (FS) without ictal video-electroencephalography is challenging. Delayed and inaccurate diagnosis has been associated with worse long-term treatment outcomes. The Functional Seizures Likelihood Score (FSLS)

is a machine learning-based diagnostic score that identifies patients with probable FS. We evaluated if the FSLS improved the ability of clinicians to accurately identifying FS as compared to epilepsy.
Methods: We constructed 117 anonymized cases using data from patients with documented FS, epilepsy, mixed epileptic and FS, or physiologic seizure-like events. Text-based clinical history was presented followed by the FSLS. Readers were asked the most likely diagnosis after viewing the history and history plus FSLS. We used mixture modeling combined with mixed effects logistic regression to perform data-driven grouping of participants based on patterns of diagnostic performance.
Results: Overall, 163 readers saw 1,142 cases (median of 4 cases/reader). More formal training in seizures was associated with better performance (epileptologists' accuracy 67%, mental health clinician accuracy 52%), but there was substantial individual-level variation. Mixture modeling identified 6 data-driven groups. Groups 2 (high performers, 11% [16/146 quality readers]) and 5 (reference, 55% [81/146 quality readers]) benefitted from the FSLS (accuracy improvement 12-15%, $p<0.05$) because they were persuaded by the FSLS more often than they were misled by the FSLS. Other groups had no net change in performance ($p>0.75$).
Conclusions: Certainty of diagnosis of FS was related to formal training, but there was substantial variability. When viewing an FSLS prediction that disagreed with the readers' initial impression, the challenge was differentiation between persuasion and being misled by the FSLS. Most (66%) readers identified when to be persuaded by the FSLS, but other readers did not utilize the FSLS effectively. The implementation of machine learning should focus on identifying clinical settings where it supplements, not replaces, clinician's knowledge.

Genotype-Informed Single-Cell Analysis of Focal Cortical Dysplasia Elucidates Developmental Origins and Molecular Mechanisms
Presenting Author: ***Sattar Khoshkhoo, MD, Brigham and Women's Hospital***
Co-Authors: *Sara Bizzotto, PhD, Sorbonne Université, Institut du Cerveau (Paris Brain Institute), Maya Talukdar, PhD, Boston Children's Hospital, Edward Stronge, PhD, Boston Children's Hospital, Rosita Ramirez, BS, Brigham and Women's Hospital, Yingxi Yang, PhD, Boston Children's Hospital, August Yue Huang, PhD, Boston Children's Hospital, Qiwen Hu, PhD, Harvard Medical School, Yingping Hou, PhD, Brigham and Women's Hospital, Ashton Tillett, BS, Brigham and Women's Hospital, Brian Chhouk, BS, Boston Children's Hospital, Alissa D'Gama, MD, PhD, Boston Children's Hospital, Michael Hildebrand, PhD, University of Melbourne, Ingmar Blümcke, MD, University of Erlangen, Annapurna Poduri, MD, MPH, Boston Children's Hospital, Christopher Walsh, MD, PhD, Boston Children's Hospital/HHMI*
Background: Somatic mosaic variants are the most common cause of intractable pediatric focal epilepsies and frequently associated with malformations of cortical development such as focal cortical dysplasia (FCD). Histopathological hallmarks of FCD type 2 (FCD2) are cortical mislamination and the presence of morphologically abnormal cells such as dysmorphic neurons (DNs) and balloon cells (BCs) which are indicative of pathogenic variants activating the PI3K-mTOR signaling pathway. However, the molecular identities of DNs and BCs and their developmental origins are still debated.
Methods: To examine the transcriptional changes in FCD we performed single nucleus RNA sequencing (snRNA-seq) on 18 surgically resected FCD2 samples, representing a range of pathogenic variants in PIK3CA, MTOR, DEPDC5, etc., and 17 non-FCD controls. To directly investigate the cell-autonomous and non-cell-autonomous mechanisms of PI3K-mTOR somatic variants in FCD2, which is one of the key outstanding questions in the field, we developed a new method called Genotyping of Transcriptomes Enhanced with Nanopore sequencing (GO-TEN) that infers cellular genotype through targeted long-read sequencing of cDNA. We used GO-TEN to perform genotype-informed transcriptional profiling of single nuclei and analyzed both their cellular lineages as well as molecular profiles. We also performed orthogonal validation of our findings using another novel approach, ResolveOME, that pairs snRNA-seq with very accurate DNA-based genotyping using droplet digital PCR. We applied bioinformatic approaches such as Gene Set Enrichment Analysis and CellChat to determine the intracellular and intercellular processes involved in epileptogenesis in FCD2.
Results: Differential gene expression and pathway enrichment confirmed cell-autonomous upregulation of mTORC1 signaling in all the major cell types, although interestingly we noted non-cell-autonomous, and likely compensatory downregulation of these pathways in the neighboring, non-variant-carrying neurons. Moreover, the FCD-associated microglia exhibited a transcriptional program consistent with a pro-inflammatory state associated with microglial activation. Surprisingly, no new cell clusters representing DNs or BCs were identified and genotyping data confirmed that pathogenic variant-carrying cells have well-differentiated neuronal or glial identities, with enrichment of pathogenic variants in cells of the neuro-ectodermal lineage, pointing to neural progenitor cells as possible loci of somatic mutation. CellChat analysis suggested significant dysregulation of cellular connectivity among the variant-carrying cells, in particular affecting excitatory and inhibitory neurons.
Conclusion: In summary, our study highlights genotype-specific transcriptional changes and a pro-inflammatory state in FCD2 which could be potential targets for precision therapies in the future. Additionally, our findings suggest that dorsal telencephalic progenitors are the likely source of most somatic variants in FCD2, informing the timing and potential mechanisms of these variants.

Genetic Testing in Adult Epilepsy Patients: Genetic Risk Index for Seizure Etiology Score (Gen-RISE) for Identifying Optimal Candidates

Presenting Author: ***Yi Li, MD, PhD, Stanford University, Stanford, CA***

Co-Authors: *David Lee, BS, Stanford University School of Medicine, Cynthia Peng, MD, Stanford University School of Medicine, Dominic A. Hovsepian, MD, South Valley Neurology, Jacqueline Summers-Stromberg, MD, Stanford University School of Medicine, Scheherazade Le, MD, Stanford University School of Medicine, Kimford J. Meador, MD, Stanford University School of Medicine, Babak Razavi, MD, PhD, Stanford University School of Medicine, Carly Siskind, LCGC, Stanford University School of Medicine, Jacinda B. Sampson, MD, PhD, Stanford University School of Medicine*

Introduction: Although genetic testing has been recommended as a standard component of the diagnostic evaluation for epilepsies with unknown etiology, its optimal application in adult populations remains poorly defined. The current study aims to assess the diagnostic yield of genetic tests for adult epilepsy patients, identify the associated risk factors and develop a formal clinical risk score to help guide appropriate patient selection for genetic testing.

Methods: This study was conducted through a retrospective chart review of adult patients evaluated by the Stanford Comprehensive Epilepsy Center, from January 1, 2018, to December 31, 2024. The Stanford Research Repository Tool (STARR) was utilized to identify potential patients. Inclusion criteria were: (1) a diagnosis with at least one of the ICD-10 codes related to epilepsy (G40.0-G40.9, G40.A, G40.B); (2) electronic medical documentation containing text with either "genetic test" or "genetic epilepsy," or a lab result coded as “genetic testing" or “lab unlisted”; (3) age ≥ 18 years. Exclusion criteria were: (1) lack of detailed genetic testing results, and (2) genetic testing records unrelated to epilepsy, such as cancer or prenatal screening. For the patients included in the final analysis, a detailed chart review was conducted, and data points were extracted for further analysis, including the types and timing of genetic testing, genetic testing results, sex, epilepsy risk factors (such as family history of epilepsy, history of intellectual disability/developmental delay(ID/DD), perinatal injury, traumatic brain injury, status epilepticus, febrile seizures, and central nervous system (CNS) infections), age of seizure onset, seizure semiology, types of epilepsy, EEG findings, imaging results, medication, and epilepsy surgery.

Results: A total of 6,681 adult patients with an ICD-10 diagnosis of epilepsy were identified. From this population, a final cohort of 508 patients aged 18 years and older was included, all of whom had undergone genetic testing due to suspected genetic etiology or unknown etiology as determined by their epileptologist and had genetic results available for review. The cohort consisted of 267 (52.56%) males and 241 (47.44%) females. The mean age of patients in the cohort was 26.47 ± 11.67 years old. The mean age of seizure onset was 10.78 ± 11.52 years, with 49.6% of patients having medically refractory epilepsy.

Various types of genetic testing were conducted, including panel testing (n=317, 62.4%), whole exome sequencing (WES) (n=127, 25.0%), microarray (n=137, 26.9%), single gene testing (n=56, 11.0%), Fragile X testing (n=69, 13.6%), karyotyping (n=62, 12.2%), and mitochondrial testing (n=30, 5.9%). Genetic panel testing was performed by major commercial clinical labs in the United States, with most panel sizes ranging from 163 to 302 genes. In our cohort, WES had the highest diagnostic yield for detecting pathogenic variant findings (53/127, 41.73%), followed by genetic panel testing (96/317, 30.28%), and microarray testing (30/137, 21.8%). The mean age at which genetic testing was performed was 20.0 ± 13.8 years, indicating a delay of 9.63 ± 10.36 years in genetic testing after seizure onset. We identified pathogenic or likely pathogenic variants in 167 patients (32.87% of the entire cohort), distributed across 107 distinct genes. The most frequently implicated genes in the full cohort were TSC2 (n=12, 7.2%), SCN1A (n=10, 6%), and MECP2 (n=9, 5.4%), followed by DEPDC5 and LGI1 (n=5 each, 3%). The genetic landscape differed based on age of seizure onset. In the early-onset epilepsy (≤3 years; n=85), SCN1A and TSC2 were the most common genes (n=10 each, 11.8%), followed by SCN2A, STXBP1, and TSC1 (n=3 each, 3.5%). In contrast, in the later-onset cases (>3 years; n=82), the most frequent genes were MECP2 (n=8, 9.8%), followed by DEPDC5 and LGI1 (n=4 each, 4.9%), and ATXN10, KCNA2, KCNT1, and KRIT1 (n=2 each, 2.4%). A multivariable logistic regression model identified intellectual disability/developmental delay (ID/DD) ($p < 0.001$), seizure onset at or before age 3 ($p < 0.001$), and abnormal EEG findings ($p = 0.03$) as significant predictors of a positive pathogenic genetic diagnosis. The model demonstrated moderate predictive ability (AUC = 0.72). Based on this, we developed the Genetic Risk Index for Seizure Etiology (Gen-RISE) score, a clinical tool to estimate the probability of a pathogenic variant related to epilepsy. The Gen-RISE log-odds score is calculated as: Gen-RISE = (1.3 * [ID/DD]) + (0.8 * [Seizure Onset ≤3]) + (0.3 * [EEG Finding]) - 2.4. In this formula, the variables for [ID/DD] and age of seizure onset ≤3 years old are binary (1=present, 0=absent), while the EEG Finding is an ordinal variable (1=Normal, 2=Epileptiform Discharges, 3=Nonspecific Findings, 4=Not Available). A Gen-RISE score above 0 predicts a >50% likelihood of identifying a pathogenic variant, while a score above 0.8 indicates a >70% likelihood.

Conclusion: Genetic testing should be an integral part of the diagnostic evaluation for adult epilepsy patients with unknown or suspected genetic causes. Our findings demonstrate that approximately one-third of these patients may have identifiable genetic variants, particularly those with specific clinical risk factors. We have subsequently devised a novel, first-ever, score, Gen-RISE, which offers a practical and objective tool to identify optimal adult candidates for genetic testing, thereby improving diagnostic efficiency and patient care.

Noradrenergic Circuit Response to Seizures in a Mouse Model of Dravet Syndrome
Presenting Author: ***Joanna Mattis, MD, PhD, University of Michigan, Ann Arbor, MI***
Co-Authors: *Meiling Zhao, PhD, University of Michigan, Anam Noor, University of Michigan, Ann Arbor, MI, Chandni Rana, University of Michigan, Ann Arvor, MI, Joseph Barden, University of Michigan, Ann Arbor, MI*
Rationale: While seizures typically last only seconds to several minutes, the postictal period – from the end of a seizure to the patient's return to baseline – can persist for much longer. Postictal symptoms significantly increase the clinical burden of epilepsy: indeed, Seizure Severity Questionnaire (SSQ) responses indicate that many patients with refractory epilepsy find the postictal period to be even more bothersome than seizures. Impaired arousal ranks among the most common postictal symptoms. Here, we investigated the impact of seizures on neuronal activity within the locus coeruleus (LC), a critical component of the ascending arousal network, and on the release of norepinephrine (NE).
Methods: We used the well-characterized Scn1a+/- mouse model of Dravet Syndrome, which we crossed with Dbh-Cre mice to enable access to LC noradrenergic (LC-NE) neurons. To measure in vivo LC-NE activity, we virally introduced a Cre-dependent fluorescent calcium indicator, GCaMP (in LC); to detect downstream NE release, we introduced a fluorescent NE reporter, GRABNE (in hippocampus). We then evoked naturalistic seizures via hyperthermia while performing simultaneous electrocorticography (ECoG) and fiber photometry recordings.
Results: We obtained intriguingly discrepant results across our two recording sites: LC-NE activity was inhibited by seizures, whereas we observed a rapid and large increase in NE release downstream. We performed additional control experiments to validate the GRABNE finding. We additionally sought to explain our discrepant results by testing the ability of hippocampal excitatory activity to trigger local NE release irrespective of LC-NE somatic activity.
Conclusions: This work applies high temporal resolution in vivo imaging techniques to Scn1a+/- mice during seizures to identify evoked changes in LC-NE neurons and in downstream NE release. Given the crucial role of noradrenergic circuits in supporting arousal, we hypothesize that this contributes to the impaired arousal of the postictal period. Ongoing and future experiments will establish the dynamics of recovery of noradrenergic circuit function and determine whether enhanced NE signaling can rescue postictal signs and symptoms.

The Neuropathological Signature of Late-Onset Epilepsy: A Multicenter Autopsy Study
Presenting Author: ***Ifrah Zawar, MD, MS-CR, University of Virginia, Charlottesville, VA***
Co-Authors: *Mark Quigg MD, MSc, University of Virginia, Charlottesville, VA, Carol Manning, PhD, University of Virginia, Charlottesville, VA, Jaideep Kapur, MD, PhD, University of Virginia, Charlottesville, VA*
Background: The risk of developing epilepsy substantially increases after the age of 50, also known as late-onset epilepsy (LOE). Up to 50% of LOE cases are attributed to neurodegeneration and stroke. However, the relationship between LOE and postmortem neuropathology remains unexplored. We compared post-mortem findings in longitudinal followed individuals who did and did not develop LOE using multicenter data from 42 Tertiary Care Centers in the US from 2005 to 2024. Individuals with normal and impaired cognition were included.
Method: Individuals were grouped by those who developed LOE (epilepsy starting after the age of 50) and those who did not (controls). Those who developed early-onset epilepsy (before age 50) were excluded. Baseline demographics, mortality, and postmortem findings of evidence of Alzheimer's Disease (AD), Frontotemporal lobar degeneration (FTD), Lewy body, vascular pathologies, and neurodegeneration were compared among the groups using Pearson's Chi-squared test, Fisher's exact test, and t-test. Because of extensive contingency tables, Fisher's Exact Test with simulated p-value (based on 2,000 replicates) was applied to neuropathological outcome categories, using a Monte Carlo simulation approach.
Result: Of 13,131 deceased individuals, LOE participants suffered significantly higher mortality rates compared to those without LOE ($p<0.001$). After excluding individuals with early-onset epilepsy, 7,519 participants who underwent autopsy were identified. Of these, 158 had developed LOE prior to death, while the remaining 7,361 without epilepsy served as controls (Figure 1). At baseline, traumatic brain injury ($p=0.001$) and active depression ($p=0.017$) were more prevalent among those with LOE (Table 1). Individuals with LOE died at a significantly younger age ($p <0.001$). Those with LOE had evidence of more AD pathology and more advanced ATN (amyloid, tau, and neurodegeneration), as evidenced by a higher Braak stage for neurofibrillary (tau) degeneration ($p<0.0001$), higher thal phase of amyloid burden ($p=0.002$) and a higher CERAD score density of neuritic (amyloid) plaques ($p <0.0001$), compared to controls (Figure 2). LOE participants also exhibited more neurodegeneration, as evidenced by cerebral atrophy ($p < 0.0001$), hippocampal atrophy ($p < 0.0001$), and locus coeruleus hypopigmentation ($p < 0.0001$), compared to controls (Figure 2). Lewy body pathology was more common in those with LOE compared to controls ($p=0.017$). FTD pathology was less prevalent among LOE participants ($p=0.01$), while vascular pathology, Circle of Willis atherosclerosis, lobar atrophy, and substantia nigra hypopigmentation were comparable among the two groups.
Conclusion: This study shows that individuals who develop LOE, compared to those who do not, experience earlier mortality and postmortem evidence of more severe ATN pathology. For the first time, our study provides the neuropathological basis of LOE. These findings suggest that LOE may represent an early or parallel manifestation of underlying neurodegenerative disease, particularly AD. Recognizing LOE as a potential marker of accelerated neurodegeneration has critical implications for early identification, risk stratification, and targeted intervention in aging populations.

Headache and Pain

Daily Light Exposure Habits of Youth with Migraine: A Prospective Pilot Study
Presenting Author: ***Carlyn Patterson Gentile, MD, PhD, Children's Hospital of Philadelphia, Philadelphia, PA***
Co-Authors: *Ryan Shah, BS, Thomas Jefferson University, Blanca Marquez de Prado, PhD, Children's Hospital of Philadelphia, Nichelle Raj, BS, Children's Hospital of Philadelphia, Christina L. Szperka, MD, MSCE, Children's Hospital of Philadelphia, Andrew D. Hershey, MD, PhD, Cincinnati Children's Hospital Medical Center, Geoffrey K. Aguirre, MD, PhD, University of Pennsylvania*
Background: Eighty percent of youth with migraine report photophobia. It is unknown if photophobia leads to light avoidant behavior, which may further worsen light sensitivity and lead to sleep disruption. The technological development of wearable continuous light loggers allows us to address these open questions. We conducted a pilot study to determine the feasibility of measuring light exposure using wearable light loggers in youth with migraine.
Methods: Youth 10 – 21 years old with a headache-specialist confirmed ICHD-3 diagnosis of migraine were recruited from CHOP headache clinics. Each participant recorded 7 consecutive days of light logging data from the ActLumus device worn as a pendant around the neck paired with a text-based daily migraine symptom diary during a typical school week between November and March 2024. Validated questionnaires were used to capture headache and migraine frequency, headache-related disability, visual sensitivity, fear-of-pain, and sleep disturbance and impairment. Percent time spent within recommended light exposure levels was calculated for the day, 3 hours prior to bedtime, and night. Power analysis was calculated to determine sample size needed for group comparison of baseline characteristics across light intensity and light timing metrics to aid in the design of larger studies.
Results: Twenty youth with a median age 17 years [IQR 16, 19], 70% of whom were female completed 7 days of continuous light logger recording and daily headache diary. Data completion rates were high with 136/140 (97.1%) useable days of light logger data, and 100% compliance on the daily headache diary. Participants spent a mean of 14.5% +/- SD 7.0 of daylight hours getting the minimum recommended light exposure, while they were more consistently under the maximum light levels recommended 3 hours prior to bed (77.5% +/- 21.6 of the time), and at night (99.1% +/- 2.9 of the time). Youth with chronic migraine (i.e. at least 15 headache days and 8 migraine days per month) showed a significant shift in light exposure patterns to later in the day. Power analysis revealed that many migraine-characteristic group differences (e.g. no/mild vs. moderate/severe headache-related disability) in light exposure metrics would require sample sizes of 50 to 150 to reach 80% power with an alpha of 0.05. Participant feedback on the study was positive; 85% would recommend the study to others.
Conclusion: Measuring daily light exposure is feasible in pediatric populations with photophobia and reveals intriguing trends in youth with migraine that warrant further study.

Movement Disorders

Preterm Birth and Cortical Parvalbumin Interneuron Inhibition Causes Dystonic Leg Adduction Behavior in Mice
Presenting Author: ***Bhooma Aravamuthan, MD, DPhil, Washington University School of Medicine, St. Louis, MO***
Co-Authors: *Femi Folorunso, MSc, Washington University in St. Louis, Kat Gemperli, BA, Washington University in St. Louis, Benjamin Norin, BA, Washington University in St. Louis, Rebecca Joshua, MSc, Washington University in St. Louis, Rafael Galindo, MD, PhD, Washington University in St. Louis*
Introduction: Cerebral palsy (CP) is the most common lifelong motor disability with a prevalence of 1 of every 500 people, rivaling the prevalence of Parkinson's disease. In the US, CP due to preterm birth is the most common cause of dystonia, a debilitating movement disorder with few targeted treatments. We have shown that cortical injury is the best predictor of dystonia in children with CP following preterm birth, a phenomenon we have dubbed cortical dystonia of prematurity. Others have shown that abnormal inhibition of the sensorimotor cortex is associated with idiopathic non-CP dystonia in adults. Our objective was to determine whether preterm birth in mice could yield a dystonic phenotype and whether this phenotype was associated with inhibition of sensorimotor cortex parvalbumin interneurons (PVINs), the most common inhibitory neurons in the cortex.
Methods: Most models of prematurity in mice utilize injuries after birth (postnatal day 0, P0) but before human equivalent term gestation (P10). However, to model true preterm birth in C57BL/6J mice, we induced early delivery of pups using mifepristone at embryonic day 18.3 (E18.3), or roughly 22 hours prior to typical term delivery at E19.2 and approximately 22 weeks human-equivalent gestation. We assessed these mice for dystonic gait on a treadmill and open field using our clinically derived metrics of increased leg adduction variability and amplitude and quantified parvalbumin immunoreactivity in the sensorimotor cortex and striatum. In a separate cohort of parvalbumin-Cre (PV-Cre) mice, we stereotaxically injected AAV8-hSyn-DIO-hM4D(Gi)-mCherry in the bilateral sensorimotor cortex to allow for expression of inhibitory Gi Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) selectively in sensorimotor cortex PVINS. We injected AAV8-hSyn-DIO-mCherry in littermate controls to allow for expression of the mCherry reporter alone. Three weeks after viral injections, we injected all mice with 1 mg/kg clozapine-N-oxide to induce chemogenetic inhibition of PVINs in mice expressing inhibitory DREADDs and no PVIN effect in the control mice. We then assessed dystonic behavior and parvalbumin immunoreactivity as above. Comparisons were by t-tests with Bonferroni corrections for multiple comparisons.

Results: Compared to term-born mice (n=34), mice born preterm (n=24) displayed significantly increased leg adduction amplitude (p=0.01), increased leg adduction variability (p=0.002), and increased time in tripedal/quadrupedal support (p=0.02) during treadmill gait (forced high speed gait between 5-11 cm/sec) but not during open field (self-paced low speed gait at 1 cm/sec). Mice born preterm also had a significantly lower number of PVINs in the sensorimotor cortex (p=0.03) but not in the striatum (p=0.1) compared to term-born mice. Mice who underwent chemogenetic inhibition of PVINs (n=8) compared to control mice (n=8), displayed increased leg adduction amplitude (p=0.02) and variability (p=0.03) and also demonstrated a significantly lower number of sensorimotor cortex PVINs (p=0.001).
Conclusions: Preterm birth in mice yields dystonic gait and reduced PVIN number specifically in the sensorimotor cortex. Chemogenetic inhibition of PVINs also yields dystonic behavior in mice but unexpectedly also causes loss of these PVINs. Future work will assess whether chemogenetic excitation of PVINs can improve dystonic gait in mice born preterm, thus serving as a novel cortical target for dystonia of prematurity.

Home Training for Cerebellar Ataxias: A Randomized Clinical Trial
Presenting Author: ***Scott Barbuto, MD, PhD, Columbia University Medical Center***
Co-Authors: *Michael Spinner, MS, Columbia University Medical Center, Seonjoo Lee, PhD, Columbia University Medical Center, Joel Stein, MD, Columbia University Medical Center, Lori Quinn, PT EdD, Teachers College, Sheng-Han Kuo, MD, Columbia University Medical Center, Yaakov Stern, PhD, Columbia University Medical Center*
Background & Objective: Spinocerebellar ataxias are a group of disorders that cause severe disability due to progressive incoordination. Balance training has shown to improve some functional abilities in individuals with ataxia whereas the effects of aerobic training are still relatively unknown. In this study, home balance training was compared to home aerobic training to begin to understand if one training method is superior to the other.
Methods: We conducted a single center, assessor-blinded, randomized controlled trial. Individuals with cerebellar ataxia were assigned (1:1) to either home balance or aerobic training. Aerobic training consisted of 30-minute cycling sessions, 5x per week at greater than 80% maximum heart rate as determined by cardiopulmonary exercise testing. Individuals assigned to balance training were given three sets of exercises of varying difficulty. After instruction on how to correctly perform each exercise, participants were expected to train at home for 30-minutes 5x per week. Individuals graded exercises on a 1 to 10-point scale with higher scores indicating higher balance challenge. Individuals were instructed to maintain a balance challenge score of at least a six.
Individuals in both groups were given a Fitbit Charge 5 to monitor training frequency, duration, and intensity. During the first 6-months, individuals had study support comprised of biweekly phone calls and monthly workout log checks from their watch. After 6-months, individuals were expected to continue to train, but this study support was withdrawn. Assessments were conducted at 0, 6, 9, and 12-month in-person visits. The primary outcome was improvement in ataxia severity as measured by the Scale for the Assessment and Rating of Ataxia (SARA). Secondary measures included: 1) training feasibility as measured by individuals hitting at least 80% of training goals for frequency, duration, and intensity. 2) training safety. 3) Balance as measured by the TUG and DGI. 4) Gait as measured by gait speed. 5) Fatigue as measured by the Fatigue Severity Scale. 6) Quality of Life (QOL) as measured by the WHOQOL-Bref 7) Fitness level as measured by maximal oxygen consumption (VO2max).
For comparisons of demographic data and the baseline outcome measures between the two groups, the two-sample t test and the chi-squared test were used as applicable. All analysis was done under intent-to-treat principles. The primary and secondary outcomes were analyzed using mixed effect model. Each mixed-effect model includes the outcome as the dependent variable and group (two levels: aerobic training vs. balance) and time (four levels: 0, 6, 9, and 12-months) and the interaction effect between group and time as the fixed effects. Within subject correlation was accounted by adding random intercept. For significant time by group interaction, the within-group changes were estimated using least squared mean. The mixed-effect model allows missing values under the missing-at-random assumption. To ensure the missing-at-random assumption, we compared the demographics and baseline clinical characteristics between participants who dropped and those who completed the trial. For all outcomes, multiple comparison correction was done to control for false discovery rate. The mixed effect models only, including completers was also performed as a sensitivity analysis. For all hypotheses, two-tailed tests were performed at the 5% significance level.
Results: Thirty-one individuals were randomized to each group with 6 dropouts in the balance group and 5 in the aerobic group after the one-year program. There were no differences in baseline characteristics between the two groups. There were no serious adverse events caused by training, and over 80% of individuals in both groups hit all training goals at 6-months. Adherence to training goals in both groups dropped, however, when study support was withdrawn and was only around 40% at 1-year. There was a mean improvement in ataxia severity of 2.5 SARA points (SD 1.92) in the aerobic group compared to an improvement of 1.0 points (SD 1.87) in the balance group at 6-months. Improvement in SARA from baseline was approximately 1.5 points (SD 1.68) at 9 and 12-months for the aerobic group whereas there was no improvement in SARA at 9 and 12-months for the balance group. Interestingly, individuals in the aerobic group who halted or limited training had improvements revert to baseline; individuals who continued to train regularly had an average improvement of almost 4.0 SARA points (SD 1.84) at one-year. In terms of secondary outcomes, there was a statistically significant improvement in fatigue scores and fitness levels for individuals in the aerobic group when compared to the balance group. Gait speed, TUG, and DGI scores improved in both the aerobic and balance training group, but there was not statistical difference detected between them. QOL scores did not improve in either group.

Discussion & Conclusions: An estimated 150,000 Americans are living with spinocerebellar ataxia, and the average annual healthcare cost to the United States is over 1.9 billion dollars. There are currently no effective treatments or cures for genetic causes of these diseases. Thus, there is a critical need to find treatments that slow disease progression and allow affected individuals to live more functional lives. This study examined the impact of home balance and aerobic training on spinocerebellar ataxias. Results indicated that there was a statistically and clinically significant improvement in ataxia severity with aerobic training compared to balance training. Improvements in fitness level and fatigue were also noted. Individuals needed to continuously train however, as individuals who halted training had symptoms revert to baseline. Individuals who continued to train maintained benefits.

The Sedentary Index (SI) for Daily Life Activity Monitoring in Progressive Supranuclear Palsy (PSP)

Presenting Author: ***Marian Dale, MD, MCR, Oregon Health & Science University***

Co-Authors: *Carla Batista, PhD, Oregon Health & Science University, Anjanibhargavi Ragothaman, PhD, Oregon Health & Science University, Zachary Nhem, BS, Oregon Health & Science University, Ashlynn Lawston, BS, Oregon Health & Science University, Graham Harker, BS, MPH, Oregon Health & Science University, Douglas Maxwell, PhD, PAL Technologies, Craig Speirs, PhD, PAL Technologies, David Loudon, PhD, PAL Technologies, Martina Mancini, PhD, Oregon Health & Science University*

Objective: To confirm the feasibility of daily life physical activity monitoring in PSP using a single activPAL sensor, and to examine preliminary associations between overall sedentary behavior, patient demographics, and home exercise per diary records.

Background: People with PSP have limited activity levels in daily life due to balance impairment and fear of falling. Two prior studies have examined home activity monitoring in PSP using the activPAL sensor. One study found decreased walking duration in PSP compared to Parkinson's, ataxia, and age matched controls [1]; the second study found that low walking activity in PSP correlated with subsequent falls [2]. To our knowledge no prior studies have examined the relationship between disease severity, home exercise patterns, and the SI in PSP.

Methods: Two individuals with PSP wore an activPAL activity monitor on their thigh for 7 continuous days and their care partners recorded sleep and exercise sessions. We collected demographics, a Montreal Cognitive Assessment, and an on-medication PSP Rating Scale (PSPRS). The SI was calculated as the percentage of the waking day spent in sedentary behaviors.

Results: Subject one: 79-year-old male, MOCA 24/30, PSPRS 23/100 (gait and midline subscore 3), exercise sessions over 7 days=5, average SI over 7 days= 79%. Subject two: 63-year-old male, MOCA 21/30, PSPRS 41/100 (gait and midline subscore 14), exercise sessions over 7 days=3, average SI over 7 days= 91%.

See Figure 1: The Sedentary Index (SI) shows the proportion of the waking day spent in sedentary behaviors such as sitting or resting quietly. The reference population is drawn from 4,494 days of accelerometer data from 632 adults aged 63 ±8 years (NCI IDATA cohort study).

Conclusions: Collection of 7 days of continuous data from a single activPAL monitor is feasible for patients and their care partners. Preliminarily, we see a correspondence between increased disease severity in PSP, decreased home exercise, and increased SI. The sedentary index may be a viable outcome in future clinical trials.

References:

[1] Klenk J, Srulijes K, Schatton C, Schwickert L, Maetzler W, Becker C, Synofzik M. Ambulatory Activity Components Deteriorate Differently across Neurodegenerative Diseases: A Cross-Sectional Sensor-Based Study. Neurodegener Dis. 2016;16(5-6):317-23. doi: 10.1159/000444802. Epub 2016 May 21. PMID: 27197840.

[2] Srulijes K, Klenk J, Schwenk M, Schatton C, Schwickert L, Teubner-Liepert K, Meyer M, K C S, Maetzler W, Becker C, Synofzik M. Fall Risk in Relation to Individual Physical Activity Exposure in Patients with Different Neurodegenerative Diseases: a Pilot Study. Cerebellum. 2019 Jun;18(3):340-348. doi: 10.1007/s12311-018-1002-x. PMID: 30617629.

Blood-Derived Alpha-Synuclein Strains in Lewy Body Diseases are Associated with Extracellular Vesicles and Induce Cellular Inclusions

Presenting Author: ***George Kannarkat, MD, PhD, University of Pennsylvania, Philadelphia, PA***

Co-Authors: *Travis Unger, BS, University of Pennsylvania, Robert Skrinak, BS, University of Pennsylvania, Caroline Lewis, BS, University of Pennsylvania, Kelvin Luk, PhD, University of Pennsylvania, Thomas Tropea, MD, University of Pennsylvania, Daniel Weintraub, MD, University of Pennsylvania, Alice Chen-Plotkin, MD, University of Pennsylvania*

Background: There is increasing evidence for the diversity and heterogeneity of conformations of alpha-synuclein (aSyn) with specific biochemical properties, called "strains", across neurodegenerative diseases such as dementia with Lewy bodies (DLB), Parkinson's disease (PD), and multiple systems atrophy (MSA). In line with this evidence, we have demonstrated that two conformation-selective monoclonal antibodies raised against recombinantly generated aSyn strains and used in an ELISA format can 1) differentiate blood from individuals with PD versus DLB and 2) predict cognitive trajectory in PD. Moreover, these antibodies detect aSyn species readily in blood but not cerebrospinal fluid. The pathologic significance of these blood-derived forms of aSyn is not understood.

Methods: Using aSyn-strain selective antibodies, aSyn was immunoprecipitated from blood plasma from neurologically normal individuals and individuals with PD or DLB. The pathologic potential of these isolated aSyn species was assessed by using seed amplification assays (SAA) and by application to cellular models of synucleinopathy. Cellular pathology was assessed by

immunofluorescence microscopy.
Results: aSyn immunoprecipitated with strain-selective antibodies induced fibrillization in SAA in a strain-selective and disease-specific manner. aSyn species isolated from PD blood plasma were more robustly able to induce fibrillization relative to those from DLB or healthy controls. In cellular models, aSyn strains from PD plasma were also able to induce detergent-insoluble inclusions in a strain-selective manner.
Conclusions: Misfolded, phosphorylated, and aggregated forms of aSyn are being increasingly identified outside of the brain including the skin, gut, and blood. However, the pathologic relevance of these forms of aSyn is not yet understood. We have demonstrated that two blood forms of aSyn associated clinically with cognition in synucleinopathies indeed have differing pathologic properties in vitro. These findings will have to be extended to in vivo models. Understanding the heterogeneity and diversity of aSyn in both brain and peripheral compartments will help develop better therapeutics and a better mechanistic understanding of pathogenesis of aSyn-related neurodegenerative diseases.

Cerebellar Cholinergic Denervation in Parkinson Disease and Its Gait Correlates
Presenting Author: ***Baijayanta Maiti, MD, PhD, Washington University in St. Louis School of Medicine***
Co-Authors: *John L O'Donnell, PhD, Neurology, Washington University in Saint Louis School of Medicine, Kerri S. Rawson, PhD, Program in Physical Therapy, Washington University in Saint Louis School of Medicine, Meghan C. Campbell, PhD, Neurology and Radiology, Washington University in Saint Louis School of Medicine, Gammon M. Earhart, PT, PhD, Washington University in Saint Louis, Joel S. Perlmutter, MD, Washington University in Saint Louis*
Abstract: A mélange of disabling motor and non-motor manifestations frequently afflicts people with Parkinson disease (PD). One particularly disabling component of motor dysfunction is gait impairment that limits function, leads to falls, reduces quality of life and ultimately leads to residential care placement. Gait imbalance is a key contributor of morbidity and mortality in PD and does not respond well to traditional dopaminergic therapy. Most functional neuroimaging studies focused on nigrostriatal dopaminergic pathways and do not adequately explain gait impairments in PD. This suggests involvement of other neurotransmitter systems or brain regions beyond the nigrostriatal pathway and possibly new targets for imaging biomarkers. The purpose of this cross-sectional study was to investigate the cholinergic denervation of the cerebellum and their contributions to gait impairment in PD. We conducted PET analysis with radioligand [18F] VAT targeting vesicular acetylcholine transporter (VAChT) contrasting cerebellar cholinergic activity in 64 patients with PD and 41 age-matched healthy control participants. VAT nondisplaceable binding potential (BPND) was calculated by Logan graphical analysis using 30-110 minutes of PET scan data with optimized eroded white matter reference region. Comprehensive spatiotemporal gait measures were acquired with a GAITRite walkway for behavioral correlations. The PD participants had significantly reduced VAChT expression in distinct cerebellar regions including hemispheric motor and cognitive lobules and midline vermis. The reduced cerebellar cholinergic activity (VAT BPND) correlated with measures of variability in stride length, step time and single support time in PD participants after controlling for confounding variables. These results demonstrate regional cholinergic denervation of the cerebellum in PD and its gait correlates. Our data reflects the potential of cerebellar cholinergic measures as novel imaging biomarker of gait impairment in PD.

Immunological Mechanisms in Cervical Dystonia
Presenting Author: ***Laura Scorr, MD, MSCR, Emory University***
Co-Authors: *Gamze Kilic-Berkmen, PhD, Emory University, Lou-Ella George-Alexander, PhD, Emory University, J. Lucas McKay, PhD, MSCR, Emory University, Diane Sutcliffe, MS, Emory University, Katja Lohmann, PhD, University of Lubeck, H. A. Jinnah, MD, PhD, Emory University*
Background: Although several potential causes have been identified for cervical dystonia (CD), the vast majority of cases are idiopathic. Prior studies have pointed to a relationship between CD and autoimmune disease, suggesting immune and inflammatory mechanisms may play a pathogenic role in a subgroup of cases.
Objective: The overall goal was to delineate which aspects of the immune system may be most relevant to the biology of CD.
Methods: The methods included a broad anti-neuronal antibody screen, a multiplex immunoassay investigating 37 immunological markers, analysis of the relative immune cell frequencies by flow cytometry, transcriptomics, and sequencing of HLA alleles related to autoimmune disorders. For each of these methods, different numbers of subjects were available. Where possible, CD subjects were divided into subgroups with or without coincidental autoimmune thyroid disease to enrich a population where immune mechanisms might be relevant.
Results: Screens for anti-neuronal antibodies did not reveal significant differences between CD (N=58) and controls (N=30). Blood based transcriptomic studies revealed abnormalities in immune and inflammatory pathways in CD (N=20) versus controls (N=10), and the multiplex assay pointed more specifically towards abnormal T cell signaling in CD (M=20) versus controls (N=20). Flow cytometry revealed more than a third of CD cases (N=40) versus matched controls (N=40) had changes in the relative frequencies of monocytes, NK cells, B cells, and T cell subsets. Sequencing HLA alleles indicated a possible association of CD (N=549) versus controls (N=4,802) with HLA B and DPA1, which have been reported to mediate the penetrance of autoimmune disorders.
Conclusions: Altogether, the association of CD and blood-based immune measures point to abnormalities in cell-mediated immune mechanisms. Further studies with larger numbers of cases investigating immune cell subset function are needed to further delineate

this subgroup. Ultimately, these studies may guide the development of novel biomarkers or treatment strategies targeting the immune system.

Improving Neuronal Function as a Therapeutic in Spinocerebellar Ataxias
Presenting Author: *Sharan Srinivasan, MD, PhD, University of Michigan*
Co-Authors: *Isabel Soto, PhD, University of Michigan, Michael Bonomo, BS, University of Michigan, David Peppercorn, University of Michigan, Allison Guo, University of Michigan, Brianna Nelthrope, University of Michigan, Hannah Shorrock, PhD, University of Michigan, Henry Paulson, MD, PhD, University of Michigan*
Background and Objectives: Spinocerebellar Ataxias (SCAs) are dominantly inherited degenerative disorders resulting in dysarthria, impaired coordination, and gait disability. Motor symptoms largely derive from aberrant firing of cerebellar Purkinje neurons (PCs) due to dysfunction in specific ion channels, which represent viable drug targets. To advance target discovery, we looked to the single clinically effective intervention in human SCA patients: robust cardiovascular exercise. Exercise is a mainstay of clinical care and improves motor function, but the mechanisms driving benefits in SCAs remain unclear, and precise delineation may allow pharmacological intervention to 'mimic' exercise in disabled patients.
Methods: We studied Atxn154Q/2Q knock-in mice (an SCA1 model) engaged in voluntary cage wheel running alongside WT littermates and sedentary controls. Mice were exercised at different time points for varying periods of time. Effects of intervention were assessed using behavioral phenotyping (open field, balance beam, and rotarod), cerebellar slice electrophysiology, histological evaluation, and transcriptional profiling.
Results: Voluntary cage wheel running was most effective when started at a pre-symptomatic stage, resulting in a complete rescue of motor ataxia. Cerebellar slice recordings showed improved PC firing. Bulk RNA sequencing demonstrated rescue of splicing defects known to pathologically drive PC dysfunction in SCAs. Further, we developed a small molecule activator of BK potassium channels, BK-20, to mimic splicing correction. BK-20 improves motor symptoms and rescues PC degeneration in SCA1 mice.
Discussion and Conclusion: To uncover novel therapeutic targets, it is crucial that we identify the driving mechanisms of effective clinical measures, such as cardiovascular exercise. Here, we show that exercise may elicit benefits in motor ataxia through correction of dysfunctional cerebellar circuitry. Thus, drugs that modulate ion channel activity may serve as a pharmacomimetic of exercise for these devastating disorders.

Neurocritical Care and Traumatic Brain Injury

Neural Encoding of Classical Music in Comatose Acute Brain Injury Patients
Authors: *Ayham Alkhachroum, MD, MSc, University of Miami*
Co-Authors: *Brian Manolovitz PhD, University of Miami Miller School of Medicine, Tulay Koru-Sengul, PhD, University of Miami Miller School of Medicine, Ana Bolaños Saavedra, MD, University of Miami Miller School of Medicine, Elena Mishkovsky, BS, University of Miami Miller School of Medicine, Esther Monexe MSPH, University of Miami Miller School of Medicine, Angela G. Velazquez MD, Columbia University Irving Medical Center, Nina Massad MD, University of Miami Miller School of Medicine, Mohan Kottapally, MD, University of Miami Miller School of Medicine, Amedeo Merenda MD, University of Miami Miller School of Medicine, Tatjana Rundek, MD, PhD, University of Miami Miller School of Medicine, Jan Claassen MD, Columbia University Irving Medical Center, Mitsunori Ogihara PhD, University of Miami, Kristine O'Phelan MD, University of Miami Miller School of Medicine*
Background: Approximately 900,000 patients experience coma each year in the US. Acute brain injuries (ABI), mainly traumatic (TBI) and hemorrhage injuries (ICH and SAH), are among the most common causes of coma. In this study, we aimed to investigate music encoding detected on electroencephalogram (EEG) in behaviorally unresponsive patients in the intensive care unit shortly after injury.
Methods: This is a two-center prospective observational cohort study of behaviorally unresponsive ABI patients. We recruited patients at the University of Miami/Jackson Memorial Hospital and Columbia University Medical center. Using the temporal response function test (TRF), we tested neural encoding on EEG to Chaconne, Partita for violin No.2 by J. S. Bach, and to Mozart's Sonata K448 (the Mozart effect). TRF is a mapping between a stimulus feature (acoustic waveform generated by the audio of music or language), and EEG response (brain waveform) using a correlation coefficient. We collected basic demographics, clinical data, and outcomes. The endpoint was the Glasgow Outcome Scale-Extended (GOSE; 1-8, with higher levels indicating better outcomes) at 3-, 6-, and 12-months post injury. Favorable outcomes were defined as GOSE 4 or more at 12 months (can be left home alone for at least 8 hours a day).
Results: In 107 patients (49 TBI, 46 ICH, 9 SAH, 2 other etiologies), 28 (26%) patients had neural encoding to classical music. Patients with neural encoding to music when compared to those without encoding were younger (49.6 vs. 56 yo), more likely to have traumatic injuries (50% vs. 44%), had GCS on admission (6 vs. 6), and similar rates of withdrawal of life-sustaining therapies (WLST 25 vs. 24%). Patients with music encoding were more likely to reach functional independence at 12-month follow-up (30% vs. 19%), and (44% vs. 29%) after excluding patients with WLST.
Conclusion: One out of four comatose acute brain injury patients may encode classical music shortly after injury. Patients with music encoding were more likely to be functionally independent at 12-month

Incorporation of Visio-Vestibular Deficits to Optimize Risk Stratification in Pediatric Concussion

Presenting Author: ***Daniel Corwin, MD, MSCE, Children's Hospital of Philadelphia***

Co-Authors: *Melissa L. Martin, MS, University of Pennsylvania, Philadelphia, PA, Madeline Consuelos, BA, Children's Hospital of Philadelphia, Melissa Godfrey, MPH, Children's Hospital of Philadelphia, Roger Zemek, MD, University of Ottawa, Ian Barnett, PhD, University of Pennsylvania, Kristy Arbogast, PhD, Children's Hospital of Philadelphia, Christina Master, MD, Children's Hospital of Philadelphia*

Objective: To assess the predictive performance of 1) the previously-validated 5P rule, 2) a model augmenting 5P with visio-vestibular examination (VVE) deficits, and 3) a newly derived rule, stratified by sex, to distinguish pediatric patients at-risk for persisting symptoms after concussion (PSaC).

Methods: We analyzed two prospective cohorts: a "specialty cohort" of patients 8-<18 years evaluated ≤7 days following injury at our network of concussion specialty care sites for model derivation/internal validation, and an "emergency department (ED)" cohort of patients 8-<18 years evaluated ≤72 hours following injury for external validation. We compared the following models in predicting PSaC: (1) 5P; (2) 5P+VVE; and (3) a novel score, generated from 35 candidate predictors, both all participants and stratified by sex. We performed forward stepwise logistic regression augmented by random forest to generate new models. Models were compared using the area under the receiver operating characteristic curve (AUC).

Results: In total, 1609 participants were included in the specialty cohort, 75 in the ED cohort. In the specialty cohort, AUCs were: 5P rule=0.57 (95% confidence interval: 0.54-0.60); 5P+VVE=0.65 (0.63-0.68); newly derived model=0.65 (0.60-0.70), for females=0.70 (0.63-0.77) and for males=0.59 (0.52-0.66). In the ED cohort, AUC were: 5P rule=0.66 (0.55-0.82), 5P+VVE=0.73 (0.63-0.86); newly derived model=0.74 (0.65-0.88), for females=0.81 (0.70-0.85) and for males=0.50 (0.41-0.72).

Conclusions: Augmenting the 5P score with VVE abnormalities best identified acute pediatric patients with concussion at highest risk for prolonged recovery. Clinically implementing the 5P+VVE model can assist clinicians in determining which patients will most benefit from expedited specialist care.

A Translational Neuroprognostication Program Is Associated with Improvements in Provider Satisfaction, Guideline-Compliant Care, And Utilization

Presenting Author: ***David Fischer, MD, University of Pennsylvania***

Co-Authors: *Benjamin S. Abella, MD, Icahn School of Medicine at Mount Sinai, Alice Ford, MD, University of Pennsylvania, John Greenwood, MD, University of Pennsylvania, Saleem Halablab, MD, University of Pennsylvania, Stephen Hampton, MD, University of Pennsylvania, Monisha A. Kumar, MD, University of Pennsylvania, Connor Law, BS, University of Pennsylvania, Joshua M. Levine, MD, University of Pennsylvania, Sahily Reyes-Esteves, MD, University of Pennsylvania, Peter Schwab, MD, University of Pennsylvania, Andrea L.C. Schneider, MD, PhD, University of Pennsylvania*

Background & Purpose: Neuroprognostication for disorders of consciousness is profoundly impactful, frequently influencing whether life-sustaining treatments are continued or withdrawn. Research and guidelines in the field of neuroprognostication have evolved rapidly, but these changes have poorly translated to clinical practice. We implemented a novel neuroprognostication program that facilitates the translation of research, while offering specialized, multidisciplinary, and longitudinal care. We used a multimodal approach to investigate the impact of this program on provider attitudes, guideline-compliant testing, and neurology utilization. We focus on neuroprognostication in the context of cardiac arrest, the most common indication for neuroprognostication in our health system.

Methods: To evaluate the impact of this program on provider attitudes, we disseminated surveys to critical care providers (physicians, trainees, and nurses) and neurologists assessing the perceived utility of, and satisfaction with, neuroprognostication. Surveys were disseminated in the years before (2021, 2022) and after (2023) program implementation, across three hospitals within our health system. To evaluate the impact of this program on guideline-compliant patient care, within the same timeframe, we abstracted neuroprognostication testing and outcomes for consecutive out-of-hospital cardiac arrest patients admitted without command-following. We then used Fisher exact tests to compare program-exposed survey respondents and patients to historical controls (2021 and 2022 respondents and patients) and contemporary controls (2023 program-naïve respondents and patients). To evaluate the impact on guideline-compliant care, we reviewed post-arrest neuroprognostication guidelines, identified tests endorsed by all (electroencephalogram, head computed tomography, brain magnetic resonance imaging 2-7 days post-arrest, somatosensory evoked potentials ≥48 hours post-arrest, and pupillary response ≥72 hours post-arrest), then compared the frequency of guideline-compliant testing between groups. Finally, to evaluate the impact on neurology utilization, we reviewed neurology consultations between 2017-2024, comparing consult rate and duration before and after program implementation.

Results: We received 545 survey responses, where program-exposed respondents reported greater usefulness of neuroprognostication relative to contemporary and historical controls (94% vs 68% and 69%, respectively, p<0.01) and high satisfaction (63% reporting the program was "much better" than conventional neuroprognostication). Among 547 post-arrest patients, program-exposed patients, contemporary controls, and historical controls all frequently underwent at least one guideline-compliant test (100%, 100%, 96%, respectively, p=0.14), but program-exposed patients underwent all five guideline-compliant tests more frequently than contemporary or historical controls (23% vs 7% and 1%, respectively, p<0.001). Reviewing 31,990 neurology

consultations between 2017-2024, program implementation did not reduce general neurology consultation volume and was associated with an 8% increase in post-arrest consultations and a 34% increase in visits per consultation; 79% of such visits qualified as critical care time.
Conclusions: A specialized neuroprognostication program not only facilitates translational research, but was associated with favorable attitudes among providers, increased guideline-compliant patient care, and increased utilization of neurologic services. These findings encourage further study of this paradigm, which may help optimize the current practice of neuroprognostication, while improving it for the future.

Phospholipid Biomarkers as Predictors of Outcome after Aneurysmal Subarachnoid Hemorrhage
Presenting Author: ***Aaron Gusdon, MD, University of Texas Health Science Center***
Co-Authors: *Bosco Seong Kyu Yang, MD, MS, University of Texas Health Science Center, Jude P.J. Savarraj, PhD, University of Texas Health Science Center, Hua Chen, BS, University of Texas Health Science Center, Sarah N. Hinds, MS, University of Texas Health Science Center, Glenda L. Torres, MS, University of Texas Health Science Center, Xuefang S. Ren, PhD, University of Texas Health Science Center, Neeraj Badjatia, MD, MS, University of Maryland School of Medicine, Huimahn A. Choi, MD, MS, University of Texas Health Science Center*
Background: Lipid metabolites have been associated with outcomes after aneurysmal subarachnoid hemorrhage (SAH). We set out to determine concentrations of CSF and plasma lipids predictive of delayed cerebral ischemia (DCI) and the effect of key lipids on monocyte function.
Methods: Plasma and CSF samples were prospectively collected within 24h of aneurysm rupture from two tertiary care centers. All clinical data including DCI diagnoses were prospectively adjudicated by at least two neurointensivists at weekly meetings. Control plasma samples were collected from critically ill patients without neurological complications, and control CSF samples were collected from patients undergoing elective neurosurgical procedures (e.g. microvascular decompression or posterior fossa decompression for Chiari malformation). Metabolite concentrations were determined using a triple quadrupole mass spectrometer with dedicated standard curves for each lipid. Machine learning (ML) pipelines were developed using clinical and metabolite data to predict DCI. Monocyte cell lines (THP-1) were treated with control or SAH plasma, and mitochondrial membrane potential and intracellular cytokine staining was determined using flow cytometry.
Results: Plasma and CSF samples were analyzed from 80 SAH patients with 40 plasma and 15 CSF controls included. In the CSF, lysophosphatidylcholines (LPCs) and sphingolipids (SLs) were not significantly increased after SAH compared with control. However, lysophosphatidic acid (LPA) was significantly increased in SAH compared with control CSF samples (p=0.0004). Furthermore, increased CSF LPA within 24h of aneurysm rupture was associated with a significantly higher risk of DCI (p=0.007). In the plasma, LPA and SLs [sphingosine, sphingosine 1-phosphate (S1P), and sphinganine] were significantly increased compared with critically ill controls and were also predictive of DCI. Early elevations in plasma LPA 16:0 were predictive of DCI after correction for relevant covariables including clinical severity [OR 1.37 (95%CI 1.12, 1.90)]. A Youden cutoff of 10.8 nM for LPA 16:0 optimized sensitivity and specificity for DCI prediction. ML models using XGBoost and incorporating LPA and S1P data improved prediction of DCI compared with using clinical variables alone [AUC 0.79 (95%CI 0.70, 0.88) vs AUC 0.64 (95%CI 0.59, 0.70)]. Levels of phospholipase D1 (PLD1) were significantly higher in both CSF (p=0.003) and plasma (p=0.02) among patients who developed DCI, while levels of autotaxin were not significantly different. Treatment of THP-1 cells with plasma from SAH patients who developed DCI increased intracellular cytokine levels and compromised mitochondrial oxidative function. This effect could be reversed by treatment with an LPA receptor antagonist.
Conclusions: Early elevation in CSF LPA as well as plasma LPA and S1P were predictive of DCI. Increased PLD1 may drive LPA production. Monocyte inflammatory phenotype could be reversed by blocking LPA signaling.

Targeting Regulatory T cells Enhances Neurogenesis and Improves Long-term Recovery After Traumatic Brain Injury
Presenting Author: ***Saef Izzy, MD, FNCS, FAAN, Mass General Brigham, Harvard Medical School***
Co-Authors: *Taha Yahya, Msc, Brigham and Women's Hospital, Harm Tjebbe Imkamp, Brigham and Women's Hospital, Maryam Hazim Al Mansi, PhD, Brigham and Women's Hospital, Francesca Percopo, Brigham and Women's Hospital, Jonathan Christenson, Brigham and Women's Hospital, Howard L. Weiner, MD, Brigham and Women's Hospital*
Objective: Develop novel strategies to enhance neurogenesis and modulate immune responses, improving long-term recovery outcomes after traumatic brain injury.
Background: Traumatic brain injury (TBI) causes severe cognitive deficits and neurodegenerative risks, with no effective treatments currently available. Neuroinflammation, particularly the dysregulation of microglia, plays a crucial role in the pathogenesis of both TBI and neurodegeneration. Emerging studies suggest that TBI can stimulate neurogenesis, though strategies to enhance this process are limited. This work hypothesized that nasal anti-CD3 therapy modulates neuroinflammation via regulatory T cells, improving long-term functional recovery and promoting neurogenesis following TBI.
Design/Methods: We performed controlled cortical impact (CCI) traumatic brain injury in adult C57BL/6J mice. We analyzed the effects of nasal aCD3 on neurogenesis and immune modulation in a murine TBI model in vitro and in vivo using behavioral testing, immunohistochemistry, RT-qPCR, flow cytometry, and microglial bulk RNA-seq studies at acute (24 hours), subacute (7 days), and

chronic (1 year) after TBI.
Results: We found that TBI led to worsening cognitive and anxiety-like behavior and upregulation of microglial oxidative stress, oxidative phosphorylation, and stress-related metabolic pathways at 1-year post-injury. Nasal anti-CD3 treatment mitigated these behavioral deficits, upregulating genes related to microglial homeostasis and synaptic function (e.g., Abcc3, Mef2a, Mertk). Gene Set Enrichment Analysis (GSEA) revealed that nasal anti-CD3 mitigated the TBI-induced upregulation of neurodegenerative and metabolic pathways. Notably, nasal anti-CD3 treatment significantly induced anti-inflammatory upstream regulators such as IL-10 and TGF-β1. Furthermore, the profiles of TBI-induced microglia overlapped with those observed in several neurodegenerative diseases, which were modulated by the nasal anti-CD3 treatment. In addition, flow cytometry after TBI revealed decreased Ki67 expression, indicating reduced inflammatory cell proliferation, and increased CD133, marking early neural progenitor activation. Elevated Sox2 and PSA-NCAM at 7 days post-TBI showed enhanced stem cell activity, while histology confirmed increased neurogenesis through DCX+BrdU+ cells at 7- and 14-days post-injury. Nasal anti-CD3 treatment induced regulatory T cells, which promoted neural progenitor activity, evidenced by increased Nestin expression in Tregs co-cultured with neurospheres. Treg depletion via diphtheria toxin in DEREG mice reduced neurogenesis at the acute and subacute time points, highlighting Tregs' critical role in the neurogenic effects of nasal anti-CD3 following TBI.
Conclusions: Nasal anti-CD3 effectively reduced chronic cognitive and anxiety deficits and modulated neurodegenerative changes in microglia following chronic TBI. Treg plays a critical role in neurogenesis at the acute, subacute, and chronic phases following TBI. Understanding Treg-neuronal progenitor cells' direct and indirect communications after injury could reveal new therapeutic targets for TBI and other acute neurological diseases. Nasal anti-CD3 represents a promising therapeutic strategy for treating TBI patients.

Association Between Deviations from Cerebral Autoregulation-Derived Optimal Blood Pressure and Outcome After Pediatric Cardiac Arrest

Presenting Author: ***Matthew Kirschen, MD, PhD, MSCE, Children's Hospital of Philadelphia, University of Pennsylvania***
Co-Authors: *Andrea L.C. Schneider, MD, PhD, Perelman School of Medicine at the University of Pennsylvania, Tanmay Majmudar, MD, Ohio State University, Jesse Hsu, PhD, Perelman School of Medicine at the University of Pennsylvania, Ryan Burnett, BS, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Rebecca Douglas, RN, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Samridhi Sawhney, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Kathryn Graham, BS, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Kenya Agarwal, MSN, RN, ACCNS-P, CPN, CCRN, Children's Hospital of Philadelphia, Chelsea Whelan, RN, BSN, CCRN, Children's Hospital of Philadelphia, Tiffany S. Ko, PhD, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Ryan W. Morgan, MD, MTR, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Vinay Nadkarni, MD, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Ramon Diaz-Arrastia, MD, PhD, Perelman School of Medicine at the University of Pennsylvania, Robert A. Berg, MD, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Alexis A. Topjian, MD, MSCE, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania*
Objective: To determine if deviations above or below personalized cerebrovascular autoregulation (CAR)-derived optimal mean arterial pressure (MAPopt) after pediatric cardiac arrest are associated with outcome.
Design: Retrospective analysis of prospectively collected data.
Setting: PICU at Children's Hospital of Philadelphia between 10/2018 and 12/2023.
Patients: 18 years-old after cardiac arrest.
Measurements: We computed cerebral oximetry index (COx), a metric of CAR, using a moving, linear correlation between time-synchronized brain tissue oxygenation (StO2) from near-infrared spectroscopy (NIRS) and MAP. A multi-window weighted algorithm determined each patient's MAPopt over time. We compared each patient's MAP to their CAR-derived MAPopt during the first 72 hours post-arrest. Unfavorable outcome was Pediatric Cerebral Performance Category 4-6 at hospital discharge with >=1 change from baseline. We tested association between burden (combining magnitude and duration) MAP<MAPopt-5mmHg and unfavorable outcome, and between duration of MAP>MAPopt and favorable outcome using logistic regression models adjusted for age, pre-arrest developmental disability, and measures of arrest severity.
Main Results: Among 147 patients included (median age 4.5 [IQR=1.1-11.7] years, 59% male), 52% had unfavorable outcome. Median time from return of circulation to data collection was 4 [IQR=2.1-8.3] hours. Median burden of MAP<MAPopt-5mmHg was greater for unfavorable compared to favorable outcome groups (192 [IQR=114-310] vs. 147 [IQR=86-199] mmHg*min/hour, p=0.002). A one standard deviation higher burden of MAP<MAPopt-5 was associated with 2.4 times increased odds of unfavorable outcome (95%CI=1.24,4.51). Patients with favorable outcomes spent greater duration with MAP>MAPopt than patients with unfavorable outcomes (48% [IQR=38-56] vs. 40% [IQR=28-52], p=0.011). One standard deviation higher duration of MAP>MAPopt was associated with 2.5 times increased odds of favorable outcome (95%CI=1.20,5.13).
Conclusions: Greater burden MAP<MAPopt-5mmHg in the first 72 hours after pediatric cardiac arrest was associated with increased odds of unfavorable outcome after controlling for potential confounders, and greater duration MAP>MAPopt was associated with increased odds of favorable outcome.

Associations of Traumatic Brain Injury with Expression Levels of Blood-Based Neurodegenerative and Neuroinflammatory Biomarkers

Presenting Author: ***Andrea Schneider MD, PhD, University of Pennsylvania***

Co-Authors: *Sabrina Abbruzzese, MS, University of Pennsylvania, Philadelphia, Alexa Walter, PhD, University of Pennsylvania, Ronit Patel, BS, University of Pennsylvania, Cillian Lynch, PhD, University of Pennsylvania, Danielle Sandsmark, MD, PhD, University of Pennsylvania, Douglas Smith, MD, University of Pennsylvania, Ramon Diaz-Arrastia, University of Pennsylvania*

Objective: To determine if relative concentrations of blood-based neurodegenerative and inflammatory biomarkers differ by injury severity and change over the first 2-weeks following traumatic brain injury (TBI).

Methods: Plasma samples from 127 patients with TBI (mean age=40, 29% female) were collected at day 1 and 2-weeks post-injury and 39 healthy controls (mean age=38, 54% female) had one blood draw. TBI severity was defined using the Glasgow Coma Scale (GCS). Samples were assayed utilizing the Alamar NULISAseqTM CNS Panel, a highly sensitive multiplex immunoassay measuring 123 neurodegenerative and inflammatory proteins. Differential expression analysis was performed adjusting for age and sex. False discovery rate correction was applied.

Results: Our analysis included 105 TBI day-1 samples, 68 TBI 2-week samples, and 39 healthy control samples. Compared to controls, day-1 post-injury samples had 18 upregulated proteins, with glial fibrillary acidic protein (GFAP), serum amyloid A1, and interleukin-6 having the largest log-fold differentials; there were 5 downregulated proteins. By TBI severity, there were 20 upregulated (including phosphorylated tau 181, 217, and 231, among others) and 2 downregulated day-1 post-injury proteins in individuals with GCS 3-12 (n=18) compared to individuals with GCS 13-15 (n=85). At 2 weeks post-injury only 4 proteins were elevated compared to controls (neurofilament light [NfL], neurofilament heavy, GFAP, and S100 calcium-binding protein A12 [S100A12]); no proteins were downregulated. NfL, GFAP, and S100A12 were consistently upregulated at day-1 and 2-week timepoints.

Conclusion: Select neurodegenerative and neuroinflammatory biomarkers are upregulated/downregulated in individuals with TBI acutely post-injury, with evidence for differential expression by injury severity.

Neurodegeneration and Cell Death

Is Ferroptosis an Early Pathogenic Change in Cerebral X-Linked Adrenoleukodystrophy?

Presenting Author: ***Eric Mallack MD, MBE, MS, Kennedy Krieger Institute***

Co-Authors: *Christina Nemeth Mertz, PhD, Kennedy Krieger Institute, Mert Sisman, PhD, Weill Cornell Medicine, Thanh D. Nguyen, PhD, Weill Cornell Medicine*

Background: Cerebral Adrenoleukodystrophy (CALD) is a devastating, X-linked neurodegenerative disorder that occurs in 60% of affected males, most often in childhood. Significant challenges are associated with a diagnosis of CALD including early identification, high phenotypic variability, detection of patients with variants of uncertain significance, rigorous MRI screening, patient selection for high-risk therapies, variable responses to treatment, and the development of long-term cognitive deficits post-treatment. To address the need for early, more prognostic biomarkers which provide mechanistic insights into disease, we performed an exploratory analysis to measure two early pathological events known to occur in the normal appearing white matter (NAWM) of CALD: lipid peroxidation and microglial apoptosis. Given the unifying mechanistic relationship of apoptosis to lipid peroxidation, we hypothesize that ferroptosis may play an early role in the pathogenesis of disease prior to the onset, and in advance of, the spatiotemporal spread of CALD. We investigated this hypothesis using Quantitative Susceptibility Mapping (QSM) Source Separation followed by immunohistochemical validation and quantification of these findings in primary brain tissue. QSM is a quantitative MRI technique that decodes the distribution of tissue-specific perturbations in the local magnetic field induced by the MRI scanner's externally applied magnetic field. It can be decomposed into two sources: paramagnetic molecules such as iron which enhance (positive susceptibility (QSMp)), or diamagnetic molecules such as myelin which repel (negative susceptibility (QSMn)), the external field. The magnetic susceptibility of lipids increases when membranes undergo peroxidation as demonstrated in multiple sclerosis, whereas the increase in positive susceptibility due to iron overload has been mechanistically posited to represent ferroptosis in multiple neurodegenerative disorders.

Methods: We analyzed MR datasets from an 8yo with progressive CALD and a 6yo with stable CALD. QSM was reconstructed from complex multi-echo 3D gradient echo images using a fully automated Morphology Enabled Dipole Inversion algorithm zero-referenced to the ventricular cerebrospinal fluid. Maps were generated through nonlinear field fitting and background field removal, then processed using maximum spherical mean value filtering. R2* maps were generated via auto-regression on linear operators. Source separation was carried out using R2*-based approach. The magnitude atlas was normalized and registered using Advanced Normalization Tools onto the NIHPD pediatric atlas. A sex-specific normative QSM control atlas was created using data from 52 male subjects aged 5-10 years. The QSMn and QSMp maps from two ALD patients were compared to the normative male atlas in 3-D slicer. Immunohistochemical analysis of primary brain tissue from an adult patient with CALD was performed using antibodies against ACSL4 and GPX4, known markers within the ferroptosis pathway, in normal healthy appearing cortex and white matter, and

in areas of demyelination defined by direct observation of the bulk tissue sample. Quantification and colocalization of these proteins were done within the context of iron deposition (Prussian Blue) and cell type including astrocytes (GFAP), oligodendrocytes (MBP, PLP1), neurons (SMI32, MAP2), and microglia (IBA1, CD68).
Results: Our preliminary analysis reveals pathological alterations in iron and myelin signals not only within the cerebral lesion, but also in areas of the brain that appear normal on T1/T2 MRI (Z-score +2SD). The QSMn signal in the 8yo with progressive CALD reveals loss of myelin within the T2 lesion and high QSMn signal in the perilesional NAWM – the next area to demyelinate. There is high QSMp signal in the remote NAWM of the left hemisphere and parieto-occipital, peri-lesional NAWM representing abnormal iron accumulation. The 6yo boy with self-stabilized CALD revealed lesional myelin loss. Contrary to the other patient, there is overall less elevated QSMn signal in the perilesional NAWM, and there is a much smaller positive QSMp signal, indicating that his disease stability may correlate with lower degrees of perilesional lipid peroxidation and remote iron accumulation in NAWM. Within primary CALD postmortem tissue, GPX4 and ACSL4 signals are found within microglia and neurons, respectively, mostly within gray matter adjacent to NAWM. Analysis of the NAWM in the tissue sample revealed significant glial scarring within fragmented white matter tracts, hypertrophic astrocytes, and fragmented oligodendrocytes and neurons. Interestingly, astrocytes colocalize with myelin debris within NAWM suggesting an astrocyctic contribution towards CALD lesion development.
Discussion: To our knowledge, this is the first evidence of elevated iron content on QSM specifically, and imaging studies in general, in CALD. The imaging findings provide evidence that CALD is active in advance of its visibility by standard MRI. Concordantly, cell type specific expression of ferroptotic markers and astrocytic activation suggests an early contribution of ferroptosis to disease pathogenesis within normal, healthy appearing white matter tissue, in advance of CALD lesion formation. Taken together, QSM may inform the high phenotypic variability in CALD, including those at risk for developing CALD, progression versus those with stable disease, and differentiate ALD from patients with variants of uncertain significance. Further exploration and validation of the cellular findings would be the first demonstration of ferroptosis in CALD and would be a novel avenue for research in this disorder.

CRISPR-Based Screens to Uncover Chaperone Modifiers of Polyglutamine Protein Aggregation
Presenting Author: ***Biswarathan Ramani, MD, PhD, University of California San Francisco***
Co-Authors: *Kean Ehsani, BS, University of California San Francisco, Martin Kampmann, PhD, University of California San Francisco*
Abstract: Polyglutamine (polyQ) diseases, including Huntington's disease, are caused by abnormally expanded polyQ-encoding CAG repeats. Extensive evidence supports a pathogenic role of mutant protein misfolding and aggregation. We developed novel FRET-based fluorescent reporters of polyQ protein aggregation in human cells to conduct deep, unbiased CRISPR-based screening of all known endogenous chaperones and co-chaperones as potential modifiers. The screens confirmed several known chaperone modifiers (HSPA8, DNAJB6, and DNAJB1), but additionally revealed several previously unexplored hits, including DNAJC7, BAG6, DNAJA1, and OGT. We confirmed that direct knockdown of DNAJC7 potently accelerates aggregation polyQ protein aggregation, including in both the nucleus and cytoplasm. In contrast, DNAJC7 knockdown does not impact aggregation of a polyglycine tract (the causative mutation in neuronal intranuclear inclusion disease), indicating DNAJC7 can exhibit selectivity towards polyQ proteins. Immunoprecipitation confirmed pulldown of endogenous DNAJC7 with polyQ proteins containing aggregation-prone repeat lengths. Direct overexpression of DNAJC7 does not reduce aggregation of polyQ proteins unless performed on a DNAJC7 knockout background. In summary, CRISPR-based screening revealed new chaperone modifiers of polyQ protein aggregation, highlighting the utility of these new FRET-based reporters for high-throughput identification of disease targets. In addition, we have recently also developed a mouse in vivo screening platform that provides a comprehensive profile of neuron-essential chaperones and other proteostasis genes. Ongoing work includes screening for neuron-essential chaperones in a mouse model of Huntington's disease.

Neurodevelopment

Corpus Callosum Volumes are Decreased in a Mouse Model of Congenital Zika Virus
Presenting Author: ***Shannon Agner MD, PhD, Washington University in St. Louis***
Co-Authors: *Ethan Liu, BS, Washington University in St. Louis, James Quirk, PhD, Washington University in St. Louis, Benjamin Kohn, MS, Washington University in St. Louis, Jeffrey Neil, MD PhD, Washington University in St. Louis*
Background: In 2016 after a large outbreak of Zika virus in Brazil, a clear epidemiologic link between an increase in infants born with microcephaly and an outbreak of Zika virus was made. Congenital Zika virus (CZV) infection causes wide phenotypic variation amongst exposed infants. The pathogenic mechanisms and etiologies for the teratogenic effects of Zika virus are still not clearly defined. Furthermore, there is data to suggest that congenital Zika syndrome, characterized by microcephaly, intractable epilepsy and cerebral palsy, only constitutes 5-14% of children within utero Zika exposure. Therefore, the large majority of children within utero Zika exposure have present but mild developmental delays. Our laboratory has developed a mouse mode of CZV that has mild cognitive and behavioral abnormalities, and we hypothesized that structural brain abnormalities may account for these differences.
Methods: Pregnant humanized STAT2 knock-in (Jax: 031630) dams underwent footpad injection with 10^4 focus forming units of Zika virus or mock solution at embryonic day 6.5. Pups were weaned in accordance with approved institutional IACUC protocol. In vivo MRI was obtained at postnatal day 60 (P60). 6 mock- (3 male, 3 female) and 6 Zika-infected (3 male, 3 female) mice underwent

T2- weighted brain imaging. Total brain volumes, total ventricle volumes and corpus callosum volumes were manually segmented on a per-slice basis in ITK-SNAP. All data were compared by unpaired t-test for comparisons with equal variances and t-test with Welch's correction for unequal variances.
Results: The ratio of corpus callosum volume to total brain volume in Zika infected mice was significantly less than in mock infected mice (0.022 ± 0.001 vs. 0.020 ± 0.001, p = 0.04). Absolute corpus callosum volumes were 6.240 ± 0.2605 mm3 vs. 5.906 ± 0.3117 mm3, p = 0.07 in mock compared to Zika-infected mice, respectively. Total brain volume and ventricle volume showed a trend toward increased volume in the Zika-infected mice (total brain volume: 285.6 mm3 ± 7.580 mm3 vs. 293.3 ± 13.84 mm3, p = 0.27; ventricle volume: 8.452 mm3 ± 0.9350 mm3 vs. 9.023 ± 0.9441 mm3, p = 0.32).
CONCLUSIONS: In a mouse model of congenital Zika virus, P60 mice within utero Zika virus exposure show differences corpus callosum volumes but not total brain volumes or ventricle volumes. This data suggests that the phenotype of this mouse model may accurately mirror some of the neuroimaging findings in Zika-exposed infants with mild neurodevelopmental abnormalities. Future work will be needed to further characterize these findings and to understand the mechanisms that lead to these white matter abnormalities.

Synergistic Interaction Between Fibroblast Growth Factor 8 (FGF8) and Retinoic Acid (RA) Promotes Rostral Cortical Identity in Human Induced Pluripotent Stem Cell (hiPSC)-derved Cerebral Organoids
Presenting Author: ***Cathryn Cadwell MD, PhD, University of California, San Francisco***
Co-Authors: *Urvashi Thopte, MS, University of California San Francisco, H. Hanh Larson, BS, University of California San Francisco, Yewon Jung, PhD, University of California San Francisco*
Abstract: The cerebral cortex is parcellated into highly specialized regions characterized by unique cytoarchitecture, connectivity, and function. The prefrontal cortex (PFC) is of particular interest given its dramatic expansion in primates, especially humans, and its implication in the pathogenesis of several neurodevelopmental disorders (NDDs) including autism spectrum disorder, attention-deficit/hyperactivity disorder, and schizophrenia. Despite the importance of human PFC in normal brain function and in NDDs, the mechanisms underlying PFC areal specification during human brain development are not well understood. Fibroblast growth factor 8 (FGF8) is a canonical rostral patterning molecule that is known to specify PFC in mice. Recent work has also implicated retinoic acid (RA) signaling in early patterning of the primate, but not rodent, PFC. Here, we leverage a human induced pluripotent stem cell (hiPSC)-derived organoid model to identify the optimal conditions of FGF8 and RA exposure that drive a PFC-like rostral identity in vitro. We find that RA alone induces a caudal phenotype, but when organoids are pre-treated with FGF8 prior to RA, they develop rostral phenotypes, suggesting and interaction between RA and FGF signaling pathways during human cortical areal specification. Future studies will leverage this model to further dissect the molecular mediators and gene regulatory networks driving PFC areal specification in human cortical progenitors and how this process may be disrupted in NDDs."

Multiple Genes Encoded Within the 22q11.2 Neurodevelopmental Risk Locus Interact Within Juxtaventricular Glial Cells To Regulate Sensorimotor Behavior
Presenting Author: ***Philip Campbell MD, PhD, University of Pennsylvania***
Co-Authors: *Isaiah Lee, BS, University of Pennsylvania*
Abstract: Deletion of a 3Mb region on chromosome 22 (22qDS) encoding 45 protein coding genes predisposes humans to multiple neurodevelopmental disorders and is one of the greatest genetic risk factors for schizophrenia, though the cellular and molecular mechanisms underlying these associations remain incompletely understood. Through an unbiased zebrafish behavioral screen of loss of function animals of conserved genes within the 22qDS deleted region, we identified that loss of prodha, a mitochondrially localized enzyme involved in L-Proline metabolism, leads to marked sensorimotor behavioral phenotypes. Further, we find that prodha is specifically enriched in juxtaventricular glial cells, comprised of radial astrocytes/glia and ependymal cells, and that its loss leads to a cellular and transcriptomic phenotype characterized by hyperproliferation. RNA sequencing of prodha mutant juxtaventricular glial cells also reveals an upregulation of genes involved in mitochondrial translation and microRNA biogenesis. Interestingly, two other genes encoded within the 22qDS deleted region (mrpl40, a component of the mitochondrial ribosome, and dgcr8, a required component for miRNA biogenesis) have key roles in these pathways. Double mutant analysis of prodha with either mrpl40 or dgcr8 reveals that both genes function to compensate for loss of prodha, with double mutants displaying aggravated phenotypes compared to single prodha mutants. Finally, we show that cell type-specific expression of prodha within juxtaventricular glial cells is sufficient to rescue all prodha mutant sensorimotor behavioral phenotypes. Together, this work reveals a novel role for multiple 22qDS genes within juxtaventricular glial cells in behavioral regulation suggesting a glial mechanism may underlie brain and behavioral phenotypes in 22qDS.

Potential For Early Variance of Citric Acid Cycle Metabolites Contributing to Lasting Mitochondrial and Epigenetic Disruption After Prenatal Hypoxia in Glutamatergic Neurons
Presenting Author: ***Ana Cristancho MD, PhD, Children's Hospital of Philadelphia, The University of Pennsylvania***
Co-Authors: *Sabrina DaSilva, PhD, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Margaret Cassidy, PhD, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Rebecca*

Ahrens-Nicklas, MD, PhD, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania
Abstract: Pathologic transient hypoxic exposure to the fetal brain during critical periods of development leads to a broad spectrum of neurodevelopmental disabilities. In a murine model, we uncovered no early cell death shortly after transient prenatal hypoxia (5% inspired oxygen for 8 hours at embryonic day 17.5). However, we detected less glutamatergic neuron complexity and abnormal hyperpolarization in animals one month after the insult, which correlated to decreased seizure threshold and cerebral palsy-like hind limb weakness in adult animals. To uncover the mechanisms driving these persistent structural and functional deficits, we conducted joint multiomic single-nucleus transcriptomic and epigenetic profiles of juvenile animals (postnatal day 25-30). Surprisingly, we find persistent repression of the mitochondrial function transcriptome from prenatal hypoxia. These changes correlate with decreased complexes I and II function and increased reactive oxygen species production in isolated cortical mitochondria from prenatal hypoxia-exposed juvenile animals. Regions with reduced chromatin accessibility after prenatal hypoxia are enriched for the Nrf1 motif, a master regulator of mitochondrial biogenesis and function. Emerging evidence suggests that amongst the most critical consequences of prenatal brain injuries, including hypoxia, is the disruption of the metabolome and epigenome. Metabolites for epigenetic modifications, including histone and DNA methylation and histone acetylation, require ATP-dependent mechanisms that directly link energy metabolism to epigenetic regulation that may alter cell maturation. Thus, to unravel the effect of hypoxia on the metabolic profile of the fetal brain, we performed targeted metabolomics on organic acids, amino acids, and fatty acids immediately after hypoxia. We find a striking difference between normoxia and hypoxia, driven by a global increase in amino acids and a decrease in fatty acids. Interestingly, there is substantial variance in organic acids related to the citric acid cycle, supporting the possibility that the brain is prioritizing energy metabolism to promote survival. One of the citric acid cycle metabolites with the most significant increase in variance is alpha ketoglutarate, a critical co-factor for DNA methylation and hydroxymethylation regulation. As Nrf1 binding is sensitive to DNA methylation, we are currently testing whether DNA methylation distribution is variably disrupted after prenatal hypoxia, contributing to abnormal distribution of Nrf1 binding and abnormal mitochondrial gene expression and function in glutamatergic neurons. Should we find increased DNA methylation at Nrf1 binding sites related to decreased alpha-ketoglutarate, rescuing this pathway may allow us to restore maturation to affected neurons to improve neurodevelopmental deficits from prenatal hypoxia.

Somatic Mutations in Focal Epilepsy Identified Through Re-Analysis of Epilepsy Consortium Exome Data
Presenting Author: ***Diane Shao MD, PhD, Boston Children's Hospital***
Co-Authors: *Michael Chen, BS, Harvard Medical School, Junseok Park, PhD, Boston Children's Hospital, Alice E. Lee, PhD, Boston Children's Hospital, Christopher A. Walsh, MD, PhD, Boston Children's Hospital, Yue Huang, PhD, Boston Children's Hospital*
Background: Focal epilepsy constitutes over 60% of all epilepsies, yet large-scale studies of both rare and common genetic variation have consistently failed to identify genome-wide significant genes. Despite the demonstrated role of post-zygotic somatic mutations in focal cortical malformations and surgically resected tissue, no systematic evaluation of somatic mosaicism in large-scale epilepsy exome datasets has been conducted. We hypothesized that reanalysis of blood-derived exomes using somatic-aware bioinformatics pipelines would identify a disease-associated somatic mutations, potentially resolving some of the missing heritability in focal epilepsies.
Objective: To evaluate whether somatic mutations detectable in peripheral exome sequencing data contribute to the genetic landscape of focal epilepsy, and to identify specific genes with recurrent deleterious somatic mutations across epilepsy cohorts.
Methods: We re-analyzed 337 parent–proband trios from the Epi4K developmental and epileptic encephalopathy (DEE) cohort using MosaicHunter, a Bayesian algorithm for somatic variant detection. Candidate somatic variants were filtered for high pathogenic potential (based on allele fraction, functional annotation, and gnomAD frequency) and validated using Sanger or amplicon sequencing. We compared mosaic variant enrichment between Epi4K versus an unaffected trio cohort, assessed expression profiles in human fetal brain cell types, and evaluated gene-level recurrence across three additional epilepsy datasets: Epi25K, Boston Children's Hospital cohorts, and non-trio Epi4K cases. We performed burden testing of candidate genes in epilepsy versus control cohorts from Epi25K and mapped variant locations to protein functional domains.
Results: Our analysis identified 323 mosaic variants in 337 probands from Epi4K, of which 66 were rare and function-altering. 95% of these somatic variants had not been reported in prior Epi4K germline analyses. Six variants occurred in known epilepsy genes, including *CHD2*, *CDKL5*, *SCN2A*, *NEDD4L*, *ALG13*, and *SLC35A2*. Orthogonal sequencing validated 85.3% of 34 selected candidates. Compared to control trios, epilepsy probands showed enrichment for rare damaging somatic variants in genes expressed in neurons ($p<0.0001$). Notably, the candidate gene list showed significant connectivity to known epilepsy genes in network analyses and remained enriched after controlling for gene size and mutability. Cross-cohort validation revealed a significant excess of damaging somatic variants in candidate genes in Epi25K epilepsy cases versus controls ($p < 0.001$). Two genes showed statistically significant enrichment: *KMT2D* ($p = 3.7e-5$) and *NEDD4L* ($p = 0.002$). Somatic variants in *KMT2D* were highly localized to functional domains (PHD, SET, FY-rich) and were enriched in individuals with focal and lesional epilepsy. Among individuals with *KMT2D* somatic mutations, phenotypes ranged from infantile spasms to lesional focal epilepsy.
Discussion: Somatic mutations detectable from blood-derived exomes explain a previously unrecognized component of focal epilepsy's genetic architecture, where germline studies have largely fallen short. Our findings position *KMT2D* and *NEDD4L* as recurrent, functionally enriched somatic risk genes, particularly in lesional focal epilepsies. These results suggest that early post-

zygotic mutations with widespread tissue distribution contribute to epileptogenesis via subclinical mosaicism. Integrating somatic-aware variant detection into standard genomic analysis workflows may uncover diagnoses in previously unsolved cases and improve precision medicine approaches in epilepsy.

Neurogenetics and Gene Therapy

Examining the Epileptogenic Effect of Impaired NAD+ Metabolism in Gabaergic Neurons
Presenting Author: ***Divakar Mithal MD, PhD, Ann and Robert H. Lurie Children's Hospital***
Co-Authors: *Navdeep S. Chandel, PhD, Northwestern University, Britta Kuusik, BS, Northwestern University/Lurie Children's*
Abstract: Primary Mitochondrial Diseases (PMDs) result from intrinsic dysfunction of mitochondria and have a prevalence of 1 in 5,000. Although over half experience neurologic symptoms, PMDs are heterogeneous both genetically and phenotypically. Given the disease heterogeneity, metabolic pathways common to multiple forms of PMD are appealing therapeutic targets. However, the full extent of mitochondrial metabolism in neurons is incompletely understood as in addition to generating energy in the form of ATP through the electron transport chain (ETC), mitochondria also generate metabolites through the TCA cycle and reactive oxidation species, any of which may contribute to neuronal function. For example, GABAergic inhibitory interneurons have large mitochondrial mass and are essential for regulating excitatory neuronal circuits but how altered mitochdrial metabolism affects neuronal function is poorly understood. To determine the effects of altered mitochondrial metabolism, a conditional knockout mouse model was employed. The mitochondrial complex I subunit NDUFS4 was conditionally deleted using a GAD-Cre that selectively drives expression in GABAergic neurons. Mice with the conditional NDUFS4 deletion in GABAergic neurons died from a terminal seizure at postnatal day 60. Selective rescue of NAD+ regeneration at mitochondrial complex I using a genetic construct extended survival for the mice, delaying seizure onset by approximately 40 days. There was no significant difference in the number of surviving GABAergic neurons in conditional knockout mice compared to wild-type controls. Measurement of metabolites in the brains of conditional knockout mice did not demonstrate a significant change in any specific metabolites compared to wild-type controls, although GABA appeared to be lower. However, heavy 13-C glucose labeling indicated that TCA-cycle derived GABA was less in the conditional knockout mouse. Taken together the data suggest that impaired mitochondrial metabolism in GABAergic neurons is not cytotoxic per se, but rather causes a decrease in the TCA cycle which lowers GABA levels.

Exploring the Genomic Landscape of MECP2 Duplication Syndrome: Correlating Phenotypic Traits and Guiding Therapeutic Strategies
Presenting Author: ***Davut Pehlivan, MD, Baylor College of Medicine***
Co-Authors: *Jesse Bengtsson, PhD, Pacific Northwest Research Institute, Sameer S. Bajikar, PhD, University of Virginia, Ming Yin Lun, MS, Pacific Northwest Research Institute, Christopher M. Grochowski, PhD, Baylor College of Medicine, Holly K. Harris, MD, Baylor College of Medicine, Texas Children's Hospital, Bernhard Suter, MD, Baylor College of Medicine, Haowei Du, PhD, Baylor College of Medicine, Shalini N. Jhangiani, MS, Baylor College of Medicine, Donna M. Muzny, MS, Baylor College of Medicine, Richard A. Gibbs, PhD, Baylor College of Medicine, Anna Lindstrand, MD, PhD, Karolinska University Hospital, Fritz J. Sedlazeck, PhD, Baylor College of Medicine, James R. Lupski, MD, PhD, Baylor College of Medicine, Huda Y. Zoghbi, MD, Baylor College of Medicine, Claudia Carvalho, PhD, Pacific Northwest Research Institute*
Objective: MECP2 Duplication syndrome (MDS) is a rare genetic condition resulting from copy-number gains involving the MECP2 gene. The most common clinical manifestations include infantile hypotonia, severe neurodevelopmental delays, frequent respiratory infections, refractory epilepsy, and gastrointestinal problems. Each individual exhibits unique duplication sizes and gene content, which are considered to contribute to clinical variability. However, so far, studies have not established a consistent genotype-phenotype correlation. Our previous research involving a cohort of 30 MDS individuals revealed that at least 26% of the duplications are complex genomic rearrangements (CGRs), primarily in the form of inverted triplications flanked by duplications (DUP-TRP/INV-DUP). Individuals with triplications spanning MECP2 exhibited more severe phenotypes. We hypothesize that CGRs are more prevalent in MDS than previously anticipated, and that a lack of understanding of these rearrangements impedes accurate genotype-phenotype correlations.
Methods: We utilized custom-designed, high-resolution array comparative genomic hybridization (aCGH) targeting the X and Y chromosomes, along with short-read whole-genome sequencing (WGS) to examine the genomic structure at the Xq28 region in 137 unrelated individuals with MDS. Individuals with CGR additionally underwent long-read WGS and genomic optical mapping to decipher the structure. We correlated genomic structures with transcriptomic and quantitative phenotyping analysis using Human Phenotype Ontology (HPO) semantic similarity score.
Results: Copy number variations (CNVs) ranged from 64 kb to 16 Mb, displaying the following structural distribution: 48% tandem duplications, 22% terminal duplications, 20% Duplication-Triplication-Duplication (DUP-TRP/INV-DUP) structures, and 10% other complex genomic configurations. De novo events were predominantly observed in the terminal duplication group (65%), compared to the tandem duplication (17%) and CGR groups. RNA sequencing data from lymphoblastoid cell lines revealed that the MECP2 transcript in MECP2 triplications is significantly different from all duplications, but not between other genomic structures. Genotype-

phenotype analyses demonstrated a progressive worsening of phenotypic features, including overall survival, developmental levels, microcephaly, epilepsy, tube feeding and genitourinary/eye abnormalities, in the following sequence: tandem duplications, other CGRs, terminal duplications, translocations, and triplications involving MECP2. HPO analysis revealed distinct patterns among these genomic subgroups. Importantly, the recently initiated genetic-based treatment for MDS is developed in accordance with this classification.
Conclusion: MECP2 copy number changes alone do not solely determine disease phenotype; the structure of genomic rearrangements also significantly influences clinical manifestations and severity. Adopting a comprehensive analytical approach enhances our understanding of the impact of genomic disorders, leading to more effective therapeutic strategies.

Neuroinflammation and Neuroinfection

Genetic Variation in HEXB and GM2 Metabolism Modifies Prenatal Viral Infection and Brain Injury
Presenting Author: ***Youssef Kousa, MS, DO, PhD, Children's National Hospital***
Co-Authors: *Rozel Razal, Graduate Student, Children's National Research Institute, Allison Horvath, BS, Children's National Research Institute, Lani Tran, BS, Children's National Research Institute, Clara Abdelmalek, MS, Children's National Research Institute, Eunbin Park, MS, Children's National Research Institute, Tamer Mansour, MD, PhD, University of California Davis/Mansoura University; Egypt*
I**ntroduction**: Prenatal viral infections can cause irreversible brain damage and fetal death. While some fetuses are severely injured, others retain no discernible ill effects from infection. It remains unclear why defensive shields provided by maternal immunity, placenta, and fetal tissues do not always protect the developing brain. Through comparative genomic analyses of infants exposed prenatally to Zika virus, and confirmatory tests in multiple neural platforms, we uncovered a specific pathway that, when altered, modifies brain injury from prenatal infection.
Results: Our key data from human and mouse studies have correlated the severity of prenatal brain injury with disruption in beta-hexosaminidase B (HEXB) and lysosomal activity of infected brain cells. Genomic human studies from the 23-center PING Consortium (founded by the senior author) identified a series of loss-of-function mutations in HEXB among infants with Zika-induced brain injury. In mice and human iPSCs, our analyses confirm the causative nature of this linkage. Supported by prior work, we also find that buildup of extracellular GM2 gangliosides is linked to viral infection and tissue injury; since GM2 breakdown results from HEXB's enzymatic activity in lysosomes, dysregulation of HEXB can change the exterior features of a target cell, making it more likely to be infected.
Conclusion: Our research project identifies a novel and key pathway connecting HEXB, GM2 and lysosomal function in steering the brain's response against viral infections. Of note, this pathway influences multiple steps of the viral infection cycle within host cells and may therefore underlie infection and pathogenicity for multiple viruses that adversely affect the developing brain. We anticipate that our findings will facilitate, for the longer term, the development of prenatal neuro-precision interventions to protect the developing brain—humanity's most precious resource.

Neuromuscular Disease

Identifying Upper Motor Neuron Pathology and Molecular Signatures in the Amyotrophic Lateral Sclerosis (ALS) Motor Cortex
Presenting Author: ***Frank Diaz MD, PHD, Cedars-Sinai Medical Center***
Co-Authors: *Sreekanth Madhusoodhanan, PhD, Cedars-Sinai Medical Center, Sophia Mostowy, BS, Cedars-Sinai Medical Center, Michel Zamojski, PhD, Cedars-Sinai Medical Center, Pablo Avalos, MD, Cedars-Sinai Medical Center, Pascal Sati, PhD, Cedars-Sinai Medical Center, Clive Svendsen, PhD, Cedars-Sinai Medical Center*
Background: Motor cortex dysfunction might occur early in ALS and is a potential driver of disease progression. Magnetic resonance imaging (MRI) techniques that can evaluate iron [e.g., T2* scans, susceptibility weighted imaging (SWI), and quantitative susceptibility mapping (QSM)] have emerged as promising tools to identify motor cortex involvement. However, beyond iron and microglia correlations in areas of iron-sensitive MRI signaling abnormalities, little is known about the state of the motor neurons or other non-neuronal cells in those areas. In addition, the clinical significance of the motor band sign in ALS and variants, such as Primary Lateral Sclerosis (PLS), and, Progressive Muscular Atrophy (PMA), remains unclear. A comprehensive understanding of the pathological and clinical significance of the brain MRI signals seen in ALS can further our understanding of the underlying pathophysiology, mechanisms of disease spread, and lead to new outcome measures for clinical trials.
Objectives: 1) Identify the clinical significance of the motor band sign; 2) Identify the pathological significance and molecular signatures associated with the motor band sign. Methods: 1) High resolution isotropic brain MRIs are performed in patients with ALS and variants at baseline, 6 months, and 12 months. Clinical outcome measures include quantitative strength testing and upper motor neuron scores. 2) To identify the underlying pathology brains from patients with ALS are scanned ex vivo and both

immunohistochemistry and spatial transcriptomics are performed.
Results to Date: While in ALS, the motor band sign seems to correlate with the most affected limb, the opposite appears to occur in PLS. longitudinal MRI scans are being analyzed to help clarify these preliminary results. We have optimized the 3D-pirinting protocol for the individualized brain molds and sectioning templates. Preliminary data shows that most ferritin+ cells have microglia-like morphology and co-stain with Iba1+, consistent with prior studies. We are now analyzing the apical dendrite of motor neurons, microgliosis, and astrogliosis within the MRI signal abnormalities. snRNA-seq data from the hand knob area suggests that astrocytes increase while the number of putative Betz cells remain the same. Spatial transcriptomics are being performed to further clarify the results.
Discussion: These preliminary findings highlight the clinical relevance of the motor band sign in ALS and the ongoing histopathological studies, and spatial transcriptomics studies will help identify the underlying pathology and molecular signatures.

Enterovirus D68 2A Protease Causes Nuclear Pore Complex Dysfunction and Motor Neuron Toxicity
Presenting Author: ***Matthew Elrick MD, PhD, Kennedy Krieger Institute***
Co-Authors: *Katrina Zinn, BS, Kennedy Krieger Institute, Mathew W. McLaren, BS, Kennedy Krieger Institute, Michael T. Imai, MS, Kennedy Krieger Institute, Malavika M. Jayaram, MS, Kennedy Krieger Institute, Jeffrey D. Rothstein, MD, PhD, Johns Hopkins School of Medicine*
Abstract: Acute flaccid myelitis (AFM) is a polio-like paralytic disease of children. It is caused by enterovirus infection, and increased circulation of Enterovirus D68 (EV-D68) has been associated with multiple worldwide outbreaks of AFM in recent years. AFM has been attributed to infection of spinal motor neurons by EV-D68, however the mechanisms linking infection to toxicity are unknown. The enterovirus life cycle involves the disruption of nucleocytoplasmic transport, allowing RNA binding proteins that typically reside in the nucleus to participate in viral replication in the cytoplasm, and disrupting the nuclear export of host mRNA to favor viral translation and replication. Similar deficits in nucleocytoplasmic transport have been implicated in neurodegenerative disorders, most notably the motor neuron disease Amyotrophic Lateral Sclerosis (ALS). We therefore hypothesized that enterovirus-induced nucleocytoplasmic transport dysfunction contributes to the selective motor neuron toxicity that occurs in AFM.
Here, we demonstrate that the EV-D68 2Apro and 3Cpro proteases cleave six nucleoporins, but that this disrupts the expression of 17 nucleoporins in total. The activity of 2Apro, but not 3Cpro, disrupts the permeability barrier of the nuclear pore complex and prevents active transport of protein cargoes but not the export of RNA. In an induced pluripotent stem cell (iPSC)-derived spinal motor neuron model of AFM, inhibition of 2Apro with telaprevir is neuroprotective, independent of its potential antiviral effects. These findings point to the role of the nuclear pore complex in AFM pathogenesis and suggest possible targets for neuroprotective therapies.

Deciding with Confidence: Feeding Tubes and Amyotrophic Lateral Sclerosis
Presenting Author: ***Bridget Perry PhD, CCC-SLP, MGH, Institute of Health Professions***
Co-Authors: *Tabitha Kao, CCC-SLP, MGH Institute of Health Professions*
Introduction: For people living with amyotrophic lateral sclerosis (pALS), whether to have a feeding tube placed is a difficult medical decision that affects both nutritional status and quality of life (Labra et al., 2020). In addition to scientific evidence and clinical expertise, patient preferences are a vital component of the decision-making process, necessary to ensure that medical decisions are high-quality and made with confidence. (Grad et al., 2017; Hamilton et al., 2017). At present, we have a limited understanding of the quality and confidence with which feeding tube decisions in this population are made (Genuis et al., 2023). The purpose of this study was to determine whether pALS are confident in their feeding-tube decisions and to determine which patient characteristics and components of the decision-making process impact decision-making confidence for pALS. Identifying factors associated with high decisional confidence will help pALS, their caretakers, and medical providers make quality decisions around feeding tube placement.
Method: Data was collected as part of an online survey conducted from December 2023-October 2024 using Research Electronic Data Capture (REDCap), a secure web-based platform (Harris et al., 2009). Questions included participant demographics, feeding tube discussion content (e.g., risks, benefits, timing, information sources), decisional confidence and regret (SURE test, Decision Regret Scale), swallowing and communication function (e.g., ALS Functional Rating Scale), and quality of life. For this study, participant-related factors (ALS onset location, treatment facility type), feeding tube discussion content (amount of time spent discussing feeding tube benefits, risks, and other nutritional management options), discussion timing (when the discussion occurred, how ready the pALS was for the discussion), and discussion source (information received from healthcare professionals and others) were extracted. Decisional confidence was measured using the SURE test, a four-item screen used to identify individuals with decision-making conflicts. Total scores range from 0 to 4, with scores below 4 indicating decisional conflict. The participants were dichotomized by low and high decisional confidence, with 4 being high confidence and 0-3 being low confidence. Independent samples t-tests and chi-squared tests of independence were conducted to assess baseline differences in age, sex, and race between the two groups. Binary logistic regressions were conducted to determine whether discussion content, timing, and source predicted high confidence.
Results: Of 74 pALS who had made decisions about feeding tube placement, 50 (68%) had high decisional confidence and 24 (32%) had low confidence. 57 (77%) had opted for feeding tube placement, and 17 (23%) had not. Thirty-seven (50%) were male, 36 (49%)

were female, and 1 (1%) was unknown, with age averaging 63 years (24-84 years). Forty-four (59%) had limb onset, 28 (38%) had bulbar onset, 1 (1%) had another onset, and 1 (1%) had unknown onset. At data collection, 22 (30%) had ALS for more than five years, 13 (18%) for 3-5 years, 27 (36%) for 1-3 years, 8 (11%) for less than a year, and 4 (5%) were unknown. Participants treated at multidisciplinary ALS care clinics were three times more likely to have high confidence than those at other types of facilities, $\beta = 0.96$, SE = 0.29, z = 3.29, p = 0.001. Participants who had the feeding tube placement discussion with healthcare providers before it was medically needed were 2.36 times more likely to have high confidence, $\beta = 0.86$, SE = 0.32, z = 2.69, p = 0.01. Additionally, when participants perceived these discussions as occurring at the right time, they were 2.6 times more likely to have high confidence, $\beta = 0.96$, SE = 0.30, z = 3.15, p = 0.002. Finally, those who discussed feeding tube placement with dietitians were 3.40 times more likely to have high confidence, $\beta = 1.22$, SE = 0.58, z = 2.09, p = 0.04. There were no differences between groups in terms of age, sex, and race. The results indicate that the amount of time pALS discussed feeding tube placement with their healthcare providers did not have a significant relationship with confidence.

Discussion: Over 30% of pALS were not confident when they made the decision to have or not have a feeding tube placed. Those who received care in a multidisciplinary care clinic had increased confidence in the decision. This is likely because the comprehensive and coordinated interprofessional care available at multidisciplinary ALS care clinics provides pALS with opportunities to discuss options with various specialties, resulting in more informed decisions (Hogden et al., 2017). Second, pALS were more confident in their decision when information about feeding tube placement was provided before it was felt to be medically needed and when they felt prepared to receive it. Studies have indicated that when pALS are unwilling or unprepared to discuss medical care decisions, treatment can be delayed. Experts have called for a proactive rather than reactive approach to nutritional management (Rogus-Pullia & Plowman, 2020). Early discussions around medical decisions give patients more time to consider difficult decisions (Marques et al., 2018). Finally, decisional confidence did not appear to be affected by the time spent discussing feeding tube placement with their healthcare provider. Meeting with a dietitian did result in higher decisional confidence. As evidence-based information is critical for quality decision-making (Brehaut et al., 2003), this finding suggests that discussion quality is more important than quantity. Future research is needed to investigate (1) the specifics of what quality information pALS need to increase decisional confidence, and (2) how best to provide quality information efficiently and effectively to improve decisional confidence."

Brain Structure and Cognitive Endpoints in Myotonic Dystrophy Type 2

Presenting Author: ***Araya Puwanant, MD, MS, Wake Forest University School of Medicine***

Co-Authors: *Laura Flashman, PhD, Wake Forest University School of Medicine, Joseph Rigdon, PhD, Wake Forest University School of Medicine, Suzanne Craft, PhD, Wake Forest University School of Medicine, Peggy Nopoulos, MD, University of Iowa*

Background: Myotonic dystrophy type 2 (DM2), a complex multisystemic genetic disorder, is caused by a CCTG repat expansion in the cellular nucleic acid binding protein (CNBP) gene, where RNA-gain-of-function is the primary disease mechanism. While progressive muscle weakness is the key symptom in DM2, nearly 70% of patients report that impaired cognition is among the most disabling symptoms. A sparse literature describes executive dysfunction, impaired processing speed, and episodic memory loss in DM2. Yet the mechanisms that lead to cognitive dysfunction are poorly understood as brain imaging studies are extremely limited. Nonetheless, previous studies suggest that cerebral white matter is primarily affected in DM2, with reduced WM volume and abnormalities of WM integrity derived from diffusion tensor imaging (DTI).

Method: 3T brain MRIs were acquired in 38 adults with DM2 and 24 age and gender-matched controls. Brain morphometry and white matter integrity were assessed using T1-MPRAGE and DTI sequences, respectively. DTI scalars, including fractional anisotropy (FA), radial diffusivity (RD), and mean diffusivity (MD), were compared between groups. A comprehensive battery of cognitive measures was performed and correlated with MRI measures.

Results: Among 62 participants (55% female), mean age (57.5 vs. 60.1 years) and education level (16.2 vs. 17.0 years) were not different between groups. Compared to controls, individuals with DM2 showed a marked reduction in cortical gray matter volume (t-value, 4.46; $p<0.0001$). While cerebral white matter volume did not differ significantly, widespread disruptions in white matter integrity (lower FA, higher RD) were among the most prominent changes in the DM2 group (mean differences of FA, 0.035; $p<0.0001$ and RD, 0.00005; $p<0.0001$), suggesting that pathology is within white matter microstructure. Cognitively, the DM2 group demonstrated significant deficits in executive function (mean difference, 10.9; $p<0.003$) and episodic memory (mean difference, 8.6; $p<0.017$). In addition, several plasma biomarkers – including neurofilament light (NfL), glial fibrillary acidic protein (GFAP), and phosphorylated tau (P-tau) – were significantly elevated in the DM2 group.

Conclusion: Our data provide robust evidence of brain involvement in DM2, particularly in white matter microstructure and cognitive domains such as executive function and episodic memory. The elevation of plasma p-tau, NfL, and GFAP supports the evidence of tau misprocessing and axonal degeneration in DM2. Future studies incorporating cerebrospinal fluid biomarkers and longitudinal design are needed to further validate these results and elucidate disease mechanisms of brain dysfunction in DM2.

Neuro-oncology

Phenotypic Diversity of Reversible Tumorigenesis in Human Cerebral Organoids
Presenting Author: ***Maya Graham, MD, PhD, University of California San Francisco***
Co-Authors: *Paolo Codega, PhD, Abbvie, Carl Campos, BA, Memorial Sloan Kettering Cancer Center, Meaghan Grogan, BA, Memorial Sloan Kettering Cancer Center, Marc Rosenblum, MD, Memorial Sloan Kettering Cancer Center, Charles Coleman, BS, Icahn School of Medicine at Mount Sinai, Saul Carcamo, PhD, Icahn School of Medicine at Mount Sinai, Dan Hasson, PhD, Icahn School of Medicine at Mount Sinai, Subhiksha Nandakumar, MS, Memorial Sloan Kettering Cancer Center, Cristina Antonescu, MD, Memorial Sloan Kettering Cancer Center, Jamal Benhamida, MD, Memorial Sloan Kettering Cancer Center, Tejus Bale, MD, PhD, Memorial Sloan Kettering Cancer Center, Andreas von Deimling, MD, Heidelberg University Hospital, Nicholas Socci, PhD, Memorial Sloan Kettering Cancer Center, Ingo Mellinghoff, MD, Memorial Sloan Kettering Cancer Center*
Abstract: Human cerebral organoids have emerged as a new approach to modeling the role of cancer-associated genes in tumorigenesis ex vivo. Here, we asked if organoid developmental stage impacts the phenotype of oncogene-driven transformation. Using inducible cassettes carrying key oncogenic mutations histone H3K27M, dominant negative p53 and activated PDGFRA, we show that their expression in cerebral organoids reproducibly drives high grade malignant transformation, including in orthotopic xenografts. This transformation is dependent on persistent transgene expression, as oncogene withdrawal causes complete tumor regression. Varying the timing of oncogene induction modulates transformation phenotype, with induction at one timepoint yielding a spectrum of neuro-glial tumors while induction at a later timepoint yields a rhabdomyosarcoma phenotype. Chromatin landscape analysis of transforming organoids suggests this modulation may be due to differential susceptibility of putative cells-of-origin to the canonical effects of the H3K27M oncohistone. These findings demonstrate the pivotal role of cell context in oncohistone-mediated transformation and may highlight shared vulnerabilities between phenotypically different pediatric cancers.

N-acetylcysteine-induced Lactate Production is a Targetable Metabolic Susceptibility in Glioblastoma
Presenting Author: ***Evan Noch, MD, PhD, University of Texas Southwestern Medical Center***
Co-Authors: *Sukanya Rauniyar, PhD, University of Texas Southwestern Medical Center, Kevin Zhai, MD, University of Texas Southwestern Medical Center, Saif Nirzhor, PhD, University of Texas Southwestern Medical Center, J. David Elliott, PhD, University of Texas Southwestern Medical Center, Kathleen Earhart, BA, University of Texas Southwestern Medical Center*
Abstract: Lactate shuttling between glycolytic and oxidative tumor cells maximizes tumor growth, making it a crucial onco-metabolite for energy metabolism. Glioblastoma (GBM) cells exhibit lactate dehydrogenase A (LDHA) overexpression and elevated lactate production, but little is known about the metabolic effects of lactate in GBM. Previously, we showed that treatment of GBM cells with the FDA-approved single cysteine compound N-acetylcysteine (NAC) induces mitochondrial reductive stress via H2O2 production in vitro and in vivo, which is further worsened by glucose starvation in patient-derived GBM cells. We now show that NAC treatment increases lactate production in GBM cells, which facilitates transfer of electrons to NAD+, thereby mitigating reductive stress. To test the effects of lowering lactate on NAC-induced cytotoxicity, we treated GBM cells with the mitochondrial pyruvate dehydrogenase enzyme complex inhibitor dichloroacetate (DCA). We found that combined NAC and DCA treatment exert additive cytotoxicity in isocitrate dehydrogenase (IDH) wild-type (wt) and mutant (mut) glioma cells. Acute treatment with NAC-DCA drastically reduces mitochondrial respiration in both IDHwt and IDHmut glioma cells. Furthermore, GC/MS based U-13C6-glucose metabolic flux analysis revealed that TCA cycle activity is lower in glioma cells after combined NAC and DCA treatment and that DCA prevents NAC-induced lactate production. Genetic knockout of the lactate dehydrogenase A and B enzymes, which normally interconvert pyruvate and lactate, also potentiates NAC cytotoxicity in GBM cells. Because monocarboxylate transporters facilitate lactate influx and efflux, we tested the effect of MCT inhibition on NAC-induced cytotoxicity. MCT inhibition with either Syrosingopine or AZD3965 exerts synergistic cytotoxicity with NAC in 4 patient-derived glioma cells. In a pre-clinical orthotopic GBM mouse model imaged with single-voxel 1H magnetic resonance spectroscopy, we found that intraperitoneal treatment with a cysteine-containing peptide CB4 along with DCA induces elevated glutathione formation as compared to saline-treated mice, a marker of reductive stress. Our data strongly suggest that lactate production is a targetable susceptibility of NAC-induced reductive stress. The unique sensitivity of GBM towards NAC and its dependence on lactate as an oncometabolite governing metabolic resistance may open a novel druggable pathway for treating both IDwt and IDHmut gliomas.

Sleep Disorders and Circadian Rhythms

Sleep-Wake Disturbances in Midlife: Associations with Cognitive and Physical Impairment in a Primary Care Cohort
Presenting Author: ***Minjee Kim, MD, Northwestern University Feinberg School of Medicine***
Co-Authors: *Morgan Bonham, BS, Northwestern University Feinberg School of Medicine, Fangyu Yeh, MPH, Northwestern University Feinberg School of Medicine, Scott Hur, MPH, Northwestern University Feinberg School of Medicine, Emily H. Ho, PhD, Northwestern University Feinberg School of Medicine, Lauren Rogers, PhD, Northwestern University Feinberg School of Medicine, Laura Curtis, MS, Northwestern University Feinberg School of Medicine, Julia Y. Benavente, MPH, Northwestern University Feinberg School of Medicine, Jeffrey A Linder, MD, MPH, Northwestern University Feinberg School of Medicine, Phyllis C. Zee, MD, PhD, Northwestern University*

Feinberg School of Medicine, Michael S Wolf, PhD, MPH, Northwestern University Feinberg School of Medicine
Background: Sleep-wake disturbances in midlife may be modifiable risk factors for later-life cognitive and physical decline but often go undetected. Although over 150 validated sleep questionnaires exist, it remains unclear which tools might effectively identify sleep-wake disturbances in primary care. This study aimed to determine the prevalence of sleep-wake disturbance phenotypes ("sleep phenotypes") using brief questionnaires and examine their associations with cognitive and physical impairment in middle-aged adults.

Methods: This secondary analysis utilized data from the ongoing MidCog cohort study, which includes adults aged 35-64 receiving primary care at 12 Chicagoland practices. Five sleep phenotypes were assessed: (A) obstructive sleep apnea (OSA) risk (STOP-BANG >2), (B) insomnia symptoms (Insomnia Severity Index ≥15), (C) poor sleep health (RU-SATED <7), (D) sleep disturbance (PROMIS T-score >55), and (E) short sleep duration (<6 hours; Munich Chronotype Questionnaire). Cognitive function was measured using the Montreal Cognitive Assessment (MoCA) and the NIH Toolbox Cognition Battery Fluid Composite (NIHTB-CB), with impairment defined as an age- and education-adjusted T-score <40. Physical function was measured by gait speed (Six-Minute Walk Test) and grip strength (Jamar dynamometer; maximal reading of 6 trials; 3 trials/hand), with impairment determined using reference values according to age, sex, weight, and height. Logistic regression estimated odds ratios (OR) for cognitive and physical impairment, adjusting for age, sex, comorbidities, depressive symptoms, and smoking.

Results: Among 1,026 participants (age 52±8 years; 60.9% female; 40.5% non-Hispanic Black, 36.5% non-Hispanic White, 15.4% Hispanic), the prevalence of OSA risk, insomnia symptoms, poor sleep health, sleep disturbance, and short sleep was 57.9%, 18.2%, 28.5%, 19.0%, and 7.2%, respectively. Cognitive impairment was present in 12.5% (MoCA) and 20.0% (NIHTB-CB), while slow gait speed and weak grip strength were observed in 25.7% and 3.8%, respectively. Poor sleep health was the only sleep phenotype associated with both cognitive (MoCA: OR [95% CI] = 1.13 [1.06-1.20]; NIHTB-CB: 1.20 [1.11-1.29]; p<.001 for both) and physical impairment (slow gait speed: 1.15 [1.07-1.24], p<.001; weak grip strength: 1.05 [1.01-1.08], p=.012). Insomnia symptoms were associated with slow gait speed (1.13 [1.04-1.23], p=.006) and weak grip strength (1.05 [1.01-1.09], p=.018) but not with cognitive impairment.

Conclusion: Sleep-wake disturbances were highly prevalent in midlife. Poor sleep health was associated with both cognitive and physical impairment, underscoring the potential value of sleep health screening in primary care to identify individuals at risk of cognitive and functional decline. Future research should examine whether improving sleep health in midlife can mitigate cognitive and functional decline.

ANA 2025 NINDS Author Index

Adney, Scott	M305-K
Agner, Shannon	S283-K
Albertson, Asher	S192-K
Alkhachroum, Ayham	M352-K
Aravamuthan, Bhooma	S268-K
Barbuto, Scott	S269-K
Basak, Jacob	S193-K
Busza, Ania	S194-K
Cadwell, Cathryn	K1
Campbell, Philip	K2
Cohen, Nathan	M295-K
Conrad, Erin	K3
Corwin, Daniel	K4
Cristancho, Ana	S284-K
Dale, Marian	K5
D'Gama, Alissa	K6
Diaz, Frank	S330-K
Elrick, Matthew	K7
Fischer, David	K8
Gholipour, Taha	M306-K
Graham, Maya	K9
Gregg, Nicholas	M307-K
Gusdon, Aaron	M354-K
Hemond, Christopher	M173-K
Higginbotham, Lenora	M218
Hullett, Patrick	K11
Izzy, Saef	M355-K
Kannarkat, George	S270-K
Kay, Benjamin	K12
Kerr, Wesley	M308-K
Khoshkhoo, Sattar	M309-K
Kirschen, Matthew	K13
Kousa, Youssef	S288-K
Kozberg, Mariel	K15
Li, Yi	M311-K
Maiti, Baijayanta	K16
Mallack, Eric	M281-K
Mattis, Joanna	M310-K
McDonell, Katherine	M244-K
Mithal, Divakar	S286-K
Noch, Evan	M359-K
Patterson Gentile, Carlyn	S209-K
Pehlivan, Davut	S287-K
Perry, Bridget	K17
Pluvinage, John	M177-K
Puwanant, Araya	S332-K
Ramani, Biswarathan	S282-K
Sampognaro, Paul	M245-K
Schneider, Andrea	M353-K
Scorr, Laura	S271-K
Shao, Diane	S285-K
Sharma, Richa	S196-K
Srinivasan, Sharan	K18
Timbie, Clare	M207-K
Wilcox, Douglas	K19
Zawar, Ifrah	M304-K

Friday Networking Table Assignments

First Name	Last Name	INSTITUTION	Table 1	Table 2
Scott	Adney	Northwestern University	4	3
Shannon	Agner	Washington University in St. Louis	1	1
Asher	Albertson	Washington University School of Medicine	3	5
Ayham	Alkhachroum	University of Miami	7	6
Bhooma	Aravamuthan	Washington University School of Medicine	6	5
Scott	Barbuto	Columbia University Medical Center	6	7
Jacob	Basak	University of Colorado Anschutz Medical Campus	3	3
Ania	Busza	University of Rochester	3	7
Cathryn	Cadwell	University of California, San Francisco	8	4
Philip	Campbell	University of Pennsylvania	8	5
Nathan	Cohen	Children's National Hospital	4	2
Erin	Conrad	University of Pennsylvania	5	6
Daniel	Corwin	Children's Hospital of Philadelphia	7	7
Ana	Cristancho	Children's Hospital of Philadelphia	8	3
Marian	Dale	Oregon Health & Science University	6	7
Alissa	D'Gama	Boston Children's Hospital	5	10
Frank	Diaz	Cedars-Sinai Medical Center	9	2
Matthew	Elrick	Kennedy Krieger Institute	9	4
David	Fischer	University of Pennsylvania	7	8
Taha	Gholipour	University of California San Diego	4	2
Maya	Graham	University of California, San Francisco	10	4
Nicholas	Gregg	Mayo Clinic, MN	4	6
Aaron	Gusdon	University of Texas Health Science Center	7	9
Christopher	Hemond	University of Massachusetts Chan Medical School	1	2
Lenora	Higginbotham	Emory University School of Medicine	2	9
Patrick	Hullett	University of California, San Francisco	4	6
Saef	Izzy	Mass General Brigham	7	5
George	Kannarkat	University of Pennsylvania	6	9
Benjamin	Kay	Washington University in St. Louis	2	2
Wesley	Kerr	University of Pittsburgh	4	8
Sattar	Khoshkhoo	Brigham and Women's Hospital	4	3
Minjee	Kim	Northwestern University Feinberg School of Medicine	2	7
Matthew	Kirschen	Children's Hospital of Philadelphia	7	7
Youssef	Kousa	Children's National Hospital	1	1
Mariel	Kozberg	Massachusetts General Hospital	3	1
Yi	Li	Stanford University	5	8
Baijayanta	Maiti	Washington University in St. Louis	6	2
Eric	Mallack	Kennedy Krieger Institute	10	2

Joanna	Mattis	University of Michigan	5	1
Katherine	McDonell	Vanderbilt University Medical Center	2	7
Divakar	Mithal	Ann and Robert H. Lurie Children's Hospital	10	3
Evan	Noch	University of Texas Southwestern Medical Center	10	2
Carlyn	Patterson Gentile	Children's Hospital of Philadelphia	8	7
Davut	Pehlivan	Baylor College of Medicine	10	10
Bridget	Perry	MGH Institute of Health Professions	9	8
John	Pluvinage	University of California, San Francisco	1	9
Araya	Puwanant	Wake Forest University School of Medicine	9	2
Biswarathan	Ramani	University of California, San Francisco	6	3
Paul	Sampognaro	University of California, San Francisco	2	4
Andrea	Schneider	University of Pennsylvania	7	9
Laura	Scorr	Emory University	6	9
Diane	Shao	Boston Children's Hospital	8	10
Richa	Sharma	Yale School of Medicine	3	9
Sharan	Srinivasan	University of Michigan	6	5
Clare	Timbie	University of California, San Francisco	2	1
Douglas	Wilcox	Brigham and Women's Hospital	1	1
Ifrah	Zawar	University of Virginia	5	9

Saturday – Breakout #1 Assignments

First Name	Last Name	Saturday Breakout #1	Room Name	Saturday Breakout #1 (Mentors)
Shannon	Agner	1	Bristol	Coufal
Jacob	Basak	1	Bristol	Coufal
John	Pluvinage	1	Bristol	Coufal
Douglas	Wilcox	1	Bristol	Coufal
Nicholas	Gregg	2	Bristol	Liu, Poduri
Patrick	Hullett	2	Bristol	Liu, Poduri
Divakar	Mithal	2	Bristol	Liu, Poduri
Clare	Timbie	2	Bristol	Liu, Poduri
Nathan	Cohen	3	Bristol	Chu, Jensen
Frank	Diaz	3	Bristol	Chu, Jensen
Yi	Li	3	Bristol	Chu, Jensen
Laura	Scorr	3	Bristol	Chu, Jensen
Ifrah	Zawar	3	Bristol	Chu, Jensen
Philip	Campbell	4	Bristol	Brumback, Landsness
George	Kannarkat	4	Bristol	Brumback, Landsness
Mariel	Kozberg	4	Bristol	Brumback, Landsness
Biswarathan	Ramani	4	Bristol	Brumback, Landsness
Sharan	Srinivasan	4	Bristol	Brumback, Landsness
Alissa	D'Gama	5	Dover A	McArthur
David	Fischer	5	Dover A	McArthur
Taha	Gholipour	5	Dover A	McArthur
Wesley	Kerr	5	Dover A	McArthur
Minjee	Kim	5	Dover A	McArthur
Scott	Adney	6	Dover A	Nelson, Paredes
Bhooma	Aravamuthan	6	Dover A	Nelson, Paredes
Ana	Cristancho	6	Dover A	Nelson, Paredes
Sattar	Khoshkhoo	6	Dover A	Nelson, Paredes
Joanna	Mattis	6	Dover A	Nelson, Paredes
Matthew	Elrick	7	Dover A	Lee
Maya	Graham	7	Dover A	Lee
Youssef	Kousa	7	Dover A	Lee
Evan	Noch	7	Dover A	Lee
Paul	Sampognaro	7	Dover A	Lee
Ayham	Alkhachroum	8	Dover B	Sheth, Sypek
Aaron	Gusdon	8	Dover B	Sheth, Sypek
Benjamin	Kay	8	Dover B	Sheth, Sypek
Andrea	Schneider	8	Dover B	Sheth, Sypek
Christopher	Hemond	9	Dover B	Guilliams
Katherine	McDonell	9	Dover B	Guilliams
Carlyn	Patterson Gentile	9	Dover B	Guilliams
Richa	Sharma	9	Dover B	Guilliams
Scott	Barbuto	10	Dover B	Ross, Khatri
Erin	Conrad	10	Dover B	Ross, Khatri

Marian	Dale	10	Dover B	Ross, Khatri
Lenora	Higginbotham	10	Dover B	Ross, Khatri
Baijayanta	Maiti	10	Dover B	Ross, Khatri
Asher	Albertson	11	Dover C	Sansing, Ganguly
Cathryn	Cadwell	11	Dover C	Sansing, Ganguly
Saef	Izzy	11	Dover C	Sansing, Ganguly
Ania	Busza	12	Dover C	Greer
Daniel	Corwin	12	Dover C	Greer
Matthew	Kirschen	12	Dover C	Greer
Eric	Mallack	12	Dover C	Greer
Davut	Pehlivan	13	Dover C	Geocadin
Bridget	Perry	13	Dover C	Geocadin
Araya	Puwanant	13	Dover C	Geocadin
Diane	Shao	13	Dover C	Geocadin

Saturday – Breakout #2 Assignments

First Name	Last Name	Saturday Breakout #2	Room Name	Saturday Breakout #2 (Mentors)
Scott	Adney	1	Bristol	Nelson, Weigand
Shannon	Agner	1	Bristol	Nelson, Weigand
Asher	Albertson	1	Bristol	Nelson, Weigand
Ayham	Alkhachroum	1	Bristol	Nelson, Weigand
Bhooma	Aravamuthan	1	Bristol	Nelson, Weigand
Scott	Barbuto	2	Bristol	Poduri, Sypek
Jacob	Basak	2	Bristol	Poduri, Sypek
Ania	Busza	2	Bristol	Poduri, Sypek
Nathan	Cohen	2	Bristol	Poduri, Sypek
Ana	Cristancho	2	Bristol	Poduri, Sypek
Frank	Diaz	3	Bristol	Paredes, Guilliams
Taha	Gholipour	3	Bristol	Paredes, Guilliams
Nicholas	Gregg	3	Bristol	Paredes, Guilliams
Aaron	Gusdon	3	Bristol	Paredes, Guilliams
Christopher	Hemond	3	Bristol	Paredes, Guilliams
Patrick	Hullett	4	Dover A	Coufal, Landsness
Saef	Izzy	4	Dover A	Coufal, Landsness
George	Kannarkat	4	Dover A	Coufal, Landsness
Wesley	Kerr	4	Dover A	Coufal, Landsness
Sattar	Khoshkhoo	4	Dover A	Coufal, Landsness
Minjee	Kim	5	Dover A	Khatri, Lee
Youssef	Kousa	5	Dover A	Khatri, Lee
Mariel	Kozberg	5	Dover A	Khatri, Lee
Yi	Li	5	Dover A	Khatri, Lee
Eric	Mallack	5	Dover A	Khatri, Lee
Joanna	Mattis	6	Dover A	Chu, Geocadin
Katherine	McDonell	6	Dover A	Chu, Geocadin
Divakar	Mithal	6	Dover A	Chu, Geocadin
Evan	Noch	6	Dover A	Chu, Geocadin
Carlyn	Patterson Gentile	6	Dover A	Chu, Geocadin
Davut	Pehlivan	6	Dover A	Chu, Geocadin
John	Pluvinage	7	Dover B	Brumback, Sansing
Araya	Puwanant	7	Dover B	Brumback, Sansing
Biswarathan	Ramani	7	Dover B	Brumback, Sansing
Paul	Sampognaro	7	Dover B	Brumback, Sansing
Andrea	Schneider	7	Dover B	Brumback, Sansing
Laura	Scorr	7	Dover B	Brumback, Sansing
Cathryn	Cadwell	8	Dover B	McArthur, Jensen
Diane	Shao	8	Dover B	McArthur, Jensen
Richa	Sharma	8	Dover B	McArthur, Jensen
Clare	Timbie	8	Dover B	McArthur, Jensen
Ifrah	Zawar	8	Dover B	McArthur, Jensen
Philip	Campbell	9	Dover C	Josephson, Ganguly

Erin	Conrad	9	Dover C	Josephson, Ganguly
Daniel	Corwin	9	Dover C	Josephson, Ganguly
Marian	Dale	9	Dover C	Josephson, Ganguly
Alissa	D'Gama	9	Dover C	Josephson, Ganguly
Matthew	Elrick	10	Dover C	Sheth, Paulson
David	Fischer	10	Dover C	Sheth, Paulson
Maya	Graham	10	Dover C	Sheth, Paulson
Lenora	Higginbotham	10	Dover C	Sheth, Paulson
Benjamin	Kay	10	Dover C	Sheth, Paulson
Matthew	Kirschen	11	Dover C	Greer, Liu
Baijayanta	Maiti	11	Dover C	Greer, Liu
Bridget	Perry	11	Dover C	Greer, Liu
Sharan	Srinivasan	11	Dover C	Greer, Liu
Douglas	Wilcox	11	Dover C	Greer, Liu

Saturday Poster Tour – Group Assignments & Poster Numbers

First Name	Last Name	Abstract Title	Poster Group	Poster Number	Mentor
Scott	Adney	Excitatory Neuron Dysfunction and Pharmacologic Rescue in an SCN2A Gain-of-Function Variant Associated with Early-Onset Epilepsy	1	M305-K	Chu, Poduri
Erin	Conrad	The Effect of Low-frequency Stimulation on Interictal Spike Rates	1	K3	Chu, Poduri
Nicholas	Gregg	Thalamic Stimulation Induced Modulation of Network Excitability in Epilepsy During Stereotactic-EEG	1	M307-K	Chu, Poduri
Patrick	Hullett	Medial-excitatory and Lateral-Inhibitory Networks in the Human Brain Control Emotion-Related Sympathetic Outflow	1	K11	Chu, Poduri
Davut	Pehlivan	Exploring the Genomic Landscape of MECP2 Duplication Syndrome: Correlating Phenotypic Traits and Guiding Therapeutic Strategies	1	S287-K	Chu, Poduri
Shannon	Agner	Corpus Callosum Volumes are Decreased in a Mouse Model of Congenital Zika Virus	2	S283-K	Coufal, Paulson
Cathryn	Cadwell	Synergistic Interaction Between Fibroblast Growth Factor 8 (FGF8) and Retinoic Acid (RA) Promotes Rostral Cortical Identity in Human Induced Pluripotent Stem Cell (hiPSC)-derved Cerebral Organoids	2	K1	Coufal, Paulson
Philip	Campbell	Multiple Genes Encoded Within the 22q11.2 Neurodevelopmental Risk Locus Interact Within Juxtaventricular Glial Cells to Regulate Sensorimotor Behavior	2	K2	Coufal, Paulson
Ana	Cristancho	Potential For Early Variance of Citric Acid Cycle Metabolites Contributing to Lasting Mitochondrial and Epigenetic Disruption After Prenatal Hypoxia in Glutamatergic Neurons	2	S284-K	Coufal, Paulson
Diane	Shao	Somatic Mutations in Focal Epilepsy Identified Through Re-Analysis of Epilepsy Consortium Exome Data	2	S285-K	Coufal, Paulson
Asher	Albertson	Normal Aging in Mice is Associated with Diminished Behavioral Recovery and Prolonged Disruption of Somatomotor Networks after Experimental Stroke	3	S192-K	Greer, Lee
Jacob	Basak	Microglia Interact with Dendritic Spines and Regulate Spine Numbers After Brain Injury Following Resuscitation from A Cardiac Arrest	3	S193-K	Greer, Lee
Daniel	Corwin	Incorporation of Visio-Vestibular Deficits to Optimize Risk Stratification in Pediatric Concussion	3	K4	Greer, Lee
David	Fischer	A Translational Neuroprognostication Program Is Associated with Improvements in Provider Satisfaction, Guideline-Compliant Care, And Utilization	3	K8	Greer, Lee

Aaron	Gusdon	Phospholipid Biomarkers as Predictors of Outcome after Aneurysmal Subarachnoid Hemorrhage	3	M354-K	Greer, Lee
Mariel	Kozberg	Secondary Ischemia From (Convexity) Subarachnoid Hemorrhage in A Mouse Model of Cerebral Amyloid Angiopathy	3	K15	Greer, Lee
Katherine	McDonell	Psychiatric and Behavioral Symptoms in Youth at Risk for Huntington Disease	4	M244-K	Liu, Sansing
Araya	Puwanant	Brain Structure and Cognitive Endpoints in Myotonic Dystrophy Type 2	4	S332-K	Liu, Sansing
Paul	Sampognaro	Enhancing Lysosomal Protease Activity Reduces TDP-43 Levels and Improves Neuronal Resilience in Human iPSC-Derived Neurons	4	M245-K	Liu, Sansing
Clare	Timbie	Circuits from the Amygdala to Reticular Thalamus in Thalamic Networks and Behavior	4	M207-K	Liu, Sansing
Ayham	Alkhachroum	Neural Encoding of Classical Music in Comatose Acute Brain Injury Patients	5	M352-K	Sheth, Guilliams
Ania	Busza	Longitudinal Changes in Wrist Muscle Activity Following Stroke: Preliminary Findings	5	S194-K	Sheth, Guilliams
Saef	Izzy	Targeting Regulatory T cells Enhances Neurogenesis and Improves Long-term Recovery After Traumatic Brain Injury	5	M355-K	Sheth, Guilliams
Matthew	Kirschen	Association Between Deviations from Cerebral Autoregulation-Derived Optimal Blood Pressure and Outcome After Pediatric Cardiac Arrest	5	K13	Sheth, Guilliams
Andrea	Schneider	Associations of Traumatic Brain Injury with Expression Levels of Blood-Based Neurodegenerative and Neuroinflammatory Biomarkers	5	M353-K	Sheth, Guilliams
Bhooma	Aravamuthan	Preterm Birth and Cortical Parvalbumin Interneuron Inhibition Causes Dystonic Leg Adduction Behavior in Mice	6	S268-K	Josephson
Frank	Diaz	Identifying Upper Motor Neuron Pathology and Molecular Signatures in the Amyotrophic Lateral Sclerosis (ALS) Motor Cortex	6	S330-K	Josephson
George	Kannarkat	Blood-Derived Alpha-Synuclein Strains in Lewy Body Diseases are Associated with Extracellular Vesicles and Induce Cellular Inclusions	6	S270-K	Josephson
Divakar	Mithal	Examining the Epileptogenic Effect of Impaired NAD+ Metabolism in Gabaergic Neurons	6	S286-K	Josephson
Sharan	Srinivasan	Improving Neuronal Function as a Therapeutic in Spinocerebellar Ataxias	6	K18	Josephson
Matthew	Elrick	Enterovirus D68 2A Protease Causes Nuclear Pore Complex Dysfunction and Motor Neuron Toxicity	7	K7	Geocadin
Lenora	Higginbotham	Multiplex Proteomic Analysis of Lewy Body Dementia Reveals Cerebrospinal Fluid Biomarkers of Disease Pathophysiology and Progression	7	M218	Geocadin
Benjamin	Kay	Stimulant Medications Affect Arousal and Reward, Not Attention	7	K12	Geocadin

Scott	Barbuto	Home Training for Cerebellar Ataxias: A Randomized Clinical Trial	8	S269-K	Nelson
Marian	Dale	The Sedentary Index (SI) for Daily Life Activity Monitoring in Progressive Supranuclear Palsy (PSP)	8	K5	Nelson
Baijayanta	Maiti	Cerebellar Cholinergic Denervation in Parkinson Disease and Its Gait Correlates	8	K16	Nelson
Laura	Scorr	Immunological Mechanisms in Cervical Dystonia	8	S271-K	Nelson
Richa	Sharma	Plasma Proteomic Signatures Associated with Ischemic Stroke Etiologies	8	S196-K	Nelson
Nathan	Cohen	Clinical, Radiological, And Pathological Associations of Executive Dysfunction in Children with Focal Cortical Dysplasia-Related Epilepsy	9	M295-K	Paredes, Khatri
Alissa	D'Gama	Molecular Genetic Mechanisms of Neonatal and Infantile Epilepsies	9	K6	Paredes, Khatri
Sattar	Khoshkhoo	Genotype-Informed Single-Cell Analysis of Focal Cortical Dysplasia Elucidates Developmental Origins and Molecular Mechanisms	9	M309-K	Paredes, Khatri
Joanna	Mattis	Noradrenergic Circuit Response to Seizures in a Mouse Model of Dravet Syndrome	9	M310-K	Paredes, Khatri
Taha	Gholipour	Divergent Changes in Functional Connectivity in Left- and Right-Onset Temporal Lobe Epilepsy: An Analysis of the Epilepsy Connectome Project	10	M306-K	Landsness, Brumback
Wesley	Kerr	Quantifying the Impact of Computer-aided Diagnostic Score on the Clinical Diagnosis of Functional Seizures	10	M308-K	Landsness, Brumback
Minjee	Kim	Sleep-Wake Disturbances in Midlife: Associations with Cognitive and Physical Impairment in a Primary Care Cohort	10	S379-K	Landsness, Brumback
Yi	Li	Genetic Testing in Adult Epilepsy Patients: Genetic Risk Index for Seizure Etiology Score (Gen-RISE) for Identifying Optimal Candidates	10	M311-K	Landsness, Brumback
Ifrah	Zawar	The Neuropathological Signature of Late-Onset Epilepsy: A Multicenter Autopsy Study	10	M304-K	Landsness, Brumback
Christopher	Hemond	Multiple Sclerosis and Neuroinflammation Is Associated with Hypertrophy of the Parasagittal Dura and MRI Pathology	11	M173-K	McArthur, Ganguly
Youssef	Kousa	Genetic Variation in HEXB and GM2 Metabolism Modifies Prenatal Viral Infection and Brain Injury	11	S288-K	McArthur, Ganguly
Eric	Mallack	Is Ferroptosis an Early Pathogenic Change in Cerebral X-Linked Adrenoleukodystrophy?	11	S281-K	McArthur, Ganguly
John	Pluvinage	Autoimmune Vitamin B12 Central Deficiency Underlying Idiopathic Myelopathy	11	M177-K	McArthur, Ganguly
Douglas	Wilcox	Neuro-immune Communication Across the Blood-Brain Barrier: A Critical Role for Astrocyte-T Cell Interactions in the Pathogenesis of Viral Encephalitis	11	K19	McArthur, Ganguly

Maya	Graham	Phenotypic Diversity of Reversible Tumorigenesis in Human Cerebral Organoids	12	K9	Weigand, Sypek
Evan	Noch	N-acetylcysteine-induced Lactate Production is a Targetable Metabolic Susceptibility in Glioblastoma	12	S359-K	Weigand, Sypek
Carlyn	Patterson Gentile	Daily Light Exposure Habits of Youth with Migraine: A Prospective Pilot Study	12	S209-K	Weigand, Sypek
Bridget	Perry	Deciding with Confidence: Feeding Tubes and Amyotrophic Lateral Sclerosis	12	K17	Weigand, Sypek
Biswarathan	Ramani	CRISPR-Based Screens to Uncover Chaperone Modifiers of Polyglutamine Protein Aggregation	12	S282-K	Weigand, Sypek