2023 ANA-NINDS Career Development Symposium

September 8-9, 2023
Philadelphia Marriott Downtown
Philadelphia, PA

NIH National Institute of Neurological Disorders and Stroke

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

ANA AMERICAN NEUROLOGICAL ASSOCIATION
INNOVATORS IN DISCOVERY, EDUCATION, AND CARE

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SPONSORED BY:

The American Neurological Association

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Walter J. Koroshetz, MD, FANA
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 ANA2023 Annual Meeting.

This symposium, now in its eighteenth 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 the NINDS will provide advice concerning the mechanisms involved in grant submission and evaluation.

COURSE EVALUATION

Participants are asked to complete the evaluation **Friday, November 3, 2023**. We sincerely appreciate your constructive feedback and comments and ask that you please take a few moments to complete the evaluation.

2023 ANA-NINDS Career Development Symposium Agenda

All times are listed in Eastern Daylight Time (EDT)
Salon C (5th Floor)

Friday, September 8, 2023

2:30 PM - 3:00 PM **Registration (Salon C Foyer – 5th Floor)**

3:00 PM - 3:15 PM **Welcome and Goals for the Meeting**
Speaker: *Lauren Sansing, MD, MS, FANA, Yale University School of Medicine*

3:15 PM - 3:45 PM **View of NINDS Leadership 2023**
Speaker: *Walter Koroshetz, MD, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)*

3:45 PM - 4:30 PM **Setting Yourself up for Success**
Speakers: *Stephen Korn, PhD, National Institute of Neurological Disorders and Stroke; Tish Weigand, PhD,* National Institutes of Health

4:30 PM - 5:15 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.

5:15 PM - 6:15 PM **K to Independence Panel - How I Did It**
Moderator: *Alexandra Nelson, MD, PhD,* University of California, San Francisco
Panelists:
Mercedes Paredes, MD, PhD, University of California, San Francisco
Bill Stacey, MD, PhD, University of Michigan
Eric Landsness, MD, PhD, Washington University in St. Louis
Heidi Schambra, MD, NYU Langone

6:15 PM - 6:45 PM **Leadership: Lessons from Academia and Life**
Speaker: *Nina Schor, MD, PhD, FANA,* National Institutes of Health

6:45 PM - 7:30 PM **Buffet Dinner**

7:30 PM - 9:00 PM **Chairs Panel**
Moderator: *Argye Hillis, MD, MA, FANA, Johns Hopkins University School of Medicine*
Panelists:
Louise McCullough, MD, PhD, FANA, University of Texas at Houston
Dave Standaert, MD, PhD, FANA, University of Alabama at Birmingham
Laurie Gutmann, MD, FAAN, FANA, Indiana University
Jin-Moo Lee, MD, PhD, FANA, Washington University of St. Louis
Bay Leslie-Mazwi, MD, University of Washington

Saturday, September 9, 2023

7:00 AM - 8:00 AM — **Poster Set-Up and Breakfast (Poster Set-Up in Salon D, 5th Floor)**

8:00 AM - 8:15 AM — **ANA Presidential Address: Reimagining and Rescoping the Field of Neurology: Career Preparation**
Speaker: *Frances Jensen, MD, FACP, FANA, University of Pennsylvania*

8:15 AM - 9:15 AM — **Developing a Well-Funded Research Program and Building your Portfolio**
Moderator: *Lesli Skolarus, MD, FANA, Northwestern University*
Panelists:
Henry Paulson, MD, PhD, FANA University of Michigan
Alexandra Nelson, MD, PhD, FANA, University of California, San Francisco
Beau Ances, MD, PhD, MSc, FANA, Washington University in St. Louis
Annapurna Poduri, MD, MPH, Boston Children's Hospital

9:15 AM - 9:30 AM — **Coffee Break and Head to Breakout Sessions**
Conference Rooms 408, 409, 411 & 412, 4th Floor. Please find your breakout assignments on the back of your name badge.

9:30 AM - 11:00 AM — **Breakout Session 1 (Conference Rooms 408, 409, 411 & 412, 4th Floor)**
1st – 2nd Year Awardees - Abstract for First Major Paper Discussion
3rd – 5th Year Awardees - Aims Page for R01 Discussion

11:15 AM - 12:15 PM — **Industry, Philanthropy, and other Financial Relationships**
Moderator: *Lauren Sansing, MD, MS, FANA, Yale University School of Medicine*
Panelists:
Barbara Vickrey, MD, MPH, The Icahn School of Medicine at Mount Sinai
Thomas Carmichael, MD, PhD, FANA, University of California, Los Angeles
Eva Feldman, MD, PhD, FANA, University of Michigan
David Greer, MD, MA, FANA, Boston University

12:30 PM - 1:15 PM — **Buffet Lunch (Salon C, 5th Floor)**

1:15 PM - 2:15 PM — **Building Collaborations: Developing Productive Relationships and Conflict Resolution**
Moderator*: Barbara Vickrey, MD, MPH, The Icahn School of Medicine at Mount Sinai*
Panelists:
Romergryko Geocadin, MD, FANA, Johns Hopkins University
Roy Hamilton, MD, MS, FANA, University of Pennsylvania
Bill Seeley, MD, University of California, San Francisco
Lesli Skolarus, MD, FANA, Northwestern University

2:15 PM - 2:30 PM — **Coffee Break and Head to Breakout Sessions**
Conference Rooms 408, 409, 411 & 412, 4th Floor. Please find your breakout assignments on the back of your name badge.

2:30 PM - 4:00 PM — **Breakout Session 2 (Conference Rooms 408, 409, 411 & 412)**
"What are the Biggest Challenges you are Facing and How Can we Help Each Other?"

4:15 PM - 5:45 PM — **Moderated Poster Tours (Salon D)**
Please find your poster group assignment on the back of your name badge.

Faculty List				
NAME	**LAST**	**CREDENTIALS**	**INSTITUTION**	**ROLE**
Beau	**Ances**	MD, PhD, FANA	Washington University in St. Louis	Panelist, Mentor
S. Thomas	**Carmichael**	MD, PhD, FANA	University of California, Los Angeles	Panelist, Mentor
Eva	**Feldman**	MD PhD, FANA	University of Michigan	Panelist, Mentor
Romergryko	**Geocadin**	MD, FANA, FAAN, FNCS	Johns Hopkins School of Medicine	Panelist, Mentor
David	**Greer**	MD, MA, FANA	Boston University	Panelist, Mentor
Laurie	**Gutmann**	MD, FANA	Indiana University	Panelist, Mentor
Roy	**Hamilton**	MD, MS, FANA	University of Pennsylvania	Panelist, Mentor
Argye	**Hillis**	MD, MA, FANA	Johns Hopkins School of Medicine	Moderator, Panelist, Mentor
Frances	**Jensen**	MD, FACP, FANA	University of Pennsylvania	Speaker, Mentor
Stephen	**Korn**	PhD	National Institute of Neurological Disorders and Stroke	Co-Chair, Speaker
Walter	**Koroshetz**	MD, FANA	National Institute of Neurological Disorders and Stroke	Speaker
Eric	**Landsness**	MD, PhD	Washington University in St. Louis	Panelist
Jin-Moo	**Lee**	MD, PhD, FANA	Washington University in St. Louis	Panelist, Mentor
Bay	**Leslie-Mazwi**	MD	University of Washington	Panelist, Mentor
Louise	**McCullough**	MD, PhD, FANA	McGovern Medical School at UTHealth	Panelist, Mentor
Alexandra	**Nelson**	MD, PhD	University of California, San Francisco	Moderator, Panelist, Mentor
Mercedes	**Paredes**	MD, PhD	University of California, San Francisco	Panelist, Mentor
Henry	**Paulson**	MD PhD, FANA	University of Michigan	Panelist, Mentor
Annapurna	**Poduri**	MD, MPH	Boston Children's Hospital	Panelist
M. Elizabeth	**Ross**	MD, PhD, FANA	Weill Cornell Medicine	Mentor
Lauren	**Sansing**	MD, MS, FANA	Yale University School of Medicine	Chair, Moderator, Mentor
Heidi	**Schambra**	MD	NYU Langone	Panelist, Mentor
Nina	**Schor**	MD, PhD, FANA	National Institutes of Health	Speaker, Mentor
Bill	**Seeley**	MD	University of California, San Francisco	Panelist, Mentor
Lesli	**Skolarus**	MD, MS, FANA	Northwestern University	Mentor, Moderator
Dave	**Standaert**	MD, PhD, FANA	The University of Alabama at Birmingham	Panelist, Mentor
William	**Stacey**	MD, PhD	University of Michigan	Panelist, Mentor
Barbara	**Vickery**	MD, MPH	The Icahn School of Medicine at Mount Sinai	Moderator, Mentor
Tish	**Weigand**	PhD	National Institutes of Health	Speaker

Program Chairs

Lauren Sansing, MD, MS, FANA

Yale University School of Medicine
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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 a 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.

Stephen Korn, PhD

National Institute of Neurological Disorders and Stroke
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Dr. Korn came to NINDS as Director of the Office of Training, Career Development and Workforce Diversity (now the Office of Training & Workforce Development) in January, 2006. He received his Ph.D. in Pharmacology from the University of North Carolina-Chapel Hill, and received postdoctoral training at NIH (as a PRAT Fellow of NIGMS) and at the Roche Institute of Molecular Biology (with financial support from NRSA postdoctoral fellowships). He then spent 15 years on the faculty of the University of Connecticut at Storrs, where he was a Full Professor. His area of scientific specialty is the molecular basis of ion channel gating and permeation, but he has also conducted electrophysiological and imaging research on calcium and pH transport/buffering, and synaptic transmission in the hippocampal slice. Since joining NINDS, Dr. Korn has created a number of programs for the training and career development of clinician-scientists, including 3 national K12s (for neurosurgery, pediatric neurology and emergency medicine) and a large, highly successful program to help residents and fellows transition to K awards. Under Dr. Korn's direction, the NINDS clinician K award program has maintained a transition rate from K to R01 or equivalent of 65-70%, and within the last 5 years a 38% increase in the number of K award applications and 58% increase in the number of NINDS K awards made to clinician-scientists.

Faculty

Beau Ances, MD, PhD, FANA

Washington University in St. Louis
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Beau Ances, MSc, MD, PhD, FANA is the inaugural Daniel J Brennan MD Professor of Neurology at Washington University in Saint Louis. He graduated from the University of Pennsylvania (1989); completed a masters in Health Planning and Finance at London School of Economics (1994); completed his Ph.D. and M.D. (2001) at the University of Pennsylvania; and completed Neurology residency (2005) at the Hospital of the University of Pennsylvania. He pursued a post-doctoral fellowship in Neuroimmunology at the University of California San Diego (2005-2008). His research focused on developing novel neuroimaging methods to assess changes in brain function due to HIV. He was recruited to Washington University in St. Louis (2008). Over the past 15 years, the Ances Bioimaging Laboratory (ABL) has focused on developing novel biomarkers for neurodegenerative diseases including HIV associated neurocognitive disorders (HAND), Alzheimer's disease (AD), autoimmune encephalitis, and Down syndrome. He has served on numerous NIH and private foundation study sections and more recently led a National Institute of Health (NIH) initiative to develop biotypes of central nervous system complications in people living with HIV. Dr. Ances is an author on over 270 publications (h-index 71) and his work has been cited by numerous media outlets (including the Associated Press, US News and World Report, Time, Discover, Washington Post) and been featured in a PBS documentary (Alzheimer's Disease: Every Minute Counts). He has mentored several undergraduate students, graduate students, post- doctoral candidates, and fellows. Members of his laboratory have received independent funding from NIH and private foundations.

S. Thomas Carmichael, MD, PhD, FANA

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S. Thomas Carmichael is a neurologist and neuroscientist in the Departments of Neurology and of Neurobiology at the David Geffen School of Medicine at UCLA. Dr. Carmichael is Professor and Chair of the Department of Neurology, co-Director of the UCLA Broad Stem Cell Center and co-Director of the Regenerative Medicine Theme in the David Geffen School of Medicine. He has active laboratory and clinical interests in stroke and neurorehabilitation and how the brain repairs from injury. He received his M.D. and Ph.D. degrees from Washington University School of Medicine in 1993 and 1994 and completed a Neurology residency at Washington University School of Medicine, serving as Chief Resident. Dr. Carmichael was a Howard Hughes Medical Institute postdoctoral fellow at UCLA from 1998-2001. He has been on the UCLA faculty since 2001.

Eva Feldman, MD, PhD

University of Michigan
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Eva L. Feldman MD, PhD, James W. Albers Distinguished University Professor and the Russell N. DeJong Professor of Neurology at Michigan Medicine, is a renowned neurologist and neuroscientist who has devoted her career towards understanding the etiology of neurological disorders and developing new treatments. Dr. Feldman is Director of the University of Michigan (UM) ALS Center of Excellence and the NeuroNetwork for Emerging Therapies. She is annually listed in Best Doctors in America, a Past President of the Peripheral Nerve Society and ANA—when elected President of the ANA, she was the third woman to hold this position in 130 years. She is a Fellow of the AAAS and a member of the Association of American Physicians, the National Academy of Medicine (NAM), and the immediate past chair of the Neurology and Psychiatry section of NAM. Her work is internationally recognized, with >500 published articles, 4 published books and 70 book chapters (Google Scholar h-index = 118) and >55,000 citations. She was the inaugural Director of the A. Alfred Taubman Medical Research Institute at UM when Alfred Taubman gave $100 million in 2011 to support translational research in the Institute by clinician scientists. She held this position from 2007-2017. Dr. Feldman is the only person to receive UM Medical Center Alumni Society Early and Advanced Career Distinguished Achievement Awards (2001, 2019). She has also received lifetime achievement awards from the ADA, the Juvenile Diabetes Research Foundation, the Endocrine Society, mentoring awards from the Society for Neuroscience and Michigan Medicine and the Johns Hopkins Distinguished Alumna Award.

Dr. Feldman has been continuously NIH funded since 1989, with a strong track record of successful collaborations, as she oversees an established lab with 25 exceptional scientists. Her team also conducts pioneering studies on the pathogenesis of neuropathy in metabolic diseases and identified dyslipidemia during diabetes as a key driver of nervous system damage, leading to new clinical patient care guidelines by the American Diabetes Association. Her research with the ALS exposome has identified pesticides and organic persistent pollutants as increasing ALS risk and decreasing ALS survival, and she was recently awarded an NIH Director's Transformative Award to continue this work. With a strong track record of directly translating basic research into advances in clinical treatment, she has mentored over 100 postdoctoral and clinical fellows and 10 graduate students, was PI of T32 NS07222 NIH/NINDS Training in Clinical and Basic Neuroscience for over 2 decades, and currently mentors 3 NIH K award recipients, has 4 R01s and multiple foundation grants.

Romergryko G. Geocadin

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Dr. Romergryko G. Geocadin, MD, Professor of Neurology, Anesthesiology-Critical Care Medicine, and Neurosurgery, with joint appointment in Medicine at the Johns Hopkins University School of Medicine (JHSOM). His undergraduate degree is from the University of the Philippines, medical degree from UERM College of Medicine in the Philippines, general neurology training at the NYU, and clinical and research fellowship in neurocritical care at Johns Hopkins University. He has been an ANA fellow since 2008. He became chair of the neurocritical care SIG in 2017 and in 2018, chaired the Online Education Taskforce. This taskforce became the Education Innovation Subcommittee in 2020. This ANA workgroup helped initiate and maintain ANA online education programs and website education platforms (e.g., ANA Investigates Podcast). In 2020 he was also elected to the ANA Board of Directors and appointed chair of the Professional Development Committee. In 2022, he was selected Vice President of the American Neurological Association.

David Greer, MD, MA, FANA

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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 is the editor-in-chief of Seminars in Neurology, and the past editor-in-chief for Neurocritical Care on Call. He has authored more than 350 peer-reviewed manuscripts, reviews, chapters, guidelines and books. He was the 2022 recipient of the American Academy of Neurology's A.B. Baker Award for Lifetime Achievement in Neurology Education, and has been a devoted mentor and teacher to many students, residents, fellows and faculty. 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.

Laurie Gutmann, MD, FANA

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Dr. Laurie Gutmann is Professor and Chair of Neurology and Co-Director of the Neuroscience Institute at Indiana University School of Medicine. She is a part of the Clinical Coordinating Center for the NeuroNEXT (NIH Network of Excellence for Neurologic Clinical Trials) in charge of site support, recruitment/retention, and diversity in clinical trials. She co-directs the annual NINDS funded Clinical Trials Methodology Course, working with clinical researchers designing their first clinical trials. She is co-chair of the NIH/NHLBI RECOVER-Clinical Trials Steering Committee for post-acute sequelae of COVID. Her research focus has been in neuromuscular disorders, rare diseases, and acute stroke trials. Previously, she was Professor of Neurology at West Virginia University and served as Neurology Residency Program Director and Stroke Director of their comprehensive stroke center and Professor and Vice Chair of Clinical Research at the University of Iowa. She worked for four years as a Program Officer in the NINDS/NIH Extramural Office of Clinical Research.

Roy Hamilton, MD, MS, FANA

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Dr. Roy Hamilton is a Professor of Neurology at the University of Pennsylvania, where his research focuses on employing noninvasive neuromodulation to characterize and remediate human cognition in neurological disorders. He is currently President of the Society for Cognitive and Behavioral Neurology. Dr. Hamilton has also been recognized for his advocacy for diversity in neurology and academic medicine. He is the Assistant Dean for Cultural Affairs and Diversity at Penn's Perelman School of Medicine, Vice Chair for Diversity and Inclusion for Penn Neurology, and an Associate Editor for Equity, Diversity, and Inclusion for the journal *Neurology* and its associated journals.

Argye Hillis, MD, MA

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Argye E. Hillis is a Professor of Neurology, Physical Medicine & Rehabilitation, and Cognitive Science at Johns Hopkins. She serves as the Executive Vice Chair of Neurology, and Director of the Cerebrovascular Division. Her research combines longitudinal task-related and task-free functional imaging and novel methods of structural imaging with detailed cognitive and language assessments to reveal the dynamic neural networks that underlie language and cognitive functions. Her lab studies changes from the acute stage of stroke through the first year of recovery, and how to augment recovery with language rehabilitation and other interventions.

Frances E. Jensen, MD, FANA

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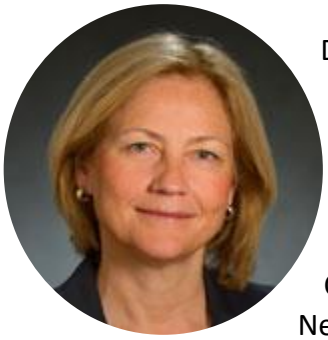

Dr. Jensen is Professor of Neurology and Chairman of Neurology at the Perelman School of Medicine, University of Pennsylvania, and Co-Director of Penn Translational Neuroscience Center. She was formerly Professor of Neurology, Harvard Medical School, Director of Translational Neuroscience and senior 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 obtained 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. Dr. Jensen received the 2007 Director's Pioneer Award from the NIH to explore the interaction between epileptogenesis and cognitive dysfunction and was elected as a member of the National Academy of Medicine in 2015. She has authored over 150 manuscripts on subjects related to her research and has been continuously funded by NIH since

1987 and received a 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. Dr. Jensen is currently President of the American Neurological Association (2020-2022) and was President of the American Epilepsy Society in 2012. She has served on multiple leadership boards including Society for Neuroscience and NIH. Dr. Jensen is a Trustee of the Franklin Institute in Philadelphia and is involved in community outreach for brain research and education. In addition, Dr. Jensen is an advocate for awareness of the adolescent brain development, its unique strengths, and vulnerabilities, as well as their impact on medical, social, and educational issues unique to teenagers and young adults, and author of the book "The Teenage Brain", released by Harper Collins in 2015/16, translated and published in over 25 languages worldwide

Walter Koroshetz, MD

National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)
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Dr. Koroshetz serves as Director of the National Institute of Neurological Disorders and Stroke. He joined NINDS in 2007 as Deputy Director and has co-led the NIH's BRAIN Initiative, the Neuroscience Blueprint, the Traumatic Brain Injury Center with the Uniformed Health Services University, the Helping to End Addiction Long Term (HEAL) Initiative, the Undiagnosed Disease, and the Acute to Chronic Pain Transition Programs, NIH Emergency Care Research and the Post Acute Sequalae of COVID-19 Initiative. Before NINDS, Dr. Koroshetz served as the Neurology Vice Chair and Director of stroke and neurointensive care, led neurology resident training at Massachusetts General Hospital as a Harvard professor.

Eric Landsness, MD, PhD

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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

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Jin-Moo Lee, MD, PhD, is the Andrew B. & Gretchen P. Jones Professor, Chairman 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 been studying the pathogenesis of stroke and Alzheimer's disease, and the interface of these two diseases of the elderly. His research spans the translational spectrum from cell and animal models of neurological diseases to clinical studies involving genetics and multimodal neuroimaging of patients. Dr. Lee has published more than 200 research articles, chapters, reviews, and editorials. In addition, he has been continuously funded by the NIH since 2000. 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.

Bay Leslie-Mazwi, MD

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Bay Leslie-Mazwi serves as Chair of the Department of Neurology at the University of Washington. He is dual trained in Neurologic Critical Care and Interventional Neurology/Endovascular Neurosurgery. He co-directs the UW Medicine Neuroscience Institute, a strategic clinical entity that compromises Neurological Surgery and Neurology. Beyond his clinical and institutional duties he has appointments on various national committees, serves in an editorial role of several major cerebrovascular and specialty journals and has multiple societal roles in the key societies in the field. He is involved in clinical trial oversight for a variety of large, randomized, multicenter cerebrovascular trials. He is deeply passionate about improving care delivery.

Louise McCullough, MD, PhD, FANA

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Dr. Louise McCullough is the Roy M. and Phyllis Gough Huffington Distinguished Chair and Professor of Neurology at McGovern Medical School at UTHealth and Chief of Neurology at Memorial Hermann Hospital – Texas Medical Center. She is a physician-scientist and a practicing vascular neurologist with clinical expertise in sex/gender disparities, the microbiome, stroke and aging, and acute stroke treatments. A renowned investigator, she is well recognized for her work in cerebral vascular disease and is known for her research identifying sex differences in cell death pathways during stroke, which have now been shown to be a major factor in the response to an ischemic insult. Working closely with the Society for Women's Health Research (SWHR) and the Office of Research on Women's Health (ORWH), she was instrumental in the National Institute of Health's requirement to include female animals in basic and translational studies.

Alexandra Nelson, MD, PhD

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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.

Mercedes Paredes, MD, PhD

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Mercedes Paredes is associate professor in the Department of Neurology and Neuroscience and Biomedical Sciences graduate programs at UCSF. A native of Los Angeles, CA, she received her undergraduate degree in biochemical sciences from Harvard University and then joined the UCSF-MSTP where she did her graduate thesis with Samuel Pleasure and Scott Baraban studying cortical malformations. She subsequently did residency in neurology at UCSF and postdoctoral training in the Alvarez-Buylla lab where she studied the development and survival of cortical inhibitory neurons. Her lab focuses on identifying features of neuronal progenitor proliferation and migration that are unique to the gyrencephalic brain, with an emphasis on the perinatal period. Their approach is to advance ways to directly investigate the human brain and better model its development using systems like the piglet cortex.

Henry Paulson, MD, PhD

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Hank Paulson, M.D., Ph.D., is the Lucile Groff Professor of Neurology at the University of Michigan, where he leads the research programs in neurodegenerative diseases, directs the Michigan Alzheimer's Disease Center, and co-directs the Michigan Neuroscience Institute. Dr. Paulson's research and clinical interests concern the causes and treatment of age-related neurodegeneration with an emphasis on polyglutamine spinocerebellar ataxias (SCAs) and other repeat expansion diseases, frontotemporal dementia, and Alzheimer's disease. Dr. Paulson has served on the scientific advisory boards of various disease-related organizations, formally led the national consortium of ataxia investigators known as CRC-SCA, and is one of five Principal Investigators on the international study of SCAs known as READISCA. He currently serves on NIH's National Advisory Neurological Disorders and Stroke Council. He is an elected Fellow of the American Association for the Advancement of Science and an elected Member of the National Academy of Medicine.

Annapurna Poduri, MD, MPH

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Annapurna Poduri, MD, MPH is Professor of Neurology at Harvard Medical School and Director of the Neurogenetics and Epilepsy Genetics Programs at Boston Children's Hospital, where she serves as Associate Chief for Academic Development in the Department of Neurology and holds the Diamond Blackfan Chair in Neuroscience. A physician-scientist with a focus on epilepsy genetics, her goals include contributing to the genetic landscape of epilepsy, creating models of human epilepsy, and developing novel treatments for genetic epilepsies. Dr. Poduri's research includes seminal discoveries of somatic mutations as the cause of the malformations hemimegalencephaly and focal cortical dysplasia. In collaboration with international epilepsy genetics consortia and colleagues, she has reported inherited and de novo forms of early onset epilepsy, and her team continues with gene discovery in epilepsy while modeling epilepsy genes in the zebrafish system. She has been a recipient of the American Neurological Association's Derek Denny-Brown Young Neurological Scholar Award (Physician-Scientist Basic Science Award), the American Academy of Neurology's Dreifuss-Penry Epilepsy Award, and the 2020 Harvard Club of Boston Influential Women designation.

M. Elizabeth Ross, MD, PhD

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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 Elect of the American Neurological Association.

Heidi Schambra, MD

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Heidi Schambra, MD is an Associate Professor of Neurology and Rehabilitation Medicine, Director of the Neuro-Epidemiology Division, Director of Research Strategy in Neurology, and PI of the Mobilis Lab at NYU Langone. Dr. Schambra is a physician-scientist who completed her medical training at Emory University, residency in the Mass General Brigham Neurology program, and neurorehabilitation fellowship at Burke Rehabilitation Hospital. During and following her clinical education, she obtained clinical research training in motor neurophysiology, neuromodulation, and stroke recovery at the NIH and Columbia University. Funded by the National Institutes of Health and the American Heart Association, Dr. Schambra's research focuses on elucidating neural mechanisms of motor recovery after stroke. Her laboratory also focuses on building measurement tools to facilitate rehabilitation dosing, and on developing mechanistically guided interventions to boost recovery.

Nina Schor, MD, PhD, FANA

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Nina F. Schor, MD, PhD is currently NIH Deputy Director for Intramural Research, a post she has held since August 2022. Before coming to NIH, Dr. Schor spent 20 years on faculty at the University of Pittsburgh, ultimately becoming the Carol Ann Craumer Professor of Pediatric Research, Chief of the Division of Child Neurology in the Department of Pediatrics, and Associate Dean for Medical Student Research at the medical school. In 2006, Dr. Schor became the William H. Eilinger Chair of the Department of Pediatrics, and Pediatrician-in-Chief of the Golisano Children's Hospital at the University of Rochester, posts she held until January 2018, when she became Deputy Director of the NINDS. For 27 years in academia, her research on neural crest development and neoplasia was continuously funded by NIH. At NINDS, she led the Division of Intramural Research and the Ultra-Rare GENe-targeted Therapies (URGenT) Network and strategic planning and career development programs. She also continues to serve as a Neurology Director for the American Board of Psychiatry and Neurology.

Bill Seeley, MD

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Dr. Seeley received his MD from the UCSF School of Medicine. He then completed an Internal Medicine internship at UCSF and Neurology residency at the Massachusetts General and Brigham and Women's Hospitals. He is currently an Associate Professor of Neurology at the UCSF Memory and Aging Center, where he participates in patient evaluation and management. He is also Director of the UCSF Neurodegenerative Disease Brain Bank. Dr. Seeley's research concerns regional vulnerability in neurodegenerative disease, that is, why particular disorders target specific neuronal populations. Dr. Seeley addresses this question through behavioral, functional imaging and neuropathological studies. The goal of his research is to determine what makes brain tissues susceptible or resistant to disease, with an eye toward translating these findings into novel treatment approaches.

Lesli Skolarus, MD, MS

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Dr. Skolarus is a Professor and Vice-Chair of Neurology at Northwestern University. She also directs community-academic consultations in the Center for Community Health. Dr. Skolarus's research uses a community-based participatory research approach to adapt and test behavioral and mobile health-based interventions to reduce the burden of neurologic disease and disability. She has been in partnership with the Flint community for 13 years. She is also a health services researcher who focuses on identifying the drivers of racial differences in post-stroke disability. Dr. Skolarus holds multiple NIH awards and has published over 125 manuscripts.

Dave Standaert, MD, PhD, FANA

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Dr. Dave Standaert is Professor and Chair of the Department of Neurology, where he holds the John N. Whitaker Endowed Chair. He received his combined degrees from Washington University in St. Louis, completed Neurology residency at the University of Pennsylvania and a research and clinical fellowship at Harvard Medical School and Massachusetts General Hospital. His primary research interest is translational studies in neurodegenerative diseases. His laboratory works on understanding both the root causes of Parkinson's disease as well as the origin of the disabling symptoms that appear after long term treatment of the disease. Dr. Standaert is Program Director for the Alabama Morris K. Udall Center of Excellence in Parkinson's Disease Research (P50NS108675) which is studying the role of neuroinflammatory reactions in disease progression. He is the Vice President of the American Neurological Association, First Vice President of the Association of University Professors of Neurology, and a Fellow of the American Academy of Neurology.

William Stacey MD, PhD

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Dr. Stacey completed his MD, neurology residency, and PhD in biomedical engineering at Case Western Reserve University. He then completed an epilepsy fellowship at the University of Pennsylvania. He is currently a Professor of Neurology and Biomedical Engineering at the University of Michigan and the Ann Arbor VA Health System. Dr. Stacey's clinical and research interests are integrally connected: he cares for adult patients with epilepsy and has an active research lab researching methods to develop improved, implantable seizure control devices. His research involves expertise in engineering, data science, dynamics, and clinical epilepsy, with the goal that these techniques may uncover new methods of treating seizures in people with uncontrolled seizures.

Barbara Vickrey, MD, MPH

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Barbara G. Vickrey, M.D., M.P.H., is Professor and System Chair of Neurology at the Icahn School of Medicine at Mount Sinai, in New York City. She specializes in research to re-design care delivery models for chronic neurological disorders and to test the impact of these re-engineered models versus care as usual, in randomized controlled trials. Among her accomplishments are demonstrating that collaboration among health care systems, community organizations, and caregivers can improve quality of care and outcomes for dementia patients and for veterans with Parkinson's disease. She has mentored 30 graduate and medical students, residents, fellows, and junior faculty in clinical and health services research, many of whom are now successful faculty members in academic medicine.

Tish Weigand, PhD

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Tish Weigand, Ph.D. is the Deputy 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. Dr. Weigand spends much of her free time sharing outdoor adventures with her husband and their three kids.

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
Laura	Adang	MD, PhD, MSTR	Children's Hospital of Philadelphia	Philadelphia	PA
Farwa	Ali	MBBS	Mayo Clinic	Rochester	MN
Benedict	Alter	MD, PhD	University of Pittsburgh	Pittsburgh	PA
Defne	Amado	MD, PhD	University of Pennsylvania	Philadelphia	PA
Bhooma	Aravamuthan	MD, DPhil	Washington university	St. Louis	Mo
Umeshkumar	Athiraman	MD	Washington university	St. Louis	Mo
Fiona	Baumer	MD, MS	Stanford University School of Medicine	Palo Alto	CA
David	Bearden	MD, MSCE	University of Rochester	Rochester	NY
David	Benavides	MD, PhD	University of Maryland School of Medicine	Baltimore	MD
Matthew	Bevers	MD, PhD	Brigham and Women's Hospital	Boston	MA
Philip	Boone	MD, PhD	Massachusetts General Hospital	Boston	MA
Jonathan	Brent	MD, PhD	Northwestern University	Chicago	IL
Matthew	Brier	MD, PhD	Washington University	St. Louis	MO
Claire	Clelland	PhD, MD, MPhil	University of California	San Francisco	CA
Melissa	Cortez	DO	University of Utah	Salt Lake City	UT
Vishnu	Cuddapah	MD, PhD	Children's Hospital of Philadelphia	Philadelphia	PA
Andrew	Edmondson	MD, PhD	Children's Hospital of Philadelphia	Philadelphia	PA
Melissa	Elafros	MD, PhD	University of Michigan	Ann Arbor	MI
Bolanle	Famakin	MD	University of Wisconsin School of Medicine and Public Health	Madison	WI
Christopher	Favilla	MD	University of Pennsylvania	Philadelphia	PA
Aaron	Gusdon	MD	University of Texas Health Science Center	Houston	TX
Juliane	Gust	MD, PhD	Seattle Children's	Seattle	WA
Christa	Habela	MD, PhD	Johns Hopkins University	Baltimore	MD
Christopher C	Hemond	MD	University of Massachusetts	Worcester	MA
H. E.	Hinson	MD, MCR	University of California	San Francisco	CA
Brandon	Holmes	MD, PhD	University of California	San Francisco	CA
Jennifer	Kim	MD, PhD	Yale University	New Haven	CT
Michael	Kornberg	MD, PhD	Johns Hopkins	Baltimore	MD
Vijay	Krishnamoorthy	MD, PhD	Duke University	Durham	NC
Michelle	Kvalsund	DO	University of Rochester Medical Center	Rochester	NY
Eric	Landsness	MD, PhD	Washington University	St. Louis	MO
Ikjae	Lee	MD	Columbia University Irving Medical Center	New York	NY
Baijayanta	Maiti	MD, PhD	Washington University	St. Louis	MO
Katherine	McDonell	MD	Vanderbilt University Medical Center	Nashville	TN

K Awardee Attendee List

FIRST	LAST	CREDENTIALS	INSTITUTION	CITY	STATE
Christopher	McGraw	MD, PhD	Mass General Hospital, Boston Children's Hospital, Harvard Medical School	Boston	MA
Jana	Mike	MD, PhD	University of California	San Francisco	CA
Hiroki	Nariai	MD, PhD, MS	University of California	Los Angeles	CA
Elizabeth	Newell	MD	University of Iowa Carver College of Medicine	Iowa City	IA
Evan	Noch	MD, PhD	Weill Cornell Medicine	New York	NY
Amber	Nolan	MD, PhD	University of Washington	Seattle	WA
Temitayo	Oyegbile-Chidi	MD, PhD	University of California, Davis	Sacramento	CA
Chia-Ling	Phuah	MD, MMSc	Washington University School of Medicine	St. Louis	MO
Elizabeth	Pierpont	PhD	University of Minnesota	Minneapolis	MN
Jessica	Rexach	MD, PhD	University of California	Los Angeles	CA
David	Robinson	MD MS	University of Cincinnati	Cincinnati	OH
Altaf	Saadi	MD, MSc	Massachusetts General Hospital, Harvard Medical School	Boston	MA
Andrea	Schneider	MD, PhD	University of Pennsylvania	Philadelphia	PA
Gwenn	Skar	MD	University of Nebraska Medical Center	Omaha	NE
Mellanie	Springer	MD, MS	University of Michigan	Ann Arbor	MI
Andrew	Stern	MD, PhD	Brigham and Women's Hospital	Boston	MA
Brian	Theyel	MD, PhD	Brown University	Providence	RI
Sara	Trowbridge	MD	Boston Children's Hospital, Harvard Medical School	Boston	MA
Jeff	Waugh	MD, PhD	University of Texas Southwestern	Dallas	TX
Brian	White	MD, PhD	Children's Hospital of Philadelphia	Philadelphia	PA
Kellen	Winden	MD, PhD	Boston Children's Hospital	Boston	MA
Yohannes	Woldeamanuel	MD	Stanford University School of Medicine	Stanford	CA
John	Younce	MD	University of North Carolina	Chapel Hill	NC
Sahar	Zafar	MBBS	Massachusetts General Hospital	Boston	MA

2023 ANA-NINDS K-Awardee Abstracts

Behavioral Neurology and Dementia

Aqueously Diffusible RNA-Bound Amyloid Beta Fibrils from Alzheimer Disease Brain

Andrew M. Stern, MD PhD[1], *Yang Yang, PhD*[2], *Shanxue Jin, PhD*[1], *Keitaro Yamashita, PhD*[2], *Angela L. Meunier, B.A.*[1], *Wen Liu, B.A.*[1], *Yuqi Cai, B.A.*[1], *Maria Ericsson, PhD*[3], *Lei Liu, PhD*[1], *Michel Goedert, MD PhD*[2], *Sjors HW Scheres, PhD*[2], *Dennis J. Selkoe, MD*[1]. [1]*Brigham and Women's Hospital, Boston, MA, USA,* [2]*MRC Laboratory for Molecular Biology, Cambridge, United Kingdom,* [3]*Harvard Medical School, Boston, MA, USA.*

Aqueously diffusing aggregates of Aβ peptide have been known since the 1990s to correlate better with dementia than amyloid plaques. These aggregates have been termed soluble protofibrils or high-molecular weight oligomers. Lecanemab, the first clearly efficacious disease-modifying therapy for Alzheimer disease, has been suggested to work by clearing protofibrils, but their structure and biochemistry have been unknown.Using a new “soaking” technique to isolate diffusible protein aggregates from human brain, we found that nearly all diffusible Aβ aggregates could be pelleted by sufficient centrifugal force, meaning they are insoluble. Aqueously diffusible Aβ aggregates were fibrils with identical cryoEM structures to detergent-insoluble Aβ fibrils from amyloid plaques. The aqueously diffusible Aβ aggregates were labeled by lecanemab and donanemab immunoEM and could exert lecanemab-dependent synaptotoxicity in mouse hippocampal slices. The brain-derived aggregates were denser than synthetic Aβ aggregates by isopycnic cesium chloride gradient centrifugation, implying the presence of nucleic acid. Ribonuclease A shifted the density and mass of diffusible Aβ aggregates, suggesting RNA binding. Immunoprecipitation and Trizol extraction revealed the presence of small RNAs. These data suggest that toxic Aβ “protofibrils” or “high-molecular weight oligomers” are insoluble and may not have a distinct structure from the Aβ aggregates found in amyloid plaques. Lecanemab and donanemab efficacy may be attributable to binding fibrillar Aβ aggregates. These diffusible Aβ fibrils may be bound to small RNA. Future work will model the determinants of fibril diffusion kinetics in the brain as well as determine the Aβ-bound RNA sequence and its role in toxicity.

Disease Associated Changes in Neuronal-Glia Interactions Implicates Neuroimmune Inhibition in Tau Dementias

Xia Han, PhD, ***Jessica E. Rexach, MD PhD****. UCLA, Los Angeles, CA, USA.*

Tau related dementias affect more than 55.2 million[1] people worldwide and are uniformly incurable. In various tau-related dementias, including Alzheimer’s disease, Frontotemporal dementia with tau pathology, and Progressive Supranuclear palsy, the accumulation of abnormal tau protein can selectively affect different brain regions and specific populations of neurons and glia cells. Tau mediated pathogenesis is still not fully elucidated, and tauopathies are still untreatable. Understanding the causal mechanisms governing selective vulnerability of neuron and glia cells across these disorders holds the potential to unveil new therapeutic strategies and identify drug targets. Emerging evidence and genetics implicate noncell autonomous mechanism of cellular vulnerability in dementia, including potential neuronal-glial and glial-glial interaction. Determining the mechanisms that regulate cell-cell interactions, which undergo changes in diseased brain regions experiencing selective vulnerability, offers a unique perspective to uncover disease mechanisms. Therefore, we combined data from single cell chromatin accessibility and RNA sequencing across various disorders and brain regions with variable vulnerability to tau pathology. This allowed us to map disorder-specific cell-cell interactions and link them to their gene regulatory drivers at the chromatin level. Our studies have uncovered multiple shared and disorder-specific changes in neuronal-glial receptor interaction pairs, revealing unexpected implications of inhibitory neuroimmune signaling in the accumulation of pathological disease states in disease tissue, in addition to disease specific changes in interactions involved in myeloid cell recruitment and cell migrations.

Cerebrovascular Disease

Non-Invasive Monitoring of Microvascular Reperfusion during Endovascular Therapy

Christopher G. Favilla, MD[1], *Rodrigo M. Forti, PhD*[2], *Wesley B. Baker, PhD*[2], *Sarah Carter, BA*[1], *Scott E. Kasner, MD*[1], *Arjun G. Yodh, PhD*[1], *Steven R. Messe, MD*[1], *Stephanie Cummings, BA*[1], *Jan-Karl Burkhardt, MD*[1], *Bryan A. Pukenas, MD*[1], *Visish M. Srinivasan, MD*[1], *John A. Detre, MD*[1]. [1]*University of Pennsylvania, Philadelphia, PA, USA,* [2]*Children's Hospital of Philadelphia, Philadelphia, PA, USA.*

Introduction: Endovascular therapy (EVT) has revolutionized acute stroke treatment, but large vessel recanalization does not always result in tissue-level reperfusion. Microvascular cerebral blood flow (CBF) is not routinely monitored during EVT, so here we aimed to leverage diffuse correlation spectroscopy (DCS), a novel transcranial optical imaging technique, to assess the relationship between microvascular CBF and outcomes after EVT. **Methods:** Frontal lobe CBF was monitored by DCS in 40 patients undergoing EVT for occlusion of the internal carotid or middle cerebral artery. *Baseline CBF deficit* was calculated as the percentage of CBF impairment on pre-EVT CT perfusion. *Microvascular reperfusion* was calculated as the percentage increase in DCS-derived CBF that occurred with recanalization. The adequacy of reperfusion was defined by *persistent CBF deficit*, calculated

as: *Baseline CBF deficit - microvascular reperfusion* (i.e. when reperfusion is adequate, the *persistent CBF deficit* approaches zero, while a large *persistent CBF deficit* reflects inadequate reperfusion). Good functional outcome was defined as 90-day modified Rankin Scale score ≤2. Infarct volume was quantified on MRI 24-72 hours post-EVT and categorized by tertiles (<10cc, 10-25cc, >25cc). **Results:** 36 (of 40) patients achieved successful recanalization, in whom *microvascular reperfusion* in itself was not associated with infarct volume or functional outcome. However, patients who achieved a good functional outcome had a smaller *persistent CBF deficit* (median: 1%; IQR: -11% to 16%) as compared to those who suffered a poor outcome (median: 28%; IQR: 2% to 50%), p=0.02. In a multivariate model, *persistent CBF deficit* was independently associated with long-term functional outcome (OR for a good outcome: 0.45 per 10% increase in persistent CBF deficit; 95% CI: 022 - 0.92). Smaller *persistent CBF deficit* was also associated with smaller infarct volume, and this relationship persisted in a multivariate model (OR for larger infarct tertile: 1.89 per 10% increase in persistent CBF deficit; 95% CI: 1.10 - 3.25). **Conclusions:** CBF augmentation alone does not predict post-EVT outcomes, but when *microvascular reperfusion* closely matches the *baseline CBF deficit* (quantified as a small *persistent CBF deficit)*, patients experience favorable clinical and radiographic outcomes. By recognizing inadequate reperfusion, bedside CBF monitoring may provide opportunities to personalize post-EVT aimed at CBF optimization.

Unchanging Long-Term Case Fatality Rates in a Population-Based Stroke Study

David Robinson, MD MS[1]*, Lili Ding, PhD*[2]*, Jane Khoury, PhD*[2]*, Rob Stanton, MD*[1]*, Kathy Alwell, RN*[1]*, Mary Haverbusch, RN*[1]*, Pooja Khatri, MD MS*[1]*, Opeolu Adeoye, MD*[3]*, Joe Broderick, MD*[1]*, Simona Ferioli, MD*[1]*, Jason Mackey, MD*[4]*, Dan Woo, MD*[1]*, Felipe De Los Rios La Rosa, MD*[5]*, Matt Flaherty, MD*[1]*, Sabreena Slavin, MD*[6]*, Sheryl Martini, MD*[7]*, Michael Star, MD*[8]*, Stacie Demel, DO, PhD*[1]*, Kyle Walsh, MD*[1]*, Elisheva Coleman, MD*[9]*, Adam Jasne, MD*[10]*, Eva Mistry, MD*[1]*, Dawn Kleindorfer, MD*[11]*, Brett Kissela, MD MS*[1]*. [1]University of Cincinnati, Cincinnati, OH, USA, [2]Cincinnati Childrens, Cincinnati, OH, USA, [3]Washington University, St. Louis, MO, USA, [4]Indiana University, Indiananapolis, IN, USA, [5]Baptist Health, Miami, FL, USA, [6]University of Kansas Medical Center, Kansas City, KS, USA, [7]VA National TeleStroke Program, Houston, TX, USA, [8]Soroka Medical Center, Beersheva, Israel, Beersheva, Israel, [9]University of Chicago, Chicago, IL, USA, [10]Yale, New Haven, CT, USA, [11]University of Michigan, Ann Arbor, MI, USA.*

Background: A decline in 30-day case-fatality rate (CFR) for stroke has been inconsistently identified across studies, and little is known about longer term CFRs. We studied temporal trends in 30-day and 5-year CFRs in a well-defined population-based stroke study. **Methods:** The Greater Cincinnati Northern Kentucky Stroke Study is a population-based study conducted in a 5-county region that is representative of the USA in terms of Black race, income, and education. The study ascertained all incident strokes in 1993/4, 1999, 2005, 2010, and 2015 using well-validated methods. All stroke subtypes were included; Ischemic strokes (IS), intracerebral hemorrhages (ICH), and subarachnoid hemorrhages (SAHs). Deaths were identified via the National Death Index. Cox proportional hazards models were used to assess all-cause fatality, by subtype, to examine temporal trends adjusting for age, sex, and race. **Results:** A total of 10372 index stroke cases were ascertained over the five study periods, including 8428 ischemic infarcts, 443 SAHs, and 1501 ICHs. IS patients showed no change in 30-day CFR over time, but did show a nonsignificant decrease in 5-year CFR. Female sex was associated with a lower 5-year IS CFR, whereas Black individuals had a lower 30-day CFR but a higher 5-year CFR. For ICH, there was a small, inconsistent increase in both 30-day and 5-year CFR in later study periods. SAH showed a lower 30-day CFR over time but no change in 5-year CFR. Age was strongly associated with both 30-day and 5-year CFR in all stroke subtypes **Discussion:** Despite widespread advances in post-stroke care, 5-year stroke CFR has not clearly improved for any stroke subtype and may have slightly worsened for ICH. 30-day CFR has improved among SAH patients. Future studies should investigate why Black individuals with IS experience lower early CFR but a higher late CFR.

Genome-Wide Mapping of WMH Spatial Patterns Reveal Region-Specific Association with Blood Pressure

Chia-Ling Phuah, MD, MMSc[1,2]*, Laura Ibanez, PhD*[3,2]*, Yichen Sun, MSc*[4,2]*, Carlos Cruchaga, PhD*[4,2]*, Jin-Moo Lee, MD, PhD*[1]*. [1]Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA, [2]NeuroGenomics and Informatics Center, Washington University School of Medicine, St. Louis, MO, USA, [3]Department of Neurology and Psychiatry, Washington University School of Medicine, St. Louis, MO, USA, [4]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA.*

Objective: We sought to study the utility of leveraging WMH spatial heterogeneity in genetic studies of CSVD. **Background:** White matter hyperintensities (WMH) are the most common imaging marker of cerebral small vessel disease (CSVD). WMH burden is the most used intermediate phenotype to understand the genetic architecture of CSVD. However, WMH have heterogeneous etiology and histopathology, where similar WMH burden have different impacts on disease and cognitive outcomes in patients with CSVD. We previously demonstrated that different CSVD subtypes are associated with distinct WMH spatial patterns on MRI. Here, we investigated the genetic determinants of these specific WMH spatial patterns. **Methods:** We performed a series of genome-wide association studies on five spatially-distinct WMH distribution patterns (deep frontal, periventricular, juxtacortical, parietal, and posterior) derived using a data-driven approach to phenotyping WMH subtypes from 3D WMH probability maps of 949 stroke-free individuals of European ancestry from the Alzheimer's Disease Neuroimaging Initiative database. Pattern-specific WMH burden relative to global burden were quantified for each WMH spatial pattern as continuous traits. Linear regression models were adjusted for age at imaging, sex, and two ancestry principal components.

Results: We identified a novel genome-wide significant locus, rs28756683 (MAF 0.26; $p = 2.40 \times 10^{-8}$) on chr7 associated with the deep frontal WMH spatial pattern - a WMH pattern related to arteriolosclerosis-related risk factors for CSVD (hypertension and diabetes mellitus). Expression quantitative trait loci mapping indicated that *POLR1F,* previously associated with blood pressure regulation in East Asians, was driving the association. No genome-wide significantly associated variants were identified for other WMH spatial patterns.
Conclusions: In this proof of principle study, we showed that data-driven WMH spatial patterns are unique intermediate phenotypes of WMH that may reduce WMH heterogeneity in global WMH burden measurements. Our results provided genetic evidence that suggests blood pressure regulation influencing the deep frontal WMH spatial pattern, concordant with its association with arteriolosclerosis. Future studies with larger sample sizes will improve detection of novel genes and pathways relevant in CSVD.

Soluble ST2 Links Peripheral and Central Innate Immunity after Intraparenchymal Hemorrhage

Matthew Bevers, MD PhD[1]*, Caroline Booraem, BA*[1]*, Karen Li, BBA*[1]*, Anirudh Sreekrishnan, MD*[1]*, Cristina Sastre, PhD*[2]*, Guido J. Falcone, MD*[3]*, Kevin N. Sheth, MD*[3]*, Lauren H. Sansing, MD MS*[3]*, W. Taylor Kimberly, MD PhD*[2]*. [1]Brigham and Women's Hospital, Boston, MA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Yale-New Haven Hospital, New Haven, CT, USA.*

Perihematomal edema (PHE) contributes to poor outcome after deep intraparenchymal hemorrhage (IPH), which is characterized by local neuroinflammation and an influx of peripherally derived innate immune cells. We previously identified soluble ST2 (sST2) as a candidate for immune-mediated secondary brain injury. Using prospectively collected cohorts from two centers, we sought to determine if sST2 was associated with functional outcome, PHE and the peripheral immune response following deep IPH.
Fifty-seven (57) patients with deep IPH were enrolled and had blood samples collected at 24±12 hours from symptom onset. Plasma was assayed for sST2 level and immune cell subsets from peripheral blood mononuclear cells were assessed by flow cytometry. Hematoma volume and PHE were measured on serial CT scans. Good outcome was defined as modified Rankin Scale 0-3 at 90 days. Linear mixed effects models were used to analyze the relationship between sST2 and PHE over time. T-Distribution stochastic neighbor embedding and targeted flow cytometry panels were used to identify shifts in immune cell populations associated with elevated sST2. Immunohistochemistry of human brain tissue was used to identify ST2-expressing cells in the perihematomal region.
Patients had a median admission GCS of 14 [IQR 9-15], a median ICH score of 2 [IQR 1-2], and hematoma volume of 8.6mL [IQR 3.7-13.8]. Receiver operating curve analysis found sST2 level to be predictive of poor outcome with an area under the curve of 0.763 (95% CI 0636 - 0.888) and Youden's optimum cut point of 61.8ng/mL ($p < 0.001$). sST2 remained an independent predictor after adjustment for ICH score (adjusted OR 2.44 [95% CI 1.00-5.44], $p = 0.049$). Measurement of PHE on serial CT scans found those patients with high sST2 to have greater edema volume over time ($\beta = 1.07$ [95% CI 0.51-1.63], $p < 0.001$). High sST2 was associated with a shift towards an innate peripheral immune response (monocytes and NK cells; 68.6±5.1% vs. 47.5±4.0%; $p = 0.003$).
Our findings demonstrate that elevated soluble ST2 links the peripheral innate immune response to PHE volume and outcome after IPH. This knowledge is relevant to future studies that seek to identify IPH patients at highest risk for immune-mediated injury or limit injury through targeted interventions.

Arginase-1 Microglia and Efferocytosis after Murine Neonatal Brain Hypoxia-Ischemia

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Background: Arginase-1 (ARG-1) is the key regulatory enzyme of inflammation and tissue repair. Recent studies in adult stroke show ARG-1 upregulation in microglia and macrophages during efferocytosis, a process of phagocytic clearance of apoptotic cells that prevents activation of inflammation. While increased ARG-1 levels are associated with better outcomes in various neuropathologies, little is known about ARG-1- expressing microglia and macrophages (ARG-1$^+$Mi/Ma) after neonatal brain hypoxia-ischemia (HI). **Methods:** We exposed mice C57BL/6 (wild-type) to hypoxia-ischemia on postnatal day 9, as follows: permanent coagulation of left common carotid artery to induce ischemia, a 1-h recovery period and exposure to 10 % oxygen/balance nitrogen at 37°C for 50 min to induce hypoxia. Animals were perfused at 1h,4h,12h, day 1, 3, 5, 8, 14 and 50 with 4 % paraformaldehyde, brains were post-fixed, sectioned on a cryostat (12 um) and examined histologically with Cresyl-violet staining to assess the degree of damage and ARG-1$^+$Mi/Ma spatiotemporal localization via immunohistochemistry (ARG-1$^+$Mi/Ma =ARG-1$^+$Iba-1$^+$cells). **Results:** ARG-1$^+$Mi/Ma localized to the ventral brain. The number of ARG-1$^+$Mi/Ma was highest early in development (P9) and decreased with age (P14,P23) to undetectable in adult mice (P50). HI triggered change in ARG-1$^+$Mi/Ma morphology from resting to activated bushy and ameboid shape. These activated ARG-1$^+$Mi/Ma then accumulated at the injury site as early as 4 h after injury, where they persisted also at 8 days after HI (at P17). HI also reactivated at least some expression of ARG-1 in adult mice as we have detected a few ARG-1$^+$Mi/Ma at the injury site. While with the Cresyl-violet staining in our model we detect injury located predominantly in the cortex and hippocampus, the HI caused accumulation and persistence of ARG-1$^+$Mi/Ma in the HI injured cortex and striatum. ARG-1$^+$Mi at the injury site touched, enwrapped and engulfed dead neurons

and expressed PPARγ suggesting the role of ARG-1^{+}Mi/Ma in phagocytosis of dead/dying neurons. **Conclusion:** ARG-1^{+}Mi/Ma formed a unique population located in specific anatomical areas of the neonatal brain. While the precise role of ARG-1^{+}Mi/Ma remains unknown, ARG-1^{+}Mi/Ma may play a role in regulation of efferocytosis specifically for the neonatal brain. Further studies are needed to elucidate the precise role of ARG-1^{+}Mi/Ma in neurodevelopment and after brain HI.

Astrocyte TLR4 Signaling Mediates Astrogliosis Following Focal Cerebral Ischemia

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Background: Astrogliosis is a key feature of central nervous system (CNS) injury that plays both a protective and detrimental role. The mechanisms responsible for determining its role in focal cerebral ischemia are unknown. Deletion of the TLR4 signaling pathway has been shown to be protective against focal cerebral ischemia in experimental ischemia models. In addition, most recently, therapies inhibiting TLR4 have shown protective effects following human stroke. Our previous published studies showed increased expression of toll-like receptor 4 (TLR4) in astrocytes following acute focal cerebral ischemia. Therefore, we hypothesized that astrocyte TLR4 signaling contributes to focal cerebral ischemia outcome by modulating astrogliosis. **Methods:** We used both in vitro and in vivo methods to determine the role of astrocyte TLR4-signaing in astrogliosis following ischemic injury. For our in vitro studies, we plated astrocytes isolated from wild-type (WT) and TLR4-/- Wistar rats on glass coverslips, which were subjected to oxygen-glucose deprivation (OGD) for 20h in a hypoxic incubator (5% Co2/95% N_2 /1% O_2). Following OGD, we used immunohistochemistry to stain for GFAP as a measure of astrocyte reactivity. For the in vivo studies, we used mice with inducible, astrocyte-specific TLR4 deletion (*Aldh1l1$^{CreERT2/+}$; TLR4$^{fl/f}$*) to determine the role astrocyte TLR4 signaling in astrogliosis following focal cerebral ischemia. Tamoxifen was used to induce TLR4 deletion, with corn oil-treated mice serving as controls. Mice were subjected to transient middle cerebral artery occlusion (MCAo), and brain sections obtained at 7 days of reperfusion. Using immunohistochemistry, brain sections were stained for GFAP, and the area covered by astrocytes and GFAP intensity were measured to evaluate astrogliosis. **Results:** In the in vitro studies, astrocytes from TLR4-null animals expressed less GFAP compared to WT astrocytes. These findings were recapitulated vivo with astrocytes in brain sections from mice with inducible, astrocyte- specific deletion of TLR4 astrocytes covering significantly less area (4.2558 $\pm$ 2.705 mm compared to 15.3976 $\pm$ 14.3537 mm, P=0.0499; n=4 per group) and had an average lower intensity compared to astrocytes from corn oil-treated mice following transient MCAo. **Conclusions:** Astrocyte TLR4 signaling modulates astrocytes reactivity and astrogliosis following focal cerebral ischemia. TLR4 contributes to the proinflammatory detrimental role of astrogliosis, and therapies inhibiting it may provide protection by inhibiting pro-inflammatory astrogliosis and promoting the anti-inflammatory reparative astrogliosis.

Targeting Microglial NF-kB to Improve Neurologic Outcomes after Aneurysmal Subarachnoid Hemorrhage

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Background: Delayed cerebral ischemia (DCI) is one of the significant contributors for poor outcomes after subarachnoid hemorrhage (SAH). NF-kB, a transcription factor and a key mediator of inflammation is upregulated after SAH and pharmacological inhibition of NF-kB is shown to attenuate vasospasm. NF-kB is also involved in critical physiological roles in brain and hence complete inhibition of NF-kB may lead to detrimental effects. So, identifying the specific cellular source of NF-kB contributing to its overproduction after SAH is critical. Interestingly, microglia are shown to activate after SAH and also associated with vasospasm. The aim of our current study is to investigate the role of microglial NF-kB in DCI and short and long-term neuro behavioral protection after SAH. **Methods:** Twelve-week-old male wild type mice (C57BL/6) were used for the experiments. Animals underwent either sham or SAH surgery via endovascular perforation model. Normothermia was maintained during the procedure. NF-kB, microglial activation and the cellular source of NF-kB were measured via Immunofluorescence staining on day 3 after SAH. Vasospasm measurement in the middle cerebral artery vessel and microvessel thrombosis by immunofluorescence staining was assessed after 72 hours of SAH. Neurological assessment was performed at baseline and for next three days after SAH. Appropriate statistical tests such as t test, one, two way, or grouped ANOVA followed by post hoc multiple comparison tests were applied using GraphPad Prism 9. Statistical significance was set at $P < 0.05$. **Results:** Our preliminary results show that NF-kB (Fig 1) and microglia are activated after SAH and microglia mediates increased expression of NF-kB (Fig 2). We also show that pharmacological inhibition of NF-kB by Pyrrolidine dithiocarbamate (PDTC) provides robust protection against vasospasm, microvessel thrombosis and neurologic deficits (Fig 3). **Ongoing Experiments and Implications:** Current experiments are focused on generating microglial NF-kB null mice. We expect that microglial selective deletion of NF-kB would attenuate vasospasm, microvessel thrombosis and improve short and long-term neurobehavioral outcomes after SAH.

Epilepsy

Impaired Early Neuronal Development In Vitro and Increased Seizure Susceptibility In Vivo in a Model of 15q11.2 Related Neurodevelopmental Disorders

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Rationale: The 15q11.2 locus is deleted in 1.5% of patients with genetic epilepsy and it confers risk for intellectual disability and schizophrenia, suggesting that this region is important for neuronal development. Of 4 genes at this locus, CYFIP1, a regulator of fragile X mental retardation protein and cytoskeleton remodeling, has been shown to regulate early neurogenesis and late synaptogenesis in mice. We examined whether there were differences in neurogenesis and neuronal activity in neurons derived from induced pluripotent stem cells (iPSCs) from patients with 15q11.2 deletion and whether deletion of the Cyfip1 gene was sufficient to increase seizure susceptibility in mice. **Methods:** A forebrain specific neuronal differentiation protocol was used to generate primarily glutamatergic cortical neurons from iPSCs from control and 15q11.2 deletion patients. Neurons were cultured on 24 well multielectrode plates with rat astrocytes. Sister cultures were immunostained to assess neuronal structure and network composition. Seizure susceptibility was determined by exposing 2-month-old mice with conditional forebrain neuron knockout of *Cyfip1* to the GABA-A receptor antagonist, flurothyl or the glutamatergic agonist kainic acid and quantification of time to seizure onset and progression to generalized tonic-clonic (GTC) seizure. **Results:** There was a reduction in electrophysiological spike rate, bursting and synchronization of culture networks in the 15q11.2 deleted human neurons compared to controls. This was associated with decreased single cell dendritic complexity, decreased dendritic length and altered structural connectivity across culture networks. Pharmacological testing showed decreased response to GABA agonists and antagonists on spike rate and synchronization, indicating decreased inhibitory control over network activity despite an increase in the relative proportion of inhibitory neurons in the 15q11.2 Del cultures. Inhibitory synapse quantification demonstrate an increase in the number of inhibitory synapses onto inhibitory neurons. Cyfip1 deficient mice demonstrated decreased latency to seizure in response to disinhibition by flurothyl but not kainic acid. **Conclusions:** These data suggest that deletion of the 15q11.2 region results in cell autonomous changes in neurons and synaptic maturation that contribute to pathologic changes in network excitability. Pharmacologic and imaging data suggest that inhibition of inhibitory neurons is one possible explanation for the paradox of decreased baseline activity and synchronization as well as a predisposition to hyperexcitability *in vivo*. Together, these in vitro and in vivo studies indicate that 15q11.2 deletion results in impaired early neuronal development that may contribute to increased seizure susceptibility in humans with the deletion.

An Unsupervised Learning Approach for Discovering Pathological High-Frequency Oscillations

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Rationale: Interictal high-frequency oscillations (HFOs) are considered one of the promising neurophysiological biomarkers of the epileptogenic zone. However, distinguishing pathological HFOs from physiological ones presents a significant challenge, yet it's crucial for their clinical application. We hypothesize that the distinctive morphological features of pathological HFOs can be discerned from physiological HFOs using an unsupervised learning approach, negating the need for pre-assigned training labels. **Methods:** We used chronic intracranial electroencephalogram (iEEG) data through subdural grids from 18 pediatric patients with medication-resistant neocortical epilepsy. After identifying 92,860 HFOs using an automated detector, each HFO event's EEG time-series data was transformed into time-frequency analysis imaging data. This data served as the input for the deep learning model, specifically a variational autoencoder (VAE). During training, the model was tasked with reconstructing the input time-frequency plot, ensuring the latent space followed a Gaussian distribution. This unsupervised approach didn't require labels indicating whether an event was pathological. Post-training, the HFO events' latent codes, stratified from all training patients, were clustered by the Gaussian Mixture Model (GMM) with K = 2. The cluster with a higher association with resection in post-surgical seizure-free patients was deemed pathological. The GMM model was then used to assign predictions, pathological or physiological, on all HFOs' latent codes from test set patients. **Results:** The effectiveness of our unsupervised method was gauged through a patient-wise 5-fold cross-validation. We projected randomly selected HFOs' latent codes into a two-dimensional (2D) space, comparing the pathological predictions from the VAE model with HFO-with-spike. Our analysis reveals that the pathological prediction from the VAE closely aligns with HFO-with-spike. Moreover, pathological HFOs, as predicted by our VAE model, established a pattern in the time-frequency plot. This pattern closely resembled the structure of an inverted T-shaped template, exhibiting characteristics akin to the ones we identified in our prior research. Using the resection ratio of pathological HFOs, as predicted by the VAE model, to forecast postoperative seizure outcomes resulted in an AUC of 0.91 ($p < 0.001$), signifying an improvement compared to the AUC of 0.82 ($p < 0.001$) obtained using the resection ratio of unclassified HFOs. Additionally, the VAE model outperformed the AUC of 0.89 ($p < 0.001$) achieved using the resection ratio of HFOs with spikes. **Conclusions:** We have demonstrated the ability to classify pathological HFOs using unsupervised machine learning with VAE, eliminating the need for any labeling. This approach could significantly enhance the clinical utility of pathological HFOs, particularly in delineating the epileptogenic zone during epilepsy surgery.

Characterizing Sleep Architecture and Its Effects on Cognition in New-Onset Temporal Lobe Epilepsy

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Temporal Lobe Epilepsy (TLE) is characterized by disordered neural network activity and temporal lobe seizures. Asmany as 3 million individuals with TLE in the United States also experience cognitive and sleep problems, resulting in poor school performance in childhood, with high risk of underemployment in adulthood, and consequent lower socioeconomic status. Individuals with TLE frequently experience sleep fragmentation, which disrupts memory consolidation and sustained attention, both of which are impaired in this disorder. While these comorbidities can be long-term consequences of repeated seizures and medications, it is now known that they also often present prior to the first recognized seizure and worsen over time even with successful seizure treatment. This suggests that an early neural network abnormality may underlie seizure development while simultaneously impairing sleep and cognitive development, even prior to the added effects of disorder chronicity. In spite of this, there has been limited research addressing mechanisms underlying these sleep and cognitive problems in TLE. This represents a critical unmet public health need and both the **National Academy of Medicine** and **NINDS** have identified this notable gap as a research priority. I will begin to address this gap with by investigating abnormal sleep architecture patterns in TLE that directly contribute to cognitive deficits using both an observational (Aim 1) and a mechanistic interventional (Aim 2) approach. In typical NREM sleep, electroencephalogram (EEG) slow wave oscillations are phase-locked and coupled with sleep spindle oscillations (SW-SSO), which facilitates memory consolidation and potentially improves attention. In TLE, disordered networks that result in interictal epileptic discharges and seizures may also contribute to altered SW-SSO coupling during sleep, resulting in memory and attention deficits. A single night of acoustic stimulation (AS) has been proven effective in enhancing SW-SSO coupling and improving cognitive performance in healthy older adults but has not been studied in TLE. My ***central hypothesis*** is that disordered networks in newly diagnosed TLE patients result in altered sleep architecture, which disrupt memory consolidation and attention capability. I will test this hypothesis by: ***(1)*** characterizing TLE sleep architecture using computational EEG - sleep spindle density, slow wave power, interictal epileptiform discharges, and SW-SSO coupling (Aim 1a), ***(2)*** linking these specific TLE-related sleep architecture patterns to cognitive processing (Aim 1b); ***(3)*** determining if AS enhances SW-SSO coupling in young adults with TLE (Aim 2a) and ***(4)*** determining if enhanced SW-SSO coupling improves memory and attention in TLE (Aim 2b).

Frequency-Responsive Ectopic Action Potentials in Neocortical Regular Spiking Neurons

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In most mammalian neurons, strong synaptic inputs to the cell body and dendrites are transformed at the axon initial segment into action potentials that propagate orthodromically down the axon and backpropagate into the dendritic arbor. Action potentials can travel bidirectionally, and are also sometimes initiated in distal segments of axon, before backpropagating to the cell body and dendrites (Nat Neurosci. 14(2):200-209; Brain Res Rev. 21(1):42-92). We refer to these as Ectopic Action Potentials (EAPs). Hippocampal pyramidal cells sometimes fire EAPs during periods of increased excitation (Science. 336(6087):1458-61). We have found that up to 71.4% of regular-spiking (RS) cells in the neocortex can fire EAPs in response to a prolonged sequence of somatic stimulations (Zhang, et al. *in prep*). Of the 37/67 cells that fired EAP's in our study, 15/37 (40.5%) fired EAPs in response to only a single stimulus protocol (30 Hz, 3 cells; 60 Hz, 6 cells; 100 Hz, 6 cells). Eleven cells (29.7%) fired EAPs in response to two protocols, and nine (24.3%) fired EAPs in response to any of the three frequencies. Two cells responded only to sequentially increasing current steps. These data suggest that some RS cells (those responding to all tested frequencies) generate EAPs, a non-canonical form of feedforward excitation, during various activated network states; other RS cells (those tuned to particular frequencies) generate feedforward excitation in response to a narrower range of states. This suggests that a subset of RS cells are 'tuned' to fire EAPs during specific—and variable, depending on the cell—activation states. This is a previously unknown property of neocortical pyramidal cells, with potential implications for both normal neural processing and disease states.

Homeostatic Sleep Need Increases Seizure Risk

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A relationship between sleep loss and seizures has been appreciated since antiquity. Sleep deprived rodents are more likely to have seizures, and people with epilepsy also report a worsening of seizures after poor sleep. Despite this longstanding evidence, the mechanisms that tie sleep loss to increased seizure risk remain unclear. Here we leverage the fly model system and find that hyperactivation of circuits encoding sleep need is responsible for worsened seizures after sleep loss. Sleep loss induced with pharmacological or thermogenetic approaches leads to worsened seizures in 4 epilepsy models. Using a novel video-tracking platform with automated seizure detection, we find that spontaneous seizures after sleep loss are more frequent, severe, and lethal. To identify underlying mechanisms, we performed a Gal4 screen of known sleep- or wake-promoting neuronal populations and find that acute thermogenetic activation of structures known to encode sleep need, including the mushroom body and dorsal fan-shaped body, leads to more severe seizures. These brain regions also demonstrate increased activity after sleep restriction. Importantly, acute optogenetic inhibition of sleep-promoting structures with GtACR1 leads to inhibition of seizures. Transcriptomics of a sleep-promoting brain region implicates loss of serotonergic receptors as mediators of this increased seizure

risk after sleep restriction. These findings demonstrate that hyperactivation of circuits that encode sleep need are responsible for the exacerbation of seizures after sleep loss. We find that manipulation of sleep circuits can be used to control seizure severity; this has translational implications for the management of epilepsy.

Predicting Post-Ischemic Stroke Epilepsy Using Quantitative Markers and Competing Risk Covariates

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Post-Ischemic-Stroke Epilepsy (PISE) is a serious complication of ischemic stroke. The SELECT score is a model that was recently developed to predict patients at risk for developing PISE. However, many patients still fall into the intermediate risk category of PISE development. We wanted to determine whether quantitative variables could help augment the SELECT score performance and whether we could further understand how to differentiate patients who are more likely to die prior to developing PISE. We retrospectively reviewed patients ≥18 years old from 2014-2020 from Yale New Haven Hospital with acute ischemic stroke for the development of post-ischemic stroke epilepsy (seizures greater than 7 days) with EEG and CT/MRI within 7 days post-stroke. We conducted bivariate cox regressions to identify quantitative features of interest then built a random survival forest model using 231 patients for training (42 PISE) and 50 (10 PISE) unique patients for testing. We found in our cohort there is low specificity of the SELECT score when the select score is 4-5, which represents 58% of our cohort. However, within this group of patients, there were very different quantitative differences in 72-hour NIHSS (HR=1.20 [CI=1.01-1.33]), infarct volume (HR=1.05 [1.03-1.07]), peak 1-hr EA burden (HR=1.14[1.01-1.27]), total power asymmetry (HR=1.75[1.21-2.53]) and total rhythmicity asymmetry HR= (1.29[1.05-1.60]) between those who developed PISE and those who did not. Based on Shapley values for the test set, there is no single modality that exclusively explains the risk of PISE, suggesting a multimodal combination may be best. Competing risk analysis suggests that some covariates are PISE specific (e.g., MCA infarction, Peak EA burden, Power asymmetry) whereas others are more highly associated with death (e.g., older age, pre-stroke mRS, afib) and others are associated with both (e.g., high NIHSS). These data suggest that quantitative variables may augment prediction beyond the SELECT score in patients who are at moderate risk for PISE.

Repetitive Transcranial Magnetic Stimulation Modulates Brain Connectivity in Children with Self-Limited Epilepsy with Centrotemporal Spikes

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Rationale: Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS), the most common focal childhood epilepsy syndrome, is associated with sleep-potentiated interictal spike waves emerging from the motor cortex that can occur in a unilateral or bilaterally-independent distribution. Electroencephalography (EEG) connectivity studies have shown that focal spikes are associated with large, diffuse increases in brain connectivity and furthermore, that connectivity is increased even during *spike-free* periods of sleep. Single pulses of transcranial magnetic stimulation (spTMS) paired with EEG can measure connectivity between the stimulated cortex and other brain regions. Repetitive TMS (rTMS) trains modulate excitability for extended periods. The purpose of this study was to investigate whether low-frequency rTMS reduces connectivity of the epileptogenic motor cortex in children with SeLECTS. **Method:** Eight children (8-12 years old, 75% male, 62.5% on antiseizure medications) underwent a sham and a real rTMS session spaced a week apart. The rTMS intervention was applied to the hemisphere with the most spikes. Connectivity before and after rTMS was measured by administering 100 spTMS to the motor cortex and then calculating the weighted phase lag index (wPLI) of the beta frequency band in the second after each pulse. wPLI is a connectivity metric robust against volume conduction and can be measured in short time increments. We tested whether there was a change in connectivity between the stimulated motor region and 7 other regions of interest (contralateral motor; and ipsi- and contralateral frontal, temporal, and parieto-occipital regions) in either the real or sham condition using one sample t-test. **Result:** Following real rTMS, there were modest but significant decreases in connectivity between the stimulated motor region and all other brain regions (contraMotor: -0.06, CI -0.01 to -0.10, p=0.04; ipsiFrontal: -0.05, CI -0.006 to -0.09, p=0.05; contraFrontal -0.04,CI -0.01 to -0.07, p=0.03; ipsiTemporal -0.06, CI -0.02 to -0.10, p=0.02; contraTemporal -0.04, CI -0.01 to -0.07, p=0.03; ipsiParietoOccipital -0.05, CI -0.008 to -0.10, p=0.05; contraParietoOccipital -0.05, CI -0.006 to -0.09, p=0.05). There were no significant connectivity differences after sham rTMS. **Conclusion:** Children with SeLECTS have global increases in brain connectivity both during spike waves and sleep. Real but not sham rTMS to the motor cortex leads to a transient global reduction in connectivity of this epileptogenic region. This mechanism could be explored to understand the pathophysiology and develop treatments for SeLECTS and potentially other pediatric epilepsy syndromes.

Zebrafish Models of Genetic and Chemical Seizures: Opportunities and Challenges

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Background/Methods: Zebrafish is a model of genetic and chemical seizures. However, a recent study showed minimal phenotypes in ~32 of 40 epilepsy genes disrupted using CRISPR/Cas9, raising questions about the factors influencing phenotypic severity (**challenge #1**). *We hypothesize that lack of seizure phenotypes in stable mutant zebrafish may relate to genetic compensation, partial knock-out escape, or lack of X-chromosome inactivation.* We are evaluating models of an X-linked genetic epilepsy in zebrafish (*cdkl5*), including a nonsense variant (*cdkl5-sa21938*) and a novel knock-in variant, to test whether truncating variants are more robust than alleles invoking nonsense mediated decay. To test whether mosaicism influences hyperexcitability in zebrafish (which lack an X-chromosome), we generated a novel mosaic conditional by inversion (COIN) allele to recapitulate mosaic LOF. Zebrafish is ideal for higher-throughput reverse genetic screening, but this approach has not been applied to seizure phenotypes (**challenge #2**). *We hypothesize that acute gene KO conferring proconvulsant resistance by loss-of-function may suggest candidates for new ASM development*, *while gene KO conferring seizures or enhanced susceptibility may suggest novel epilepsy genes.* We developed a method using machine learning to detect anti-seizure responses using calcium fluorescence with a minimum of biological replicates. To identify seizure-related genes, we propose a reverse genetic F0 screen of presynaptic targets using the MIC-Drop approach to deliver multiple sgRNA/Cas9 RNPs in oil droplets. **Results:** Challenge #1. The *cdkl5 sa21938* line shows no differences in spontaneous epileptiform abnormalities. For *cdkl5* mCOIN KI fish, we established one founder, and demonstrate *in vivo* evidence of deletion and inversion of the construct following heat-shock cre. The *cdkl5* KI line and additional characterizations using calcium fluorescence are still pending. Challenge #2. A logistic classifier detects seizure-like events in response to PTZ with high accuracy (AUC-ROC 0.98). Bootstrap simulation suggests anti-seizure responses can be detected with N=8 replicates based on robust strictly standardized mean difference (RSSMD) thresholds (RSSMD <= -0.82, TPR 92.2%, FPR 5%). Injected F0 CRISPant knock-out fish (N=12 fish per gene; 4 sgRNA per gene; 310 genes) are assessed for seizure-like activity (before and after PTZ). DNA barcodes identify gene targets from positive fish. **Conclusions:** *Cdkl5 sa21938* fish lack prominent epileptiform abnormalities, but investigations in the *cdkl5* KI and mosaic COIN KI fish will address whether genetic compensation and mosaicism modulate seizure phenotypes in this genetic epilepsy. A logistic classifier based on calcium fluorescence in larval zebrafish is suitable to detect gene-specific changes in seizure-like activity. A MIC-Drop F0 screen may identify novel seizure genes and anti-seizure targets.

Global Neurology

Distal Symmetric Polneuropathy Prevalence and Predictors in Urban and Rural Zambia: A Population-Based, Cross-Sectional Household Survey

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Introduction: Studies in Zambia and Uganda have reported high (11-12%) prevalence of distal symmetric polyneuropathy (DSP) in HIV negative populations, but little is known about DSP outside of clinical settings. This study evaluates DSP prevalence and predictors in Zambian communities to guide future interventions. **Methods:** Two-stage cluster sampling using population proportional to size sampling was undertaken in two districts. Government health facility catchments were randomly selected in each district for a door-to-door survey. All adults (≥18 years) in selected households were examined and interviewed about DSP, sociodemographic and medical characteristics, food security, and alcohol intake. DSP was defined as ≥1 bilateral symptom (pain, numbness, paresthesias) and ≥1 bilateral sign (diminished/absent distal pin, vibration, or reflexes) using the Brief Peripheral Neuropathy Scale and Utah Early Neuropathy Scale. HIV testing and counselling was offered to all participants. **Results:** Among 514 households, 1339 adults enrolled (73% participation rate). Median age was 35 (IQR 26) years and 62.7% were female. Diabetes (n=28; 2.1%) or leprosy (n=2; 0.2%) history was rare. HIV prevalence was 22% among 1080 (81%) participants tested. Urbanicity was associated with higher HIV prevalence (24% v 17%; p=0.007) and more years of education (8.8 v. 6.8; p<0.00001). DSP prevalence was 13.2% (n=177**;** 95% CI 11.4-15.2%) and did not differ by urbanicity. DSP cases were more likely to be female (14.9 v. 10.4%; p<0.02), were older (median age 56.5 versus 32 years; p<0.00001), had less education (mean 6.2 versus 8.4 years; p<0.0001), more likely to be food insecure (19.5% v. 11.5%; p=0.0001) and have low dietary diversity (15.6 v. 10.1%; p=0.004). DSP cases were more likely to have HIV, (21.5% v 11.0%;p<0.001), report prior tuberculosis treatment (26.1 v. 12.3%; p=0.0001), have diabetes (50 v. 12.4%; p<0.0001), and prior history of syphilis (25.7 v. 12.1%; p=0.0001). There was no association with alcohol intake (p=0.268). Age (OR 1.04; p<0.0001), food insecurity (OR 1.8; p=0.005), HIV (OR 1.8; p=0.008), diabetes (OR 5.1; p=0.001), and history of syphilis (OR 2.3; p=0.005) remained significant DSP predictors in a multiple logistic regression model (p<0.00001). **Conclusions:** DSP prevalence is high in Zambian communities, mirroring data from prior clinic-based studies. Community health worker engagement to identify DSP cases and screen for HIV, diabetes, and consider nutritional/dietary

interventions may reduce DSP and lessen other associated noncommunicable diseases morbidity and mortality through early intervention.

Longitudinal Cognitive Outcomes in Children with HIV in Zambia

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Objective: To describe longitudinal outcomes and predictors of cognitive outcomes in children with HIV in Zambia. **Background:** Multiple studies have shown that children with HIV are at risk for impaired cognition. However, there are limited data on longitudinal cognitive outcomes in children with HIV. **Methods:** We conducted a prospective cohort study of 208 perinatally-infected children with HIV ages 8-17, all treated with antiretroviral therapy, and 208 HIV-exposed uninfected (HEU) controls. Participants were followed for 2 years. Cognition was assessed with a custom NIH Toolbox cognition battery, and tests were combined to generate a Summary Cognition Score (SCS). The contribution of potential risk factors to outcomes was explored using regression models and group-based trajectory modeling. **Results:** HIV was strongly associated with lower SCS at baseline (β-14, 95% CI -20, -7, p<0.001). Change scores over time were similar between groups, but poorer average performance in children with HIV persisted at the two-year follow up visit (adjusted β = -11, 95% CI -22, -0.3, p=0.04). Other than HIV, the strongest predictors of baseline SCS included Socioeconomic Status Index (β =3, 95% CI 1, 5, p=0.004) and history of growth stunting (β=-14, 95% CI -23, -6, p=0.001), history of CD4 count below 200 (β = -19, 95% CI -35,-2, p=0.02) and history of WHO Stage 4 disease (β =-10, 95% CI -19 ,-0.2, p=0.04). In the group-based trajectory model, HIV+ status predicted membership in the lowest performing trajectory group (OR 2.5, 95% CI 1.2, 5.1, p=0.01). **Conclusion:** Children with HIV are at risk of poor cognitive outcomes, despite chronic treatment with antiretroviral therapy.

Headache and Pain

Measuring Descending Pain Modulation with Offset Analgesia and Onset Hyperalgesia in Patients with Chronic Musculoskeletal Pain

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Chronic pain intensity varies considerably, even in a group of patients with peripheral pain generators of equivalent disease severity. Central mechanisms may contribute to this clinical heterogeneity, as evidenced by associations between clinical pain and quantitative sensory testing (QST) measures such as temporal summation or conditioned pain modulation. However, these measures are not strongly correlated with clinical pain. One potential reason for this is that key central mechanisms are incompletely measured with current techniques. Animal models have established that descending inhibitory and facilitatory pathways strongly modulate afferent nociceptive input. Offset analgesia and onset hyperalgesia are QST measures thought to reflect descending inhibition and facilitation, respectively. The current study tests the hypothesis that a pronociceptive descending modulatory balance (offset analgesia < onset hyperalgesia) is associated with greater clinical pain. We use knee osteoarthritis as a model, enrolling patients with equivalent knee joint degeneration but high or low knee pain in a case-control observational design. In our interim analysis from this ongoing study (ClinicalTrials.gov NCT05003323), we find evidence of robust offset analgesia and onset hyperalgesia, validating our measurement technique in this population. Across individuals, there is a large range in offset analgesia, onset hyperalgesia, and offset-onset balance. There is a trend towards a more antinociceptive descending modulatory balance (offset analgesia > onset hyperalgesia) in participants with low compared with high knee pain. This suggests that robust descending inhibition may protect against intense pain from a given peripheral pain generator in musculoskeletal pain. Data collection is ongoing and future analysis will examine the relationship between pain modulation phenotypes, clinical knee pain, and functional impairment over time.

Time It Right! The Application of Circadian Medicine Interventions for the Management of Migraine

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Background & Objective: Migraine is linked to circadian rhythm dysregulation. The RLB (regular lifestyle behavior) protocol includes consistent sleep patterns, mealtimes, and exercise. We are piloting a clinical trial to test the feasibility and efficacy of the RLB intervention and examine its underlying mechanisms. **Methods:** The RLB clinical trial involves a 28-day baseline/observation period, followed by a 12-week study period where participants will receive weekly virtual training sessions, keep daily headache logs, maintain a lifestyle diary, and wear an actigraphy device. Monthly migraine frequency is the primary outcome. Secondary outcomes include RLB score, migraine severity, and headache self-efficacy. Exploratory outcomes involve measuring circadian rhythm, serum multi-omics, and MRI changes. The RLB framework uses the MOST (Multiphase Optimization Strategy) approach and includes a double-randomized preference trial (DRPT) extension to assess patient preference. **Results:** Out of 83 interested participants since July 2022 recruitment, 35 (42%) were available for phone screening of which 30 (85%) met inclusion criteria and were enrolled in the study's baseline/observation phase. Recruitment rate is 1-2 participants/week. Screening-to-enrollment

takes about three days. So far, 15 completed their baseline phase and were randomly assigned to either the APC or RLB group for the 12-week study. Three participants withdrew from the study due to time constraints and interest in drug intervention. Participants found the weekly sessions time-consuming, but appreciated the convenience of the virtual platform. All weekly training sessions had 100% attendance. The questionnaires received an 80% response rate. Participants fully complied with the wearables. Questionnaires took an average of 5 minutes to complete. 5% of data was missing. Participants' feedback included: "*This program has been really helpful. I've had decreased migraine, taking medication much less often, increased strength & physical endurance, and became even more familiar with my body's sensitivities*." The retention rate is 27/30 (90%) so far. Four/six participants in RLB intervention group experienced reduced migraine frequency from 14 to 2 days from baseline to end-of-intervention. The APC arm (n=2) had more migraines during the same period, from 14 to 16 days. The intervention group's RLB score increased by 106% while the APC group had a 47% increase. DRPT extension, actigraphy/circadian, biofluid, and MRI analysis are in progress. **Conclusion:** Preliminary results show promise for circadian-based biobehavioral interventions in managing migraine. Changing weekly sessions to biweekly may improve intervention acceptability due to time constraints.

Health Services and Health Equity Research

Clinician and Patient Stakeholder Perspectives on Cognitive Rehabilitation Interventions for Asylum Seekers and Refugees

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Background: Traumatic brain injury (TBI) disproportionately affects asylum-seekers and refugees (ASR). They endure blows to the head due to exigent circumstances necessitating resettlement (e.g., torture, war, interpersonal violence) and during their dangerous journeys to refuge. Yet TBI remains underdiagnosed and undertreated in this marginalized population. Cognitive rehabilitation represents one evidence-based approach to managing cognitive impairment, a common sequela following brain injury that has clinical, legal, and social economic consequences. Involving stakeholders in co-design processes can facilitate an intervention's acceptability, satisfaction, and implementation. Our study interviewed clinicians and ASR to better understand potential adaptations to existing cognitive rehabilitation interventions for managing cognitive impairment among ASR with TBI.
Methods: We conducted six focus groups of 16 clinicians across two academic medical centers in Boston, Massachusetts, United States. We are actively recruiting and conducting focus groups and interviews with ASR patient participants. We have analyzed the clinician's qualitative data using the Framework method and will use the same analytic approach to examine the patient qualitative data.
Results: Clinicians proposed sociocultural adaptations across seven categories: 1) Linguistic; 2) Cultural, including addressing deference to authority and traversing stigma around both brain injury and mental health; 3) Literacy level, including prior patient experience with educational frameworks and "homework" as part of skill acquisition; 4) Consideration of family role and involvement; 5) Incorporating the migratory context within a larger Trauma-Informed Care framework; 6) Strengths-based approach and individual empowerment, including focusing on individual's strengths and goals; and 7) Telehealth as a tool to address barriers like transportation. The ASR patient participant qualitative data has not yet been collected or analyzed.
Conclusion: This study qualitatively explores clinician and ASR perspectives on adaptions to cognitive rehabilitation interventions among ASR with TBI. Integrating clinicians' and patients' perspectives in intervention adaptation allows us to meet their needs in TBI recovery best. The results inform the adaptation of a cognitive rehabilitation intervention to prepare for open pilot testing.

Movement Disorders

Domains of Gait and Balance Impairment in PSP Subtypes

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Objective: Identify gait and balance profiles in progressive supranuclear palsy (PSP) subtypes. **Background:** Heterogeneous patterns of gait and balance impairment exist in PSP subtypes. These may include a slow parkinsonian gait, start hesitation, freezing, postural instability leading to falls and a wide based unsteady gait. Patients may manifest one or more than one of these impairments at any given time, and the most predominant pattern of gait dysfunction may evolve over the course of their illness. Clinical scales are used to evaluate motor deficits; however, they do not quantify the heterogeneous patterns. For example, the Unified Parkinson's Disease Rating scale (UPDRS) aggregates scores for bradykinesia, tremor, posture, and rigidity. The PSP rating scale similarly aggregates autonomic, bulbar, non-motor and motor symptoms. While gait sub scores can be reported they do not capture the heterogeneity that exists in PSP. Available tools offer a measure of disease severity. **Methods:** We used laboratory-based three-dimensional motion analysis to perform fine grain assessment of gait and balance abnormalities in PSP. We then used principal component analysis to assess distinct patterns of abnormality in PSP. Patients were grouped into PSP-Richardson syndrome (PSP-RS), cortical and subcortical groups based on the hypothesis that degeneration of regional locomotor centers will mediate differential patterns of gait impairment. **Results:** This preliminary analysis included 10 PSP-RS, 5 cortical, 5 sub-cortical

patients with disease duration of under 5 years. We identified four distinct components. Component 1 corresponded with disease severity. Higher loads signified higher variability, asymmetry, longer step time, poor balance with eyes open. Component 2 captured the slow parkinsonian quality (shorter steps, lower swing time, lower velocity, higher double support time), and as expected correlated most with UPDRS. Component 3 captured dynamic instability (higher stance time variability, step length variability, step width) and worse dynamic balance. Component 4 captured static stability (worse sway measures). The balance components correlated with fall frequency. On overall gait severity measures cortical group was least impaired (component 1) but performed worse on static and dynamic stability (component 3-4). Sub-cortical group had more slowness and hesitation (higher weights on components 1-2). **Conclusions:** Motion analysis identified distinct patterns of gait and balance dysfunction in PSP, which differed by PSP subtypes. A quantified motion assessment approach offers an opportunity to develop biomarkers specific to the gait and balance abnormality of an individual patient, beyond what is offered by clinical scales of overall disease severity.

Selection of White Matter Reference Region in Cholinergic PET Analyses

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The brainstem pedunculopontine nucleus and medial vestibular complex send cholinergic input to cerebellum and degenerate in Parkinson disease (PD). This may lead to cholinergic denervation in cerebellum. One of our key specific aims is to investigate cholinergic denervation in cerebellar regions in PD and how this relates to cross-sectional cerebellar resting-state functional connectivity and behavior. Initial selection of corpus callosum as the reference region in PET analyses proved to be suboptimal due to varying PET counts in the corpus callosum. In this study, we characterized the distribution and optimal analytical methods for the radioligand targeting vesicular acetylcholine transporter, [^{18}F]VAT. 52 healthy participants aged 21 to 97 were scanned for 2 hours using [^{18}F]VAT. We observed widespread uptake of [^{18}F]VAT, with high levels of tracer uptake in the striatum. Additionally, subcortical regions including the thalamus, hippocampus, amygdala, dorsal pons, and cerebellar regions especially vermis demonstrated high levels of uptake. In the cortical gray matter, the posterior cingulate and calcarine sulcus, among others, displayed regionally selective uptake. We next sought to identify a reference region for further kinetic analyses. For this, we analyzed postmortem tissue from the caudate, occipital lobe, vermis, and three deep cortical white matter regions from the brains of three deceased individuals (1 control and 2 with PD) using [3H]VAT autoradiography. [3H]VAT binding in white matter regions ranged from 0.03 to 38.38 (fmol/mg tissue) across all brains and white matter regions that was not different from background and did not change with the addition of unlabeled ligand, suggesting that deep white matter could be used as a reference region. We further optimized this for PET analyses using a combined white matter region obtained from FreeSurfer segmentation and varying degrees of erosion to minimize intraregional variability and age-dependent effects, identifying a 9mm erosion with threshold of 0.95 as optimal. We next determined the variability and stability of binding potential estimates using the Logan binding potential and varying model start times and durations, identifying a minimum duration of 40 minutes starting at least 25 minutes post-injection. We calculated binding potentials for several regions of interest including lateral hemispheric cerebellar lobules and vermis using partial-volume correction to minimize the effects of atrophy. Test-retest studies (N=10 participants) demonstrated good reproducibility and reliability. Analyses of PD vs control group differences in cerebellar cholinergic activity using [^{18}F]VAT with this optimized white matter reference region is currently underway.

In Humans, Striato-Pallido-Thalamic Projections are Largely Segregated by Their Origin in Either the Striosome or Matrix Compartments

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Cortico-striato-thalamo-cortical (CSTC) loops are fundamental organizing units in mammalian brains. CSTCs process limbic, associative, and sensorimotor information in largely separated but interacting networks. CTSC loops pass through paired striatal compartments, striosome (aka patch) and matrix, segregated pools of medium spiny projection neurons with distinct embryologic origins, cortical/subcortical structural connectivity, susceptibility to injury, and roles in behaviors and diseases. Similarly, striatal dopamine modulates activity in striosome and matrix in opposite directions. Routing CSTCs through one compartment may be an anatomical basis for regulating discrete functions.

We used differential structural connectivity, identified through probabilistic diffusion tractography, to distinguish the striatal compartments (striosome-like and matrix-like voxels) in living humans. We then mapped compartment-specific projections and quantified structural connectivity between each striatal compartment, the globus pallidus interna (GPi), and twenty thalamic nuclei in 221 healthy adults.

We found that striosome-originating and matrix-originating streamlines were segregated within the GPi: striosome-like connectivity was significantly more rostral, ventral, and medial. Striato-pallido-thalamic streamline bundles that were seeded from striosome-like and matrix-like voxels transited spatially distinct portions of the white matter. Matrix-like streamlines were

5.7-fold more likely to reach the GPi, replicating animal tract-tracing studies. Striosome-like connectivity dominated in six thalamic nuclei (anteroventral, central lateral, laterodorsal, lateral posterior, mediodorsal-medial, and medial geniculate). Matrix-like connectivity dominated in seven thalamic nuclei (centromedian, parafascicular, pulvinar-anterior, pulvinar-lateral, ventral lateral-anterior, ventral lateral-posterior, ventral posterolateral). Though we mapped all thalamic nuclei independently, functionally-related nuclei were matched for compartment-level bias. We validated these results with prior thalamostriate tract tracing studies in non-human primates and other species; where reliable data was available, all agreed with our measures of structural connectivity. Matrix-like connectivity was lateralized (left>right hemisphere) in eighteen thalamic nuclei, independent of handedness, diffusion protocol, sex, or whether the nucleus was striosome-dominated or matrix-dominated.
Compartment-specific biases in striato-pallido-thalamic structural connectivity suggest that routing CSTC loops through striosome-like or matrix-like voxels is a fundamental mechanism for organizing and regulating brain networks. Our MRI-based assessments of striato-thalamic connectivity in humans match and extend the results of prior tract tracing studies in animals. Compartment-level characterization may improve localization of human neuropathologies and improve neurosurgical targeting in the GPi and thalamus.

Quantifying the Value of Multimodal MRI in Outcomes Prediction for STN DBS in PD

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Objective: To compare the predictive value for motor outcomes of multimodal MRI to clinical predictors alone in STN DBS for PD.
Background: STN DBS is an effective treatment for the motor symptoms of PD, yet outcomes remain highly variable. Currently, pre-surgical levodopa response provides the most established prediction of clinical outcome, although its predictive power varies greatly across studies. MRI-based methods including resting state functional connectivity (FC), subcortical and cortical volumetrics, and DTI-based structural connectivity (SC) independently predict DBS outcomes, while a comprehensive model integrating these methods has not yet been developed.
Methods: We included 61 participants who had multimodal MRI prior to STN DBS for PD and who had adequate clinical data before and after DBS, as well as good quality volumetric, DTI, and rs-fcMRI data. We applied clinical and MRI-based predictors from published studies including thalamic and ventricular volumes, FC and SC connectivity between STN and GPI, VL thalamus, and motor cortex. Regularized linear regression using the least absolute shrinkage and selection operator (LASSO) and leave-one-out cross-validation was used for model construction and factor selection, optimized to RMSE to avoid overfitting with addition of more variables. The primary outcome was percent change in UPDRS-III from the initial preoperative OFF-medication examination to the average OFF-medication, ON-stimulation score over the first year after DBS.
Results: The "traditional" model, constrained to only clinical predictors (including levodopa response, age, sex, handedness, LEDD, preoperative UPDRS-III) was modestly predictive of motor improvement (R^2 = 0.29, RMSE = 14.9. In comparison, the total model, which included FC, SC, volumetric, and clinical predictors more strongly predicted motor improvement (R^2 = 0.55, RMSE = 13.6). Factors included in the optimized model included STN-GPI FC, GPI-VL thalamus SC, VL thalamus-motor cortex SC, ventricular volume, age, preoperative UPDRS-III, and levodopa responsiveness.
Conclusions: Multimodal MRI greatly outperforms levodopa responsiveness alone in prediction of motor outcomes for STN DBS in PD. Addition of cognitive and psychiatric features both as predictors and as outcomes may further enhance the predictive power and clinical utility of this approach.

MS and Autoimmune Neurology

Disrupted Cerebral Metabolism in Multiple Sclerosis

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Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system. Neurodegeneration begins early in MS and may be exacerbated by metabolic stress. MS is hypothesized to disrupt cerebral metabolism due to 1) demyelination which precludes saltatory conduction and increases the metabolic cost of ionic gradients, 2) inefficiencies in reactively produced mitochondria, 3) metabolic costs of re-myelination, and 4) metabolic costs of infiltrative immune cells. The extent to which metabolic abnormalities are present in early relapsing MS is unknown. This study assessed the cerebral metabolic rate of glucose (CMR_{glc}), cerebral blood flow (CBF), and cerebral oxygen extraction fraction (OEF) in 20 recently diagnosed relapsing MS (RMS) patients prior to initiation of disease modifying therapy, five non-relapsing MS (NRMS) patients with at least 10-year disease duration, and twelve healthy control participants. CMR_{glc} was measured by Patlak analysis of dynamic flurodeoxyglucose positron emission tomography, and CBF and OEF were measured by arterial spin labeling and oxygen sensitive magnetic resonance imaging, respectively. These metabolic parameters were estimated in non-lesional white matter (WM), gray matter (GM), and WM lesions (WML) using symmetric geometric transfer matrix partial volume correction. In non-lesional WM, RMS (t=2.14, p=0.044) and NRMS (t=2.47, p=0.022) patients had higher CMR_{glc} than controls. No differences in non-lesional WM

CBF were observed and OEF was mildly increased in the NRMS patients only (t=2.06, p=0.048). Increased CMR_{glc} absent significant changes in oxygen metabolism indicates increased aerobic glycolysis. No significant effects were seen in GM. In MS patients, WMLs demonstrate decreased CMR_{glc} (t=4.18, p<0.001) and CBF (t=2.81, p=0.0064) but increased OEF (t=2.93, p=0.0046) compared to non-lesional WM. Increased OEF combined with decreased CBF can indicate relative ischemia, but changes in cerebral metabolic rate of oxygen (CMR_{O2}) depend on both CBF and OEF. We calculated the WML to non-lesional WM ratio for CMR_{glc} and CMR_{O2} and found that whereas CMR_{glc} was decreased in WMLs by 27%, CMR_{O2} was only reduced by about 4%. This suggests a decrease in glycolytic metabolism in WMLs, in contrast to non-lesional WM where glycolysis is increased. These findings suggest that cerebral metabolic stress is present early and late in MS, including in non-lesional WM. Future work will investigate the effect of treatment on metabolic stress and associations with disease severity.

Investigations of Synaptic Signaling Targets of Human Anti-NMDAR Antibodies

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The most common form of autoimmune encephalitis is associated with antibodies that target N-methyl-D-aspartic acid (NMDA) receptors. NMDARs are glutamate receptors that govern cellular mechanisms of learning and memory, including synaptic long-term potentiation (LTP), through induction of post-synaptic signaling cascades and regulation of synaptic protein synthesis. In anti-NMDAR encephalitis, antibody binding to the obligate GluN1 subunit of NMDARs leads to crosslinking and internalization of NMDARs. The molecular mechanisms that lead to the diverse neuropsychiatric symptoms associated with anti-NMDAR encephalitis remain incompletely defined but are hypothesized to involve synaptic dysfunction. We previously demonstrated that human GluN1 monoclonal antibodies (GluN1 hMAbs) rapidly localize to and regulate synaptic NMDAR function at native synapses of primary neurons. Here, we sought to explore signaling targets of GluN1 hMAbs in primary neurons using biochemistry and subcellular fractionation. We utilized unbiased quantitative phosphoproteomics to evaluate signaling pathways in membrane fractions from primary cortical neurons. GluN1 hMAbs altered global membrane protein phosphorylation states associated with numerous biological processes relevant to neuronal structure and function. These data suggest that NMDAR antibodies alter neuronal signaling networks. In separate experiments, we defined activity-dependent regulation of local RNA content in the postsynaptic density (PSD) fractions of primary neurons. Pharmacological manipulation of autophagy resulted in local synaptic RNA regulation. Thus, autophagy may contribute to synaptic plasticity via regulation of local RNA metabolism. These results raise the question of whether the effects of GluN1 hMAbs impact synaptic protein homeostasis involving autophagy and local RNA metabolism at the PSD. Future studies will investigate the regulation of autophagy and RNA metabolism in the underlying pathophysiology of anti-NMDAR encephalitis. These studies may contribute to the identification of potential therapeutic targets for novel therapies for patients with anti-NMDAR encephalitis and disorders involving antibodies targeting cell surface antigens.

Longitudinal Clinical Evaluation of Paramagnetic Rim Lesions in Multiple Sclerosis

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Paramagnetic rim lesions (PRLs) are an MRI biomarker of some chronic active lesions in multiple sclerosis (MS). Longitudinal evolution of these lesions, as well as differential treatment effects, remain poorly characterized. Here we aimed to evaluate longitudinal PRL imaging characteristics including resolution or fading, as well as clinical associations and relationships with concurrent disease-modifying therapy (DMT) regimens. We retrospectively identified MS patients (all forms) from our observational cohort with MRI follow-up of ≥2 years using a standardized acquisition protocol, and assessed baseline MRI scans for PRL as determined using filtered-phase susceptibility imaging from a clinical manufacturer protocol at 3T (GE SWAN). PRL were identified as hypointense paramagnetic rims at the edge of FLAIR lesions; confluent lesions were included when sub-lesions could be identified from superstructure. All available longitudinal images were coregistered with uniform phase contrast settings, and PRL were extracted and blindly evaluated for qualitative change including "fading" or resolution. A mixed-effects multivariable logistic regression model was used to evaluate baseline predictors of fading/resolution including age, follow-up duration, and concurrent DMT(s), controlling for subject-specific repeated measures. DMTs were statistically modeled as percentage of the observation period with time-on-treatment. Baseline and longitudinal clinical associations were determined using multivariable regression. 238 patients met overall inclusion criteria, 84 of whom (35%; age 45.0±11.5, 72% female, 83% relapsing) had ≥1 baseline PRL, with median follow-up of 3.5 years. We identified 202 baseline PRL (median 2, range 1-13). Over follow-up, 9 PRL resolved (4%), 50 faded (25%), and 122 exhibited no change; 20 evolved in other ways (fragmentation, diffuse paramagnetic change, or enlargement). DMTs received for at least 1/3 of the observation period were 36 (43%) B-cell depletion, 10 (12%) fumarate, 8 (10%) alemtuzumab, and 5 (6%) each for teriflunomide, mycophenolate, and glatiramer. Our regression model adjusted for age, observation time, and subject-specific repeated measures did not show any consistent associations with age, follow-up period, or medication on fading/resolution of PRL (all p>0.05). Baseline number of PRL was associated with baseline

lower deep gray volumes, higher choroid plexus volumes, and greater central brain atrophy (all adjusted for age, sex, lesion volume, p≤0.01). In conclusion, we observed that 29% of PRL qualitatively fade/resolve over a 3.5 year follow-up; filtered-phase longitudinal PRL assessments were both feasible and rapid. PRL were associated with greater pathological baseline MRI-based volume loss, but PRL fading/resolution was not associated with age, DMT, or observation time after accounting for within-subject correlation, suggesting the need for targeted therapies to hasten resolution of CAL.

The PKC Modulator Bryostatin-1 Augments Remyelination through Therapeutic Targeting of CNS Innate Immunity

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In multiple sclerosis (MS), microglia and macrophages within the central nervous system (CNS) determine the balance between demyelination, neurodegeneration, and myelin repair. Phagocytic and regenerative functions of these CNS innate immune cells support remyelination, whereas chronic and maladaptive inflammatory activation promotes lesion expansion and disability, particularly in progressive forms of MS. No currently approved drugs convincingly target microglia and macrophages within the CNS, contributing to the critical lack of therapies promoting remyelination and slowing progression in MS. Here, we found that the protein kinase C (PKC) modulating drug bryostatin-1 (bryo-1), a CNS-penetrant compound with an established human safety profile, produces a shift in microglia and CNS macrophage transcriptional programs from pro-inflammatory to regenerative phenotypes, both *in vitro* and *in vivo*. Treatment of microglia with bryo-1 prevented the activation of neurotoxic astrocytes while stimulating scavenger pathways, phagocytosis, and secretion of factors that promote oligodendrocyte differentiation. In line with these findings, systemic treatment with bryo-1 augmented remyelination following focal demyelinating injury *in vivo*. Our results demonstrate the potential of bryo-1 and related PKC modulators as myelin regenerative and neuroprotective agents in MS and other neurologic diseases through therapeutic targeting of microglia and CNS macrophages.

Neurocritical Care and Traumatic Brain injury

Selective Neuroimmune Modulation by Type I Interferon Drives Neuropathology and Neurologic Dysfunction Following Traumatic Brain Injury

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Accumulating evidence suggests that type I interferon (IFN-I) signaling is a key contributor to immune cell-mediated neuropathology in neurodegenerative diseases. In a recently published study, we demonstrated a robust upregulation of type I interferon-stimulated genes in microglia and astrocytes following experimental traumatic brain injury (TBI). The molecular and cellular mechanisms by which IFN-I signaling impacts the neuroimmune response and neuropathology following TBI remains unknown. In this study, we utilized the lateral fluid percussion injury model (FPI) in adult C57BL/6J and IFN α/β receptor (IFNAR) deficient male mice to evaluate the impact of IFN-I/IFNAR signaling on TBI outcomes. Gene expression was assessed by Nanostring and quantitative PCR. Immune cell accumulation was quantified using flow cytometry. Neuronal loss, microglial reactivity, and interferon stimulated genes were evaluated using RNAscope in-situ hybridization and immunohistochemistry. MRI was used to assess white matter integrity, and neurobehavioral testing was performed to evaluate functional outcomes. We demonstrated that IFNAR deficiency resulted in selective and sustained blockade of type I interferon-stimulated genes following TBI as well as decreased microgliosis and monocyte infiltration. Phenotypic alteration of reactive microglia also occurred with diminished microglial expression of molecules needed for MHC class I antigen processing and presentation following TBI. This was associated with decreased accumulation of Cd8+ T cells in the brain. The IFNAR-dependent modulation of the neuroimmune response was accompanied by decreased neuronal loss, white matter disruption, and neurobehavioral dysfunction. Ongoing studies are evaluating IFN-I mediated crosstalk between microglia and peripheral immune cells, as well as the cell-specific effects of IFN-I signaling. Our data support further efforts to leverage the IFN-I pathway for novel, targeted therapy of TBI.

Anti-Seizure Medication Safety and Effectiveness in Older Adults with Traumatic Brain Injury

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Background: Older adults (age>65) are the highest risk group for traumatic brain injury (TBI) , including risk for post injury complications such as seizures. Current TBI guidelines suggest use of prophylactic anti-seizure treatment for up to 7 days after severe TBI. However there is limited data on optimal treatment approaches for older adults, who are also at highest risk for medication related adverse effects. We sought to determine the relation of ASM use with outcomes in older adults with TBI. **Methods:** This is single center study of adults (>65 years) admitted for acute TBI. The primary exposure was prophylactic ASM administration ≤ 7 (as supported by guidelines) vs. >7 days. The primary outcome was death/severe disability at discharge (modified Rankin Scale of 5-6). **Results:** 188 patients met inclusion. Median age was 82 years; 46% were female. The most common cause of TBI was falls (90%). 52% received ASM for ≤ 7 days vs. 41% for > 7 days, and 7% received no ASMs. All patients received Levetiracetam as the only ASM. After adjusting for injury severity, seizures, comorbidity score, and imaging findings, ASM

treatment for >7 days (compared with ≤7 days), was not significantly associated with death/severe disability (adjusted OR = 2.0 [95% CI 0.55-7.13]), although did have higher odds. **Conclusion:** Larger prospective comparative studies are indicated to determine the safety and effectiveness of anti-seizure prophylaxis in older adults with TBI.

Association of Dexmedetomidine Utilization with Clinical Outcomes Following Moderate-Severe Traumatic Brain Injury

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Background: Traumatic brain injury (TBI) is a major public health problem. Management of critically ill and mechanically-ventilated patients with moderate-severe TBI (msTBI) often includes sedation. Dexmedetomidine has emerged as a possible candidate for early sedation after TBI due to its potential modulation of autonomic dysfunction. We examined early sedation patterns, as well as the association of dexmedetomidine exposure with clinical and functional outcomes among mechanically ventilated patients with msTBI in the United States. **Methods:** We conducted a retrospective cohort study using data from the Premier Healthcare Database and identified a cohort of critically ill adult patients with msTBI who required mechanical ventilation (MV) from Jan 2016 to June 2020. msTBI was defined by head-neck abbreviated injury scale (AIS) values of 3 (serious), 4 (severe), and 5 (critical). We described early sedative utilization patterns. Next, using propensity-matched models, we examined the association of early dexmedetomidine exposure [within 2 days of intensive care unit (ICU) admission] with the primary outcome of hospital mortality and the following secondary outcomes: hospital length of stay (LOS), days on MV, vasopressor use after the first two days of admission, hemodialysis (HD) after the first two days of admission, hospital costs, and discharge disposition. **Results:** The study population included 19751 subjects who required MV within 2 days of ICU admission. The patients were majority male and white. The most utilized sedative was propofol (82.7%), followed by benzodiazepines (26.0%), dexmedetomidine (6.5%), and ketamine (0.9%). From 2016 to 2020, the annual percent utilization of dexmedetomidine increased from 4.05% to 8.60%. After propensity score matching, early dexmedetomidine exposure was associated with reduced hospital mortality (OR 0.43; 95% CI 0.31-0.61), higher likelihood of discharge to home (OR 1.23; 95% CI 1.01-1.50), and reduced number of days on mechanical ventilation (HR 1.16; 95% CI 1.04-1.29). Exposure to early dexmedetomidine was not associated with hemodialysis utilization (OR 0.66; 95% CI 0.39-1.10), vasopressor utilization (OR 1.12; 95% CI 0.91-1.38), hospital length of stay (HR 1.04; 95% CI 0.95-1.14), or total hospital costs (OR 1.02; 95% CI 0.94-1.09). **Conclusion:** Dexmedetomidine is an increasingly popular sedative among mechanically ventilated patients with msTBI. Early dexmedetomidine exposure may lead to improved patient outcomes when used in this population. Prospective randomized-controlled trials are needed to confirm these findings.

Biomarkers Associated with Progression of Intracranial Hemorrhage in the Prehospital TXA for TBI Trial

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Background: Progression of intracranial hemorrhage is a common, potentially devastating complication after moderate/severe traumatic brain injury (TBI). Patients that have progression of intracranial hemorrhage are more likely to require an intracranial pressure monitor and/or a craniotomy. Clinicians have few tools to predict which patients with traumatic intracranial on their initial head computed tomographic scan (hCT) scan will progress. In this study, we sought to identify clinical or imaging biomarkers which associate with intracranial progression. **Methods:** We analyzed a subset of subjects from the phase II double-blind, multicenter randomized "Prehospital Tranexamic Acid Use for TBI" trial. This subset was limited to subjects in the placebo arm of the parent trial with evidence of hemorrhage on initial hCT and a follow up hCT 6 hours after the initial hCT. Intracranial progression was defined as an increase in size by 30% or more or the development of new hemorrhage in the intra-axial and extra-axial intracranial vault between the admission/baseline and follow up hCT. Two independent radiologists evaluated each hCT, and conflicts were adjudicated by a third. Clinical and radiographic characteristics were collected, along with plasma protein biomarkers at admission (GFAP, UCH-L1, MAP, VCAM-1, ICAM-1, Ang-1, Ang-2, Thrombomodulin, Syndecan-1, Thrombospondin, IL-6, and TNF-a). **Results:** In the subset (n=104), 46% (n=48) showed progression as defined above. Age, sex, GCS motor and total GCS scores were similar between progressors and non-progressors. Those with progression had higher Marshall (2 [2-6] v. 2 [2-2], P=0.007) and Rotterdam scores (2 [2-3] v. 2[2-2], P=0.004), and larger initial hematoma sizes (2.2 [±13.7] v. 0.6 [±26.5] mL, P=0.005) than non-progressors. Of the plasma proteins, only elevated levels of GFAP (2350 [587-3730] v. 327 [158-1210] µg/dL, P=0.001) and MAP (131 [21-513] v. 37 [13-125] µg/dL, P=0.015) were associated with progression. **Conclusions:** We identified radiographic and blood-based biomarkers associated with progression of intracranial hemorrhage. Next steps include creation of predictive models of progression including these features, and validation in separate datasets.

Head Injury and Cognitive Change over 30 Years

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Background: Traumatic brain injury (TBI) is associated with short-term cognitive impairment and later-life dementia risk, but there is limited evidence regarding long-term cognitive change after head injury in community-dwelling populations. **Objective:** To examine the association between head injury and cognitive change over 30 years. **Methods:** The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing prospective cohort of 15,792 adults recruited from 4 U.S. communities in 1987-1989. Head injury was defined by self-report and hospital-based International Classification of Diseases diagnostic codes and was analyzed as a time-varying exposure over study follow-up. Cognitive testing was performed at 5 study visits (1990-1992, 1996-1998, 2011-2013, 2016-2017, and 2018-2019) and scores were combined into a previously validated global factor score. We used linear mixed effects models with random intercepts, random slopes for time from baseline (1990-1992; modeled with splines at 1996-1998 and 2011-2013), and an unstructured covariance matrix to estimate the association between head injury and the change per decade in cognition. Models were adjusted for sociodemographics, cardiovascular and APOEε4 genotype. Formal testing for interaction by age, sex, and race was performed. In secondary analyses, we considered the associations of number of prior head injuries and injury severity with cognitive factor scores. Multiple imputation by chained equations was employed to impute missing data. **Results:** Our analysis included 11,677 individuals who attended the second ARIC study visit in 1990-1992 with no history of head injury. Participants were a mean age of 58 years, 58% were female, 26% were of self-reported Black race, and 18% experienced a head injury over study follow-up, the majority classified as mild. In adjusted models, the average decline in cognition per decade was -0.045 (95%CI=-0.082,-0.007) in individuals without head injury and -0.105 (95%CI=-0.163,-0.048) in individuals with head injury (difference=-0.061, 95%CI=-0.103,-0.019). This difference in cognitive decline is equivalent to individuals with head injury being 6 years older at baseline. In secondary analyses, there was evidence supporting a dose-dependent association for greater cognitive decline with higher number of head injuries (additional decline in head injury compared to no head injury group per decade: 1 injury=-0.047, 95%CI=-0.089,-0.004 and 2+ injuries=-0.071, 95%CI=-0.167,0.024, which is equivalent to being 4.5 years and 6.9 years older at baseline for 1 and 2+ head injuries, respectively), but not with injury severity. There was no evidence for interaction by age, sex, or race (all p-interaction>0.05). **Conclusions:** Head injury was associated with accelerated cognitive decline over 30 years. Future work investigating mechanisms underlying long-term cognitive decline observed among individuals with TBI is warranted.

Symptomatic Baroreflex Abnormalities Following Concussion

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Background: Post-traumatic onset headache, brain fog, and dizziness, are common following concussion. Clinically, these symptoms are often equated to altered autonomic function and resultant changes in cerebral blood flow. Baroreceptor function plays a key role in monitoring and maintaining blood flow to the brain. Thus, impairment to this reflex arc may be of particular interest in understanding symptoms resulting from head trauma. **Methods:** Participants with concussion and healthy controls, aged 15-60, were recruited through the University of Utah electronic medical record and word of mouth. Inclusion criteria: head injury within 14 days, ongoing symptoms. Age/sex matched healthy controls, without a history of concussion or recurrent headaches. Exclusion criteria: medications that alter autonomic function and could not be held for 5 half-lives; medical diagnoses known to alter autonomic function (e.g., diabetes, heart disease, neuropathy). This study received approval from our Institutional Review Board; all participants were consented. Study participants completed symptom assessment (Rivermead) and standardized autonomic testing, including heart rate (HR) variability to deep breathing (HRDB), Valsalva, and 10-minute head-up tilt testing (HUTT) using continuous beat-to-beat heart HR and blood pressure (BP) monitoring. Physiological measures were analyzed for cardiovagal and cardiovascular adrenergic reflex function via standard methods, and for sympathetic and parasympathetic contributions during supine and HUTT states, via continuous wavelet transform to identify very low (VLF), low (LF), and high frequency (HF) domains. **Results:** 36 concussed and 19 control subjects completed the study. LF during HUTT was significantly lower in concussed subjects, compared to controls. Heart rate variability (SD and CV) generally trended lower, while mean HR (supine and upright), mean BP, and VLF power trended higher in concussed participants. There were no significant differences in parasympathetic function (mean HR range, Valsalva Ratio, HF). For concussed subjects, using univariate correlation analysis, there were moderate positive correlations between symptom scores and resting mean HR, resting HR variability, upright BP variability, and upright VLF and LF power. **Conclusions:** These data support a blunted sympathetic response to HUTT in concussed participants, where a robust increase in sympathetic activity is expected. There were also more subtle features of increased sympathetic activation in the supine state, relative to controls, though this pattern was not statistically robust. Finally, while subtle, the overall pattern suggests relative sympathetic hypofunction to upright challenge, with resting state sympathetic activation, which correlate with increased symptom burden. Subtle changes in baroreceptor function may explain clinically observed activity intolerance and related symptoms in concussed individuals.

Systemic Metabolic Alterations after Aneurysmal Subarachnoid Hemorrhage

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Background: Aneurysmal rupture resulting in subarachnoid hemorrhage (aSAH) results in a robust systemic inflammatory response. We hypothesized that a shift in circulating metabolites with prominent changes in lipids would occur early after aSAH and predict outcomes. **Methods:** aSAH patients and controls were analyzed from two tertiary care centers (University of Texas Health Science Center and University of Maryland). Clinical data for all patients were abstracted including comorbidities as well as adjudicated outcomes such as occurrence of delayed cerebral ischemia (DCI) and modified Rankin Scale (mRS) score. Paired samples were collected within 24h and at 7d after aneurysm rupture. Mass spectrometry-based untargeted metabolomics was performed. A total of 1,370 metabolites were detected. Principal component analysis (PCA) was used to segregate controls from aSAH patients. Hierarchical clustering algorithms were developed to group sets of metabolites. Volcano plots were utilized to visualize fold changes for each metabolite relative to *P*-values comparing patients with or without DCI. Receiver operating curves (ROC) as well as multivariable logistic regression models were developed to assess utility of metabolites for predicting outcomes. **Results:** A total of 70 aSAH patients and 30 age matched controls were included. Metabolites readily distinguished control from aSAH patients in PCA analysis. Hierarchical clustering revealed significantly higher levels of free fatty acids in patients with aSAH but lower levels of acylcholines. Volcano plots demonstrated that in patients with DCI, sphingosine and sphinganine were significantly increased (fold change > 2, false discovery rate [FDR] corrected *P*-value < 0.1), while S-adenosylhomocysteine and two acylcarnitines were significantly decreased (fold change < -2, FDR corrected *P*-value < 0.1). Sphingosine had an AUC of 0.723 (95% CI 0.6001, 0.834) for predicting DCI. In multivariable regression models corrected for age, clinical severity, and sex, sphingosine [OR 10.2 (95%CI 2.46 ,59.8)] and sphinganine [OR 4.52 (95%CI 1.57, 20.9)] were associated with DCI. Levels of sphingosine 1-phosphate were higher in women with DCI but not men. Levels of the enzyme autotaxin, which can produce sphingosine 1-phosphate, were significantly higher in women than men (P=0.0045 among patients with DCI and P=0.0029 among patients without DCI). **Conclusions:** Plasma metabolites readily distinguish aSAH from controls. Increased circulating sphingosine and sphinganine were associated with DCI, while sphingosine 1-phosphate was increased in DCI only in women. Sex differences in enzymes involved in sphingolipid metabolism may contribute to risk of DCI after aSAH.

Neurodegeneration and Cell Death

Amyloid Beta Fibrils Induce Microglial Biosynthesis of Heparan Sulfate Proteoglycans Leading to Increased Tau Phagocytosis and Seeding

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Emerging evidence now establishes a central role for microglia in Alzheimer's disease. The microglia cell-surface proteome, or *surfaceome*, is a critical hub that enables neuroprotective, neurotoxic, and neuroinflammatory signaling in the diseased brain. Targeting the microglia surfaceome with selective pharmacologic agents may allow for the manipulation of diverse microglia states and function and therefore holds tremendous experimental and therapeutic potential. Precise microglia targeting requires broad knowledge of how the surfaceome remodels in the disease environment and this biology has not been systematically explored. To elucidate how microglia remodel their surfaceome in the context of Alzheimer's disease pathology, I performed mass spectrometry-based surfaceome profiling of human iPSC microglia after exposure to Aβ fibrils. My data reveals a robust upregulation of heparan sulfate proteoglycans (HSPGs) and proteins that promote phagocytosis. These Aβ-primed microglia increase their capacity to bind and phagocytose tau aggregates via HSPGs. Specifically, I have identified the glypican family of HSPGs as the key core proteins responsible for this pro-phagocytic phenotype. Using immunohistochemistry, I have demonstrated that these glypicans are specifically enriched in AD-associated microglia and are not found in healthy aged-matched control human brain. Finally, I have developed a Drosophila model of amyloid-induced tau spread. Knockdown of microglial glypicans results in reduced tau spread as well as rescue of locomotion deficits and early lethality. Taken together, this data demonstrate that Aβ alters the microglia surfaceome to promote tau uptake and spread through the brain and provides a mechanism to link Aβ and tau pathology through microglia and HSPGs.

Diffusion Tensor Imaging of the Corpus Callosum as an Early Disease Marker in Adrenoleukodystrophy

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Objective: Cerebral adrenoleukodystrophy (ALD) is a severe demyelinating disorder that must be treated at a very early stage to prevent permanent brain injury and neurocognitive decline. Demyelination typically starts in the corpus callosum. Validation of disease markers including quantitative measures of white matter microstructure could enable earlier and more effective treatment with cell therapies. The purpose of this study was to compare longitudinal diffusion tensor imaging (DTI) metrics over a 12-month interval in ALD patients with and without demyelinating lesions. **Methods:** Between May 2011 and November 2021, high-resolution anatomical MRI scans and DTI data for boys with cerebral ALD undergoing hematopoietic cell therapy (HCT) at our center (C-ALD group; N=34) were acquired at two time points: a baseline evaluation prior to HCT and 12-months post-HCT. Five

patients in an ongoing, unpublished clinical trial were excluded. MRI severity (Loes) scores were obtained and regional neuroanatomical patterns determined. Longitudinal data from an age-matched comparison group of ALD patients without cerebral involvement undergoing routine MRI surveillance (N=15) were also acquired at baseline and 12-months later. Fractional anisotropy (FA) maps were generated from DTI data. Average FA was estimated within the corpus callosum and its sub-divisions, as defined by non-linearly co-registered white matter atlas. Between-group mean and slope differences in FA were compared according to disease status, Loes score and pattern of neuroanatomical involvement using Wilcoxon rank sum tests. **Results:** Patients without cerebral lesions showed stable or increasing FA values in splenium, genu and whole cerebral white matter during the 12-month study period, with positive slopes for all regions. These findings were robust on an individual patient level for 87% of cases. Boys with early stage (Loes<5) posterior C-ALD pattern showed lower FA in the splenium than the group without lesions (p<.001), as well as difference in slope direction in FA over the 12-month period (p<.001). Two patients with frontal white matter lesions showed lower FA in the genu relative to boys without lesions and those with disease restricted to posterior regions. **Conclusion:** DTI metrics in the corpus callosum may serve as biomarkers for cerebral ALD at early stages. These quantitative metrics were sensitive to disease severity, location, and progression. Future longitudinal research could examine the sensitivity and specificity of these methods to detect emergence of brain lesions and predict functional brain changes measured via neuropsychological testing.

Rescuing Alpha-Synuclein Toxicity through Neuron-Specific Enhancement of Autophagy

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Parkinson disease (PD) is a progressive neurodegenerative disorder marked by motor and non-motor/multi-systemic symptoms that lead to profound disability. There is no effective disease-modifying therapy currently available. Neurodegeneration in PD relates to toxic aggregation of alpha-synuclein, and mounting evidence shows that alpha-synuclein can be degraded through the conserved pathway of autophagy. However, current methods to modulate autophagy fail to confer neuroprotective effects in patients. In recently published work, we identified MTMR5 (myotubularin-related phosphatase 5, encoded by the *SBF1* transcript) as a potent neuronal autophagy suppressor in neurons. MTMR5 knockdown enhances the sensitivity of neurons to induction of autophagy, and accelerates the degradation of multiple autophagy substrates, including disease-associated and aggregate- prone proteins. In line with this, we will test the central hypothesis that reducing MTMR5 in neurons augments autophagic clearance of alpha-synuclein and reduces alpha-synuclein-related neuronal death. We use human induced pluripotent stem cells (iPSCs) to determine whether manipulating *SBF1*/MTMR5 enhances alpha-synuclein turnover via autophagy and modifies alpha-synuclein proteotoxicity. We will also employ unbiased, genome-wide CRISPR-based screens to uncover key factors regulating MTMR5 in neurons. Collectively, these studies establish a novel research platform focusing on neuronal autophagy, myotubularin biology, and therapy design in PD and related neurodegenerative disorders.

Neurodevelopment

Striatal Cholinergic Interneuron Excitation Provokes Dystonia in Mice Following Neonatal Brain Injury

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Introduction: Dystonia is debilitating, often medically refractory, and difficult to diagnose. The diagnostic gold standard remains subjective identification by expert consensus. However, objective dystonia identification is necessary to study its pathophysiology in animal models. Abnormal striatal cholinergic interneuron (ChI) excitation has been observed in many mouse models of rare genetic dystonias. However, it is unclear whether striatal ChI excitation is directly causative of dystonia or whether it can worsen dystonia in mouse models of neonatal brain injury, the most common cause of dystonia in childhood. **Methods:** We have established that leg adduction amplitude and variability track with dystonia severity in people with neonatal brain injury during gait. We first sought to validate that these same metrics are associated with dystonia severity in people during seated upper-extremity tasks that did not otherwise engage the legs. We had pediatric movement specialists rate dystonia severity in seated videos of people with cerebral palsy due to neonatal brain injury and then quantified leg adduction amplitude and variability in these videos using a model trained with DeepLabCut. We comparably quantified leg adduction amplitude and variability during a tail suspension task in mice born premature (induced birth at embryonic day 18.2) and in mice subjected to global hypoxia at postnatal day 10 (equivalent to human term gestation) and then determined whether these clinically-relevant metrics of dystonia were effected by chemogenetic striatal ChI excitation in these mice. **Results:** Metrics of both leg adduction variability (n=193, multiple linear regression R2 0.546, F 34.0, p<0.001) and amplitude (R2 0.268, F 18.2, p<0.001) significantly correlated with expert assessments of dystonia severity in people with CP during seated upper extremity tasks. Mice born premature (n=21) demonstrated significantly increased leg adduction amplitude following chronic striatal ChI excitation, though term-born mice (n=33) did not (repeated measures 2-way ANOVA, p=0.03). Mice following term hypoxic injury (n=20) demonstrated significantly

increased leg adduction variability (p=0.03), which was potentiated with chronic striatal ChI excitation (p=0.02), though sham-injured mice (n=15) did not (p=0.3). **Conclusions:** Objective quantification of a clinically-derived dystonic motor features facilitated our determination that chronic striatal ChI excitation yields dystonic behavior in mice following two different types of neonatal brain injury. Therefore, objective dystonia identification, as outlined here, could aid clinical dystonia diagnosis and its study in animal models of disease. Elucidating the role of striatal ChIs in dystonia pathogenesis following neonatal brain injury is critical for targeted dystonia treatment development in the context of the most common cause of dystonia in childhood.

The Role of FOS and the BAF Complex in Neuronal Activity-Dependent Chromatin Remodeling and Gene Expression

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Pediatric neurodevelopmental disorders (NDD), including pediatric epilepsy, autism spectrum disorder, and intellectual disability, represent a major source of morbidity, yet our therapeutic options remain limited. Development of novel therapies for NDD will require a deeper mechanistic understanding of normal and abnormal brain development. Genetic programs that are activated in response to neuronal activity are fundamental to normal neurodevelopment and thus might play an important role in NDD pathogenesis. FOS is a major activity-dependent transcription factor that binds to distal enhancer elements and regulates downstream activity-dependent genetic programs in a cell-type-specific manner to promote key processes, such as synaptic pruning. Previously, FOS was shown to physically interact with the BAF chromatin remodeling complex and co-regulate stimulus-dependent chromatin accessibility and gene expression in non-neuronal cells. As pathogenic variants in many of the BAF complex subunits are a common genetic cause of NDD, the interaction between FOS and the BAF complex in non-neuronal cells suggests that mis-regulation of neuronal activity-dependent programs contributes to the pathogenesis of BAF complex-related NDD. However, the interaction between FOS and the BAF complex and the genetic networks that they regulate in neurons was previously unexplored. Using human neurons differentiated from human pluripotent stem cells (hPSCs), we identified activity-dependent FOS binding sites, some of which are near (and might help regulate) known NDD-related genes. We further demonstrate that neuronal activity leads to BAF complex binding and increased chromatin accessibility at FOS binding sites and that the activity-dependent increase in chromatin accessibility is diminished in *FOS* knock-out neurons. This work demonstrates that FOS and the BAF complex co-regulate neuronal activity-dependent transcription and provides putative downstream gene targets. To understand how human genetic variation in the FOS binding sites might alter activity-dependent gene regulation, we next used the SFARI SPARK database to find rare *de novo* variants within the FOS binding sites. We specifically focused on those variants that fell within the FOS binding motif (TGASTCA), as these would most likely disrupt FOS binding, thereby preventing BAF complex recruitment, activity-dependent chromatin remodeling, and subsequent downstream gene transcription. In preliminary data, we found that one of the rare *de novo* variants found in a patient with autism spectrum disorder does disrupt enhancer function in a reporter assay. In on-going work, we will try to understand whether the identified rare *de novo* variants in the FOS binding sites disrupt neuronal activity-dependent gene transcription and how this might contribute to NDD pathogenesis.

Neurogenetics and Gene Therapy

Variants in Cohesin Release Factors Define a Novel Class of a Cohesin Balance Disorders and Illuminate a Therapeutic Path for Cohesinopathies

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Cohesin orchestrates 3D genome organization and gene expression programs via DNA loop extrusion to form topologically associating domains (TADs). Loss of cohesin or its positive regulators (e.g. the cohesin loader NIPBL) causes prominent neurodevelopmental phenotypes including Cornelia de Lange syndrome (CdLS). Via an analysis of copy-number alterations in >900,000 individuals, we found that autosomal cohesin genes had elevated predicted haploinsufficiency (pHI) and triplosensitivity (pTS) scores (mean rank pHI 99.2%ile, pTS 96.2%ile of 17,263 genes), suggesting that a disturbance of cohesin balance in either direction is pathogenic. Thus, we hypothesized that loss of the cohesin releaser WAPL, which serves an opposing function to NIPBL, would cause a novel disorder. We sought and identified 19 cases of heterozygous *de novo WAPL* variants, including missense and truncating changes, in children and adults. Developmental delay of mild-moderate severity is ubiquitous in this case series, and some birth defects (e.g. club foot) may be enriched but are pending further phenotypic analysis. To further probe the effect of *WAPL* haploinsufficiency on neurodevelopment, we performed a gene-centric burden analysis of exome sequencing data from >30,000 individuals with developmental delay. *WAPL* variants are enriched in these cases ($q<0.05$), not only adding statistical confirmation to our subject data, but also nominating *WAPL* (along with *BMPR1A*) as one of a candidate driver gene for neurodevelopmental phenotypes in the recurrent 10q22q23 deletion syndrome. Finally, we CRISPR-engineered >50 iPSC lines with *WAPL* LoF, *NIPBL* LoF, or 10q22q23 deletions, for analysis via ongoing functional genetic methods to assay the presence and consequence of perturbed cohesin balance in these disease models.

Differential Post-Translational Sulfatase Activation Correlates with Disease Severity in Multiple Sulfatase Deficiency

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Sulfatases catalyze essential cellular reactions, including the degredation of the glycosaminoglycans (GAGs) including heparan sulfate (HS), chondrotin sulfate (CS), and dermatan sulfate (DS). All sulfatases undergo post-translational activation through the conversion of an active site cysteine into a formylglycine residue. This conversion is mediated by the formylglycine generatine enzyme (FGE), which is deficient in Multiple Sulfatase Deficiency (MSD), an ultra-rare neurodegenrative lysosomal storage disease. Historically, MSD patients were presumed to be deficient of all sulfatase activity, however, a more nuanced relationship is emerging. Each individual sulfatase may differ in their degree of post-translational modification by FGE, and this may influence the phenotypic spectrum.

Here, we evaluate if patterns of residual sulfatase activities and accumulating GAG nonreducing end (GAG-NRE) species distinguish cases from controls and stratify clinical severity groups in MSD. Using tandem mass spectrometry, we quantify sulfatase activities and GAG subspecies accumulation using three complimentary methods in samples from 13 subjects (9 severe, 4 attenuated). Sulfatases differed greatly in their tolerance of reduction in FGE activity. Enzymes mediating HS degradation demonstrated lower residual activities than those that act on CS and DS. Similarly, HS-derived urinary GAG-NRE species preferentially accumulated, distinguished MSD cases from controls and correlated with disease severity.

Accumulation patterns of specific sulfatase substrates in MSD could both provide fundamental insights into sulfatase regulation and serve as much-needed diagnostic and severity biomakers in MSD. This work highlights that biomarker investigation of an ultra-rare diseases can simultaneously inform our understanding of fundamental biology and advance clinical trial readiness. Ultimately, validation of urinary GAG profiles as MSD biomarkers will allow for the stratification of trial subjects and establish inclusion / exclusion criteria for upcoming clinical trials.

Improved Survival, Strength, and Neuroinflammation in a Mouse Model of Sporadic ALS after Novel AAV-Mediated Delivery of RNAi Targeting *Atxn2*

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Amyotrophic lateral sclerosis (ALS) is a fatal disease characterized by death of motor neurons, which at autopsy show cytoplasmic aggregates of Tar-DNA binding protein of 43kDa (TDP-43). TDP-43 associates with cytoplasmic stress granules (SGs) and leads to toxicity through both cytoplasmic gain- and nuclear loss-of-function. In 2017, a seminal study showed that inhibiting SG formation through downregulation of the SG-associated protein Ataxin-2 (Atxn2) using antisense oligonucleotides (ASOs) prolongs survival by 35% in a mouse model of sporadic ALS (Becker et al., Nature 2017), a strategy that is now in human clinical trials. However, frequent CNS administrations are required for sustained knockdown, and the intrathecal approach may have limited efficacy in reaching the brain, limiting safety and efficacy. Our group therefore developed an approach using AAV-mediated RNAi delivery to achieve lasting and targeted knockdown, a strategy that could be used to treat sporadic ALS. We designed and tested miRNAs targeting Atxn2 in cultured cells, packaging the top candidate into a novel AAV9 variant, AAV1999, that we engineered for superior CNS targeting in mice and nonhuman primates. Mouse dosing studies demonstrated 55% Atxn2 knockdown in frontal cortex and 25% knockdown throughout brainstem and cervical and lumbar spinal cord after intracerebroventricular injection. We then conducted an efficacy study in the same ALS mouse model used in the ASO study, in which wildtype human TDP-43 is overexpressed in neurons and mice exhibit a rapid decline in strength and survival. After treatment, mean and median survival were increased by 54% and 45% respectively ($p<0.0003$). Mice showed marked improvement across strength-related measures, including rotarod (2.6X duration, $p<0.005$); composite gait (40% improvement, $p<0.0001$); clasping (24% improvement, $p<0.05$); kyphosis (75% improvement, $p<0.0001$); tremor (39% improvement, $p<0.0001$); foot angling (57% improvement, $p<0.0001$); and limping (29% improvement, $p=0.005$). Interestingly, treated mice showed a marked increase in vertical activity above that seen in wildtypes, perhaps suggesting an unmasking of an FTD phenotype with improved strength. Histologically, there was an increase in motor neurons, and a significant reduction in CNS inflammatory markers. Spinal cord transcriptomics revealed markedly dysregulated transcriptomes in mutant mice, several of which were corrected by treatment and have been described in the ALS literature. AAV-mediated RNAi against *Atxn2* is therefore a promising treatment strategy for the 97% of ALS characterized by TDP-43 pathology.

Increased Degradation of FMRP Contributes to Neuronal Hyperexcitability in Tuberous Sclerosis Complex

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Autism spectrum disorder (ASD) is a highly prevalent neurodevelopmental disorder but progress in the development of therapies has been impeded by a lack of understanding of the pathological mechanisms. Several highly penetrant, single gene disorders associated with ASD have provided important insights into key pathways underlying brain development and behavior. Tuberous sclerosis complex (TSC) and Fragile X Syndrome are two key examples that are associated with abnormalities in the function of the mechanistic target of rapamycin (mTOR) and Fragile X Messenger Ribonucleoprotein 1 (FMRP), respectively, both of which have been implicated in the development of ASD. Previously, we observed that transcripts associated with FMRP were down-regulated in TSC2-deficient neurons. In this study, we found that FMRP turnover was dysregulated in TSC2-deficient rodent primary neurons, and this was associated with increased ubiquitination and reduced phosphorylation of FMRP. Moreover, increased degradation of FMRP was dependent on the presence of a recognition motif in FMRP for the E3 ubiquitin ligase, the Anaphase Promoting Complex. We then used neurons derived from induced pluripotent stem cells (iPSCs) from patients with TSC, as well as isogenic corrected and second hit cell lines. We also observed increased FMRP degradation in human neurons, which was abrogated by mutation in the ubiquitination recognition site of FMRP. Finally, we used extracellular recordings of TSC2-deficient iPSC-derived neurons to show that over-expression of FMRP is sufficient to partially rescue hyperexcitability in these cells. Taken together, we have demonstrated how FMRP is dysregulated in TSC2-deficient neurons and that this represents an important pathological mechanism in the development of abnormal neuronal activity in TSC. These data illustrate a molecular convergence between these two neurogenetic disorders and contribute to unraveling the pathogenesis of neurological symptoms in neurodevelopmental disorders.

Loss of O-glycosylation via Neuronal *Galnt2* Knock-Out in Mice Recapitulates GALNT2-CDG Patient Seizure Phenotype

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Congenital disorders of glycosylation (CDG) are a group of neurogenetic disorders that disrupt cellular glycosylation machinery and exhibit multi-system dysfunction, including severe neurological deficits. These disorders emphasize that glycosylation is an essential posttranslational modification, yet the pathophysiology of neurological dysfunction in CDG remains unclear. Most CDG disrupt N-glycosylation, however, eight patients from five families with biallelic loss-of-function mutations in GALNT2, which encodes a Golgi-localized glycosyltransferase that initiates mucin-type O-glycosylation, confirms O-glycosylation is also critical to neurologic function. GALNT2-CDG patients exhibit global developmental delay, epilepsy, autistic features, and white matter changes on brain MRI.

A mouse model of the neurological aspects of this neurogenetic disorder, GALNT2-CDG, using a floxed *Galnt2* allele and cell-type specific Cre drivers, exhibits spontaneous seizures and deficits across numerous behavioral and learning domains. Time-locked video EEG recordings exhibit frequent abnormal electrographic spikes and identify seizures in the majority of neuronal KO mice, which increase in prevalence as the mice age. Power analysis of background EEG frequency composition demonstrates abnormalities across the major EEG frequency bands with increased power in the slow activity delta frequency band and decreased power in the fast activity frequency bands. Glycoproteomic analysis of synaptosomes isolated from brain identify candidate glycoproteins and disrupted O-glycosites that likely underly these abnormalities. Genetic dissection of the circuit suggests that molecular events in both excitatory and inhibitory neurons contribute to development of spontaneous seizures. These findings demonstrate the key role of O-glycosylation in neurons and implicate a role of O-glycosylation in diverse neurological processes, including learning, memory, and neurotransmission.

Reversal of C9orf72 Mutation-Induced Transcriptional Dysregulation and Pathology in Cultured Human Neurons by Allele-Specific Excision

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Efforts to genetically reverse C9orf72 pathology have been hampered by our incomplete understanding of the regulation of this complex locus. We generated five different genomic excisions at the C9orf72 locus in a patientderived iPSC line and a WT line (11 total isogenic lines), and examined gene expression and pathological hallmarks of C9 FTD/ALS in neurons differentiated from these lines. Comparing the excisions in these isogenic series removed the confounding effects of different genomic backgrounds and allowed us to probe the effects of specific genomic changes. A coding SNP in the patient cell line allowed us to distinguish transcripts from the normal vs. mutant allele. Using ddPCR, we determined that transcription from the mutant allele is upregulated at least tenfold, and that sense transcription is independently regulated from each allele whereas antisense transcription is regulated by the opposite allele. Surprisingly, excision of the WT allele increased pathologic dipeptide repeat

expression from the mutant allele. Importantly, a single allele was sufficient to supply a normal amount of protein, suggesting that the C9orf72 gene is haplo-sufficient in cells. Excision of the mutant repeat expansion reverted all pathology (RNA abnormalities, dipeptide repeat production and TDP-43 pathology) and improved electrophysiological function, whereas silencing sense expression did not eliminate all DPRs, presumably because of the antisense expression. These data increase our understanding of C9orf72 gene regulation and inform gene therapy approaches, including ASOs and CRISPR gene editing.

Neuroinflammation and Neuroinfection

S. Epidermidis Cerebrospinal Fluid Shunt Infection Induces Transcriptome Changes

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Thousands of CSF shunts are placed each year to treat hydrocephalus, however, this is often complicated by infection. Tragically, these infections are associated with significant long-term neurologic morbidity. The cellular mechanisms underlying this neurologic morbidity are poorly understood. Using single nucleus nuclear RNA sequencing (snRNAseq) we identified acute and chronic transcriptome changes that occur in the brain following CSF shunt infection, providing potential insight into causes of neurologic morbidity. Silicone catheters were precoated with *S. epidermidis* and implanted into the lateral ventricle of the brain in C57BL/6 mice. At days 3 and 56 post-infection brain tissue immediately surrounding the catheter was removed and snap frozen for storage and nuclei isolation. SnRNAseq libraries were generated using the 10x Genomics Chromium Controller and sequenced on a NovaSeq 6000. The R package *Seurat* was used for quality control and to cluster nuclei based on transcriptomic data. Cluster identities were determined by expression of canonical cell-specific genes. Pseudobulk analysis was performed in the R package Libra, allowing identification of differentially expressed genes. Ingenuity Pathway Analysis was used for analysis of canonical pathways and upstream regulators. Twenty-two transcriptomically distinct clusters of nuclei were identified. Differentially expressed genes (DEGs) at day 3 post-infection were observed in both neuronal and glial populations. The top DEGs included genes with known connections to regulation of inflammation and infection (e.g. *Saa3*, *Acod1*, *Atp5g1*). These genes were not differentially expressed at day 56 post-infection. At day 56 post-infection, the majority of DEGs were identified in neuronal clusters. Genes encoding components of the complement system (e.g. *C4b*, *C1qa*, *C1qc*) were upregulated in specific neuronal subtypes. Pathway analysis of DEGs observed at day 56 post-infection also revealed an overrepresentation of genes involved in neuronal development. These data indicate that *S. epidermidis* CSF shunt infection results in both short- and long-term transcriptomic changes that differ by cell population. The identification of DEGs and activated pathways with connections to cognitive function and neuronal development provide potential targets for future work to explore cell type-specific roles in influencing the long-term consequences of pediatric CNS infection.

Brain Capillary Obstruction by Leukocytes is Ameliorated by Integrin Blockade in an Immunocompetent Mouse Model of CAR T Cell Neurotoxicity

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Background: Neurotoxicity, also known as ICANS (Immune Effector Cell associated Neurotoxicity Syndrome) affects 30-50% of patients treated with CAR T cells for hematologic malignancies. SIgns and symptoms include confusion, language disturbance, and in severe cases seizures, coma, and death from fulminant cerebral edema. Systemic cytokine release syndrome (CRS) occurs as CAR T cells rapidly proliferate *in vivo*, and is a key risk factor for ICANS. Despite some evidence that ICANS is a disorder of the blood-brain-barrier, we still do not understand how cytokines and immune cells interact with the neurovascular unit to cause brain dysfunction. We have developed an immunocompetent syngeneic mouse model of CD19-CAR T treatment induced neurotoxicity that shows similar kinetics to patients, with peak neurotoxicity around day 6-7 after CAR T cell infusion. *In vivo* two-photon brain imaging of the microvasculature revealed obstructed blood flow in 11.9% of cortical capillaries during neurotoxicity, compared to 1.1% in controls treated with mock transduced CAR T cells. These obstructions were almost exclusively due to CD45+ leukocytes, 30% of which were CAR T cells. **Research Question:** Can we ameliorate neurotoxicity by reversing capillary leukocyte plugging via disruption of leukocyte-endothelial adhesion? For this study, we focused on the key T cell - endothelial interactions of LFA1/ICAM-1 and VLA4/VCAM-1. **Methods:** Wild type BALB/c mice treated with 10 million murine CD19-CAR T cells or mock transduced T cells received antibodies directed against integrin alpha 4, integrin alphaaz L, or ICAM-1 on days 1,3 and 5 after CAR T cell injection. We performed daily neurologic exams and open field testing on day 5. Brain capillary plugging was assessed *in vivo via* two-photon microscopy of the brain microvasculature through a cranial window, and histologically by quantifying the number of 2-micron fluorescent microspheres that became trapped intravascularly. **Results:** Soluble ICAM-1 and VCAM-1 were increased in blood after CAR T cell treatment, but only ICAM-1 protein was upregulated in brain capillaries. Blockade of integrin alpha 4 resulted in improved spontaneous locomotion on day 5 after CAR T cells (162% of isotype treated controls, P=0.0147) and decreased capillary plugging on day 6 (49.7% of isotype controls, P=0.0179). **Interpretation:** Our data show that CAR T cell treatment increases leukocyte-endothelial interactions, likely by upregulation of adhesion molecules which may be induced by

systemic cytokine release. Blockade of the VLA4/VCAM-1 interaction resulted in improved locomotion and decreased brain capillary plugging, supporting a causative role for leukocyte plugging in the pathogenesis of ICANS.

Satellite Microglia Have a Role in Regulation of Neuronal Excitability and Change in Response to Injury

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Microglia, the primary mediators of innate immune activation in the brain, are increasingly recognized as key modulators of neuronal activity and excitability. There is growing evidence in many neurological diseases, including traumatic brain injury (TBI), that prolonged activation of the innate immune system can impede repair and promote disease, and it is not understood if or how microglia's impact on neuronal activity might contribute. One interesting microglial subtype that may be critical in the monitoring and feedback of neuronal excitability is the perineuronal satellite microglia. These microglia are juxtaposed adjacent to neurons with their soma and processes entwined around the neuronal cell body. To understand how these microglia modify neuronal excitability and change their interactions with neurons after injury, we utilized patch clamp recordings, immunohistochemistry, light microscopy and confocal imaging. We found an increase in the numbers of satellite microglia in the orbitofrontal cortex in both a murine model of TBI that is associated with network hyperexcitability and behavioral dysfunction with deficits in reversal learning several moths after TBI, as well as human tissues from donors with a history of chronic TBI compared to sham and controls, respectively. Whole cell recordings in adult transgenic mice with GFP-labeled microglia (Tmem119-EGFP), utilized to record activity in neurons adjacent to and away from satellite microglia, also indicate that satellite microglia suppress neuronal excitability as measured by the action potential and firing frequency response to a series of depolarizing current steps. However, this effect is lost at chronic time points after TBI. These findings support continued investigation of satellite microglial response and neuronal interaction after chronic injury.

Neuromuscular Disease

Higher Glycemic Index Diet is Associated with Slower Disease Progression in Amyotrophic Lateral Sclerosis

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Objective: Prior studies suggest that high caloric diet may be beneficial in attenuating advancement of amyotrophic lateral sclerosis (ALS), however, key macronutrients have not been identified. We examined whether dietary macronutrient (carbohydrate, protein, and fat) content and glycemic load and index are associated with the rate of progression and length of survival among the ALS Multicenter Cohort Study of Oxidative Stress (COSMOS) study participants. **Methods:** All 358 participants [60% male, mean (SD) age 60 (10) years] with a confirmed diagnosis of sporadic ALS enrolled in COSMOS were included in the current study. We evaluated baseline macronutrient intake in relation to change in total revised ALS functional rating scale (ALSFRS-r), and tracheostomy-free survival using linear regression and Cox proportional hazard models. Baseline age, sex, disease duration, diagnostic certainty, body mass index (BMI), ALSFRS-r, ALSFRS-r bulbar sub-score and forced vital capacity (FVC)) were included as covariates. **Results:** In univariable linear regression, total calories, carbohydrate, protein, or fat intake were not significantly associated with ALSFRS-r change at 3-months. However, baseline higher glycemic index (GI) was associated with slower progression of ALSFRS-r at 3-month follow up such that one unit of GI increase was associated with 0.19 less decline of ALSFRS-r at 3-month follow up (β= -0.19, 95% Confidence Interval (CI) [-0.30, -0.07], p=0.0015). Baseline ALSFRS-r bulbar sub-score was associated with GI and after adjusting for this, GI was still associated independently with 3-month decline of ALSFRS-r. Higher baseline glycemic load was also associated with slower progression of ALSFRS-r at 3-month follow up although the association was weaker than GI and not statistically significant (β= -0.012, 95% Confidence Interval (CI) [-0.02, 0.0002], p=0.05). In a multivariable Cox proportional hazard model, higher GI was associated with longer tracheostomy-free survival (Hazard Ratio 0.96, 95% CI [0.93, 0.99] p=0.03) after adjusting for age, sex, diagnostic certainty, disease duration, bulbar onset, baseline ALSFRS-r total score and FVC. **Conclusion:** Higher dietary GI is associated with slower functional decline and longer survival in patients with ALS.

Pathogenicity of Novel KIF5A Disease Causative Variants

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KIF5A is a neuronal specific subunit of the motor protein, Kinesin-1, which plays key roles in axonal transport and cytoskeletal dynamics. The central question of this project is how mutations in distinct regions of KIF5A lead to divergent clinical phenotypes such as Neonatal Intractable Myoclonus (NEIMY), a severe neonatal myoclonic epilepsy, and Amyotrophic Lateral Sclerosis (ALS), a motor neuron disease. Surprisingly, we found that very similar truncating mutations within the C-terminal domain of KIF5A cause both diseases. We developed *in vitro* models of KIF5A ALS and NEIMY and used these to understand the consequences on cargo transport and the cytoskeletal structure. We found that while both ALS and NEIMY causative mutations disrupt

autoregulation of the protein leading to its sequestration in the distal axon, NEIMY mutations led to more severe accumulation and aggregation. We show that gain of function is the predominant mechanism for both diseases. However, NEIMY aggregates cause cytoskeletal defects and create a physical obstruction to transport in the distal axon near the growth cone. These findings advance our understanding of the mechanistic basis underlying the clinical heterogeneity caused by mutations in KIF5A.

Predictors of Undiagnosed Peripheral Neuropathy in a Predominantly Low-Income, Black U.S. Primary Care Population

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Introduction: Peripheral neuropathy is a disabling, often painful condition associated with falls and increased risk of nontraumatic amputation. There are limited data regarding the prevalence and burden of neuropathy among minoritized U.S. populations where risk factors, namely diabetes, are most common. The Flint Neuropathy Study is an ongoing study assessing gaps in neuropathy diagnosis and risk factor management in a predominantly Black, low-income population.
Methods: We performed a cross-sectional study of patients ≥40 years of age presenting to an outpatient internal medicine clinic in Flint, Michigan. Demographics, clinical characteristics including access to healthcare, medication use, anthropomorphic measurements, fasting lipids, and Hemoglobin A_{1C} were collected. Glucose intolerance was defined using the 2021 ADA diagnosis and classification of diabetes mellitus criteria, whereas metabolic syndrome was defined using the harmonized criteria. Neuropathy was defined using the modified Toronto Clinical Neuropathy Score (mTCNS, cutoff ≥3). Patients with undiagnosed neuropathy were those who met mTCNS criteria but did not have a prior neuropathy diagnosis either by chart review or patient self-report. We examined the association between undiagnosed neuropathy and potential risk factors, including age, race/ethnicity, health insurance status, frequency of healthcare access, metabolic syndrome, undiagnosed glucose intolerance, and presence of neuropathic pain through logistic regression.
Results: We enrolled 200 participants and 169 (85%) completed all data collection. Ninety-three (55%) were female, mean age (SD) was 58.2 years (10.4), 105 (62%) Medicaid, and 116 (69%) non-Hispanic Black race/ethnicity. 135/169 (80%) saw their primary care doctor at least every 4 months. Eight-four (50%) had a history of diabetes. During the study, 3 participants were diagnosed with diabetes and 37 with prediabetes. 114/169 (67%) met criteria for metabolic syndrome. 123/169 (73%) met mTCNS criteria for neuropathy. Of those with neuropathy, 75% were previously undiagnosed and 40% endorsed neuropathic pain. Participants with undiagnosed neuropathy were more likely to be older (mean 61 years vs 55 years, (OR 1.1 [95% CI 1.01-1.1]) than those with diagnosed neuropathy. There were no other significant predictors of undiagnosed neuropathy, including frequency of healthcare access or undiagnosed glucose intolerance.
Conclusions: Despite regular access to primary care, peripheral neuropathy is substantially underdiagnosed in this predominantly Black, low-income population. Age is the only significant predictor of undiagnosed neuropathy; therefore, interventions to reduce the neuropathy diagnostic gap should target the whole population and should not be limited to those with known neuropathy risk factors.

Other

Functional Connectivity in a Mouse Model of Maple Syrup Urine Disease

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Introduction: Maple Syrup Urine Disease (MSUD) is an autosomal recessive disorder caused by an inability to catabolize branched-chain amino acids (BCAAs), resulting in irreversible neurologic injury. Novel, non-invasive, central nervous system biomarkers in MSUD are necessary to understand risk prognostication and guide timing of therapy. Structural MRI of MSUD patients has demonstrated brain edema in areas of active myelination along with decreases in white matter integrity, particularly during metabolic crises. No prior studies have used functional neuroimaging methods to assess network function in MSUD. In this collaboration between two junior faculty laboratories, we hypothesized that mice with a model of MSUD would show deficits in resting-state functional connectivity (RSFC) during metabolic crisis as assessed using widefield optical imaging (WOI). **Methods:** All procedures were approved by the institutional animal care and use committee at the Children's Hospital of Philadelphia. An astrocyte-specific model of MSUD was created by crossing a floxed DBT allele (DBT-flox/flox) with hemizygous GFAP-Cre+/- mice to mimic abnormal BCAA catabolism in the brain. 23 mice (10 control, 13 DBT-/-) were studied. Serial hemodynamic WOI was performed starting at age 8 weeks. After 8 days, mice were changed to a high-protein diet for one week. WOI data consists of images of the dorsal surface of the mouse brain, viewed from above; all analysis was performed on changes in the concentration of total hemoglobin filtered to 0.01 to 0.1 Hz. Seed-based RSFC analysis (14 seeds) was performed. RSFC maps were compared between groups at both the pre- and post-diet timepoint using pixel-wise t-tests and cluster-based inference (cluster-defining

threshold |t|>3). Significance was determined using permutation inference (10,000 permutations and a nominal familywise error rate of 0.05). All analysis was performed using custom-written code in MATLAB. **Results:** All mice exhibited the expected canonical RSFC networks at both time-points. No significant differences were seen at the pre-diet timepoint. After a week on the high-protein diet, DBT -/- mice showed increased RSFC strength between posterior somatosensory seeds and the contralateral hemisphere (right seed, p=0.018; left seed: p=0.017). None of the other 12 seeds showed statistically significant differences between groups. **Conclusions:** Contrary to expectations, we found that mice with an astrocyte-specific knock-out displayed increased RSFC strength between the posterior somatosensory cortex and the contralateral hemisphere. The etiology of increased FC strength and its location is unclear. Of note, this is a mild model of MSUD with changes in brain biochemistry and EEG, but no behavioral phenotype. Correlation with more severe models may yield additional insights.

Strategies to Increase Retention of Research Participants in Community Based Research

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Background: Strategies are needed to increase participant retention in research. Our objective was to identify practices to increase retention of research participants in a primarily Black American community. **Methods:** We randomized participants to education on stroke signs and calling 911 (intervention) or stroke primary prevention (control). Participants were contacted by postcard, phone, and text to schedule one-month follow-up visits. After 4 months of recruitment, the incentive was changed from $20 (each visit) to $10 (first visit) and $30 (follow-up visit). **Results:** There were 126 participants randomized to the intervention (52% Black American) and 128 participants randomized to the control (48% Black American) group. 31.4% of contacted participants were lost to follow-up. Of those, 37.7% had received the intervention and 62.3% had received the control condition. Compared to retained participants, participants lost to follow-up did not differ in age (mean age ± standard deviation of 41.5 ± 17.0 lost to follow-up vs. 48.2 ± 16.3 retained participants) or sex (31.2% of women were lost to follow-up vs 31.6% of men were lost to follow-up), but differed in race (26.6% of Black participants were lost to follow-up vs. 32.9% of White participants were lost to follow-up). After adjusting the incentive, monthly retention increased from 53% to 69%. More participants chose a virtual rather than in-person follow-up visit (56.8% virtual). **Conclusions:** The following practices might increase retention: a higher incentive at follow-up than at baseline, and providing the option to follow-up virtually. Future research should investigate additional practices to increase participant retention.

Inhibition of Impulsive Actions in Huntington Disease

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Background: Impulsivity is a common clinical feature of Huntington disease (HD), but the underlying cognitive dynamics of impulse control in this population have not been well-studied. **Objective:** To investigate the temporal dynamics of impulse control in HD patients using an inhibitory action control task. **Methods:** Sixteen motor manifest HD patients and seventeen age-matched healthy controls (HC) completed the Simon action control task. We applied the activation-suppression theoretical model and distributional analytic techniques to differentiate the strength of fast impulses from their top-down suppression. **Results:** Overall, HD patients produced slower and less accurate reactions than HCs. HD patients also exhibited an exacerbated interference effect, as evidenced by a greater slowing of RT on non-corresponding compared to corresponding trials (HD: 64 ms; HC: 25 ms; motor conflict x group: RT, $F[1,29] = 17.00$, $p = 0.000$). HD patients made more fast, impulsive errors than HC, evidenced by significantly lower accuracy on their fastest reaction time trials (HD: 0.78; HC: 0.92; $F[1,29] = 6.193$, $p = 0.019$). The slope reduction of interference effects as reactions slowed was similar between HD and controls, indicating preserved impulse suppression. **Conclusions:** Our results indicate that patients with HD show a greater susceptibility to act rapidly on incorrect motor impulses but preserved proficiency of top-down suppression. Further research is needed to determine how these findings relate to clinical behavioral symptoms.

Sleep Disorders and Circadian Rhythms

Local Changes in Sleep Oscillations after Stroke

***Eric C. Landsness, MD PhD**, Hanyang Miao, BS, Wei Chen, BS, Michelle Tang, BS, Spencer Blackwood, BS, Jonah Padawer-Curry, BS, Joe Culver, PhD, Adam Q. Bauer, PhD, Jin Moo Lee, MD PhD. Washington University - St. Louis, Saint Louis, MO, USA.*

Ischemic stroke disrupts neuronal activity, but the effect of stroke on sleep oscillations and their change over the course of recovery is unclear. To study changes in sleep oscillations, we used wide-field optical fluorescence imaging in mice expressing the genetically encoded calcium indicator GCaMP6 in excitatory cortical neurons fitted with plexiglass whole-cortex cranial windows. Sleep was recorded in the head-fixed position before and 24 hours, 1 week, and 4 weeks after photothrombotic stroke over the

left somatosensory (forepaw) cortex. Acutely (24 hours) following stroke, mice exhibited a loss of broadband neuronal activity over and around the region of ischemia in NREM and REM sleep that was not present to the same degree as wakefulness. In the subacute period following a stroke, we observed a sleep-independent emergence of a new, local slow oscillation (S.O.) at 1 week that renormalized over time. These local, time-dependent changes in neuronal activity and oscillations were predictive of residual stroke size in the chronic (8 weeks) period. Manipulating sleep neuronal activity or oscillations in a local- and time-specific manner may have clinical utility by altering the course of stroke recovery.

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Friday Networking Table Assignments

First Name	Last Name	INSTITUTION	Table 1	Table 2
Laura	Adang	Children's Hospital of Philadelphia	5	5
Farwa	Ali	Mayo Clinic	5	8
Benedict	Alter	University of Pittsburgh	8	7
Defne	Amado	University of Pennsylvania	4	5
Bhooma	Aravamuthan	Washington University in St. Louis	9	6
Umeshkumar	Athiraman	Washington University in St. Louis	4	2
Fiona	Baumer	Stanford University School of Medicine	5	3
David	Bearden	University of Rochester	7	7
David	Benavides	University of Maryland School of Medicine	3	1
Matthew	Bevers	Brigham and Women's Hospital	5	2
Philip	Boone	Massachusetts General Hospital	3	5
Jonathan	Brent	Northwestern University	2	9
Matthew	Brier	Washington University in St. Louis	8	1
Claire	Clelland	University of California, San Francisco	4	5
Melissa	Cortez	University of Utah	7	4
Vishnu	Cuddapah	Children's Hospital of Philadelphia	3	3
Andrew	Edmondson	Children's Hospital of Philadelphia	2	5
Melissa	Elafros	University of Michigan	7	9
Bolanle	Famakin	University of Wisconsin	3	2
Christopher	Favilla	University of Pennsylvania	7	2
Aaron	Gusdon	University of Texas Health Science Center	9	4
Juliane	Gust	Seattle Children's	2	1
Christa	Habela	Johns Hopkins University	2	3
Christopher	Hemond	University of Massachusetts	6	1
H. E.	Hinson	University of California, San Francisco	6	4
Brandon	Holmes	University of California, San Francisco	1	6
Jennifer	Kim	Yale University	8	4
Michael	Kornberg	Johns Hopkins	1	1
Vijay	Krishanmoorthy	Duke University	5	4
Michelle	Kvalsund	University of Rochester Medical Center	8	7
Eric	Landsness	Washington University in St. Louis	1	9
Ikjae	Lee	Columbia University Irving Medical Center	5	9
Baijayanta	Maiti	Washington University in St. Louis	9	8
Katherine	McDonnell		9	6
Christopher	McGraw	Mass General Hospital	4	3
Jana	Mike	University of California, San Francisco	2	2
Hiroki	Nariai	University of California, Los Angeles	7	3
Elizabeth	Newell	University of Iowa Carver College of Medicine	4	4
Evan	Noch	Weill Cornell Medicine	3	8
Amber	Nolan	University of Washington	4	1
Temitayo	Oyegbile-Chidi	University of California, Davis	6	3
Chia-Ling	Phuah	Washington University School of Medicine	9	2
Elizabeth	Pierpont	University of Minnesota	7	6

Friday Networking Table Assignments (Continued)

First Name	Last Name	INSTITUTION	Table 1	Table 2
Jessica	Rexach	University of California, Los Angeles	4	6
David	Robinson	University of Cincinnati	6	2
Altaf	Saadi	Massachusetts General Hospital/Harvard	5	7
Andrea	Schneider	University of Pennsylvania	8	4
Gwenn	Skar	University of Nebraska Medical Center	1	1
Mellanie	Springer	University of Michigan	9	9
Andrew	Stern	Brigham and Women's Hospital	1	6
Brian	Theyel	Brown University	1	3
Sara	Trowbridge	Boston Children's Hospital/Harvard	2	6
Jeff	Waugh	University of Texas Southwestern	6	8
Brian	White	Children's Hospital of Philadelphia	3	9
Kellen	Winden	Boston Children's Hospital	1	5
Yohannes	Woldeamanuel	Stanford University School of Medicine	9	7
John	Younce	University of North Carolina at Chapel Hill	8	8
Sahar	Zafar	Massachusetts General Hospital	6	4

Saturday – Breakout #1 Assignments

First Name	Last Name	Saturday Breakout #1	Room Name	Saturday Breakout #1 (Mentors)
Jonathan	Brent	1	Conference Room 408	Seeley, Lee
Brandon	Holmes	1	Conference Room 408	Seeley, Lee
Evan	Noch	1	Conference Room 408	Seeley, Lee
Andrew	Stern	1	Conference Room 408	Seeley, Lee
Sara	Trowbridge	1	Conference Room 408	Seeley, Lee
Umeshkumar	Athiraman	2	Conference Room 408	Standaert, Carmichael
Vishnu	Cuddapah	2	Conference Room 408	Standaert, Carmichael
Bolanle	Famakin	2	Conference Room 408	Standaert, Carmichael
Aaron	Gusdon	2	Conference Room 408	Standaert, Carmichael
Jana	Mike	2	Conference Room 408	Standaert, Carmichael
Benedict	Alter	3	Conference Room 408	Ances, Schambra
Matthew	Brier	3	Conference Room 408	Ances, Schambra
Christopher	Hemond	3	Conference Room 408	Ances, Schambra
Elizabeth	Pierpont	3	Conference Room 408	Ances, Schambra
Yohannes	Woldeamanuel	3	Conference Room 408	Ances, Schambra
Melissa	Elafros	4	Conference Room 409	Gutmann, Leslie-Mazwi
Ikjae	Lee	4	Conference Room 409	Gutmann, Leslie-Mazwi
David	Robinson	4	Conference Room 409	Gutmann, Leslie-Mazwi
Altaf	Saadi	4	Conference Room 409	Gutmann, Leslie-Mazwi
Andrea	Schneider	4	Conference Room 409	Gutmann, Leslie-Mazwi
Farwa	Ali	5	Conference Room 409	Hamilton, Vickrey
Baijayanta	Maiti	5	Conference Room 409	Hamilton, Vickrey
Katherine	McDonnell	5	Conference Room 409	Hamilton, Vickrey
Jeff	Waugh	5	Conference Room 409	Hamilton, Vickrey
John	Younce	5	Conference Room 409	Hamilton, Vickrey
David	Benavides	6	Conference Room 409	Sansing, Paulson
Juliane	Gust	6	Conference Room 409	Sansing, Paulson
Michael	Kornberg	6	Conference Room 409	Sansing, Paulson
Amber	Nolan	6	Conference Room 409	Sansing, Paulson
Jessica	Rexach	6	Conference Room 409	Sansing, Paulson
Gwenn	Skar	6	Conference Room 409	Sansing, Paulson
Bhooma	Aravamuthan	7	Conference Room 411	Nelson, Paredes
Christa	Habela	7	Conference Room 411	Nelson, Paredes
Christopher	McGraw	7	Conference Room 411	Nelson, Paredes
Elizabeth	Newell	7	Conference Room 411	Nelson, Paredes
Brian	Theyel	7	Conference Room 411	Nelson, Paredes
Kellen	Winden	7	Conference Room 411	Nelson, Paredes

Saturday – Breakout #1 Assignments (Continued)

First Name	Last Name	Saturday Breakout #1	Room Name	Saturday Breakout #1 (Mentors)
Laura	Adang	8	Conference Room 411	Feldman, Schor
Defne	Amado	8	Conference Room 411	Feldman, Schor
Philip	Boone	8	Conference Room 411	Feldman, Schor
Claire	Clelland	8	Conference Room 411	Feldman, Schor
Andrew	Edmondson	8	Conference Room 411	Feldman, Schor
Brian	White	8	Conference Room 411	Feldman, Schor
Matthew	Bevers	9	Conference Room 411	Greer, McCullough
Mellanie	Springer	11	Conference Room 412	Greer, McCullough
H. E.	Hinson	9	Conference Room 411	Greer, McCullough
Vijay	Krishanmoorthy	9	Conference Room 411	Greer, McCullough
Eric	Landsness	9	Conference Room 411	Greer, McCullough
Fiona	Baumer	10	Conference Room 412	Jensen, Geocadin
Jennifer	Kim	10	Conference Room 412	Jensen, Geocadin
Hiroki	Nariai	10	Conference Room 412	Jensen, Geocadin
Temitayo	Oyegbile-Chidi	10	Conference Room 412	Jensen, Geocadin
Sahar	Zafar	10	Conference Room 412	Jensen, Geocadin
David	Bearden	11	Conference Room 412	Hillis, Skolarus
Melissa	Cortez	11	Conference Room 412	Hillis, Skolarus
Christopher	Favilla	9	Conference Room 411	Hillis, Skolarus
Michelle	Kvalsund	11	Conference Room 412	Hillis, Skolarus
Chia-Ling	Phuah	11	Conference Room 412	Hillis, Skolarus

Saturday – Breakout #2 Assignments

First Name	Last Name	Saturday Breakout #2	Room Name	Saturday Breakout #2 (Mentors)
David	Robinson	1	Conference Room 408	Geodacin, Greer
Andrea	Schneider	1	Conference Room 408	Geodacin, Greer
H. E.	Hinson	1	Conference Room 408	Geodacin, Greer
Vijay	Krishanmoorthy	1	Conference Room 408	Geodacin, Greer
Sahar	Zafar	1	Conference Room 408	Geodacin, Greer
Melissa	Cortez	1	Conference Room 408	Geodacin, Greer
Baijayanta	Maiti	2	Conference Room 408	Stacey, Leslie-Mazwi
Fiona	Baumer	2	Conference Room 408	Stacey, Leslie-Mazwi
Jennifer	Kim	2	Conference Room 408	Stacey, Leslie-Mazwi
Hiroki	Nariai	2	Conference Room 408	Stacey, Leslie-Mazwi
Temitayo	Oyegbile-Chidi	2	Conference Room 408	Stacey, Leslie-Mazwi
Brandon	Holmes	3	Conference Room 408	Sansing, Ances
Aaron	Gusdon	3	Conference Room 408	Sansing, Ances
Jeff	Waugh	3	Conference Room 408	Sansing, Ances
David	Benavides	3	Conference Room 408	Sansing, Ances
Laura	Adang	3	Conference Room 408	Sansing, Ances
Matthew	Bevers	3	Conference Room 408	Sansing, Ances
Christopher	Hemond	4	Conference Room 409	Gutmann, Hamilton
Elizabeth	Pierpont	4	Conference Room 409	Gutmann, Hamilton
Farwa	Ali	4	Conference Room 409	Gutmann, Hamilton
Katherine	McDonnell	4	Conference Room 409	Gutmann, Hamilton
John	Younce	4	Conference Room 409	Gutmann, Hamilton
David	Bearden	4	Conference Room 409	Gutmann, Hamilton
Melissa	Elafros	5	Conference Room 409	Vickrey, Skolarus
Ikjae	Lee	5	Conference Room 409	Vickrey, Skolarus
Altaf	Saadi	5	Conference Room 409	Vickrey, Skolarus
Christopher	Favilla	5	Conference Room 409	Vickrey, Skolarus
Michelle	Kvalsund	5	Conference Room 409	Vickrey, Skolarus
Evan	Noch	6	Conference Room 409	Hillis, Schambra
Benedict	Alter	6	Conference Room 409	Hillis, Schambra
Yohannes	Woldeamanuel	6	Conference Room 409	Hillis, Schambra
Gwenn	Skar	6	Conference Room 409	Hillis, Schambra
Mellanie	Springer	6	Conference Room 409	Hillis, Schambra
Jonathan	Brent	7	Conference Room 411	Feldman, Ross
Sara	Trowbridge	7	Conference Room 411	Feldman, Ross
Bhooma	Aravamuthan	7	Conference Room 411	Feldman, Ross
Claire	Clelland	7	Conference Room 411	Feldman, Ross
Andrew	Edmondson	7	Conference Room 411	Feldman, Ross

Saturday – Breakout #2 Assignments (Continued)				
First Name	**Last Name**	**Saturday Breakout #2**	**Room Name**	**Saturday Breakout #2 (Mentors)**
Bolanle	Famakin	8	Conference Room 411	Standaert, Lee
Jana	Mike	8	Conference Room 411	Standaert, Lee
Jessica	Rexach	8	Conference Room 411	Standaert, Lee
Christopher	McGraw	8	Conference Room 411	Standaert, Lee
Brian	Theyel	8	Conference Room 411	Standaert, Lee
Umeshkumar	Athiraman	9	Conference Room 411	Seeley, Carmichael
Matthew	Brier	9	Conference Room 411	Seeley, Carmichael
Juliane	Gust	9	Conference Room 411	Seeley, Carmichael
Michael	Kornberg	9	Conference Room 411	Seeley, Carmichael
Christa	Habela	9	Conference Room 411	Seeley, Carmichael
Andrew	Stern	10	Conference Room 412	Nelson, McCullough
Amber	Nolan	10	Conference Room 412	Nelson, McCullough
Elizabeth	Newell	10	Conference Room 412	Nelson, McCullough
Brian	White	10	Conference Room 412	Nelson, McCullough
Chia-Ling	Phuah	10	Conference Room 412	Nelson, McCullough
Vishnu	Cuddapah	11	Conference Room 412	Paredes, Paulson
Kellen	Winden	11	Conference Room 412	Paredes, Paulson
Defne	Amado	11	Conference Room 412	Paredes, Paulson
Philip	Boone	11	Conference Room 412	Paredes, Paulson
Eric	Landsness	11	Conference Room 412	Paredes, Paulson

Saturday Poster Tour – Group Assignments & Poster Numbers

First Name	Last Name	Abstract Title	Poster Group	Poster Number	Mentor
Melissa	Elafros	Predictors Of Undiagnosed Peripheral Neuropathy In A Predominantly Low-income, Black U.s. Primary Care Population	1	1	Gutmann
Christopher	Hemond	Longitudinal Clinical Evaluation Of Paramagnetic Rim Lesions In Multiple Sclerosis	1	2	Gutmann
Ikjae	Lee	Higher Glycemic Index Diet Is Associated With Slower Disease Progression In Amyotrophic Lateral Sclerosis	1	3	Gutmann
Mellanie	Springer	Strategies To Increase Retention Of Research Participants In Community Based Research	1	4	Gutmann
Jonathan	Brent	Pathogenicity Of Novel Kif5a Disease Causative Variants	2	5	Ances
Jessica	Rexach	Disease Associated Changes In Neuronal-Glia Interactions Implicates Neuroimmune Inhibition In Tau Dementias	2	6	Ances
Gwenn	Skar	S. Epidermidis Cerebrospinal Fluid Shunt Infection Induces Transcriptome Changes	2	7	Ances
Andrew	Stern	Aqueously Diffusible RNA-bound Amyloid Beta Fibrils From Alzheimer Disease Brain	2	8	Ances
Brian	White	Functional Connectivity In A Mouse Model Of Maple Syrup Urine Disease	2	9	Ances
Fiona	Baumer	Repetitive Transcranial Magnetic Stimulation Modulates Brain Connectivity In Children With Self-limited Epilepsy With Centrotemporal Spikes	3	10	Stacey
Jennifer	Kim	Predicting Post-ischemic Stroke Epilepsy Using Quantitative Markers And Competing Risk Covariates	3	11	Stacey
Hiroki	Nariai	An Unsupervised Learning Approach For Discovering Pathological High-Frequency Oscillations	3	12	Stacey
Temitayo	Oyegbile-Chidi	Characterizing Sleep ArchitectureAnd Its Effects On Cognition In New-onset Temporal Lobe Epilepsy	3	13	Stacey
Matthew	Bevers	Soluble St2 Links Peripheral And Central Innate Immunity After Intraparenchymal Hemorrhage	4	14	Hillis
Christopher	Favilla	Non-invasive Monitoring Of Microvascular Reperfusion During Endovascular Therapy	4	15	Hillis
Eric	Landsness	Local Changes In Sleep Oscillations After Stroke	4	16	Hillis
Chia-Ling	Phuah	Genome-wide Mapping Of WMH Spatial Patterns Reveal Region-specific Association With Blood Pressure	4	17	Hillis
David	Robinson	Unchanging Long-term Case Fatality Rates In A Population-based Stroke Study	4	18	Hillis

Saturday Poster Tour – Group Assignments & Poster Numbers

First Name	Last Name	Abstract Title	Poster Group	Poster Number	Mentor
Umeshkumar	Athiraman	Targeting Microglial Nf-kb To Improve Neurologic Outcomes After Aneurysmal Subarachnoid Hemorrhage	5	19	McCullough
Bolanle	Famakin	Astrocyte TLR4 Signaling Mediates Astrogliosis Following Focal Cerebral Ischemia	5	20	McCullough
Aaron	Gusdon	Systemic Metabolic Alterations After Aneurysmal Subarachnoid Hemorrhage	5	21	McCullough
Jana	Mike	Arginase-1 Microglia And Efferocytosis After Murine Neonatal Brain Hypoxia-ischemia	5	22	McCullough
Elizabeth	Newell	Selective Neuroimmune Modulation By Type I Interferon Drives Neuropathology And Neurologic Dysfunction Following Traumatic Brain Injury	5	23	McCullough
Melissa	Cortez	Symptomatic Baroreflex Abnormalities Following Concussion	6	24	Geocadin
H. E.	Hinson	Biomarkers Associated With Progression Of Intracranial Hemorrhage In The Prehospital TXA For TBI Trial	6	25	Geocadin
Vijay	Krishanmoorthy	Association Of Dexmedetomidine Utilization With Clinical Outcomes Following Moderate-severe Traumatic Brain Injury	6	26	Geocadin
Andrea	Schneider	Head Injury And Cognitive Change Over 30 Years	6	27	Geocadin
Sahar	Zafar	Anti-seizure Medication Safety And Effectiveness In Older Adults With Traumatic Brain Injury	6	28	Geocadin
Farwa	Ali	Domains Of Gait And Balance Impairment In PSP Subtypes	7	29	Nelson
Baijayanta	Maiti	Selection Of White Matter Reference Region In Cholinergic Pet Analyses	7	30	Nelson
Katherine	McDonnell	Inhibition of Impulsive Actions in Huntington Disease	7	31	Nelson
Jeff	Waugh	In Humans, Striato-pallido-thalamic Projections Are Largely Segregated By Their Origin In Either The Striosome Or Matrix Compartments	7	32	Nelson
John	Younce	Quantifying The Value Of Multimodal Mri In Outcomes Prediction For Stn Dbs In Pd	7	33	Nelson
Benedict	Alter	Measuring Descending Pain Modulation With Offset Analgesia And Onset Hyperalgesia In Patients With Chronic Musculoskeletal Pain.	8	34	Vickrey
David	Bearden	Longitudinal Cognitive Outcomes In Children With HIV In Zambia	8	35	Vickrey
Michelle	Kvalsund	Distal Symmetric Polneuropathy Prevalence And Predictors In Urban And Rural Zambia: A Population-based, Cross-sectional Household Survey	8	36	Vickrey
Altaf	Saadi	Clinician And Patient Stakeholder Perspectives On Cognitive Rehabilitation Interventions For Asylum Seekers And Refugees	8	37	Vickrey
Yohannes	Woldeamanuel	Time It Right! The Application Of Circadian Medicine Interventions For The Management Of Migraine.	8	38	Vickrey

Saturday Poster Tour – Group Assignments & Poster Numbers

First Name	Last Name	Abstract Title	Poster Group	Poster Number	Mentor
Laura	Adang	Differential Post-translational Sulfatase Activation Correlates With Disease Severity In Multiple Sulfatase Deficiency	9	39	Seeley
Bhooma	Aravamuthan	Striatal Cholinergic Interneuron Excitation Provokes Dystonia in Mice Following Neonatal Brain Injury	9	40	Seeley
Brandon	Holmes	Amyloid Beta Fibrils Induce Microglial Biosynthesis Of Heparan Sulfate Proteoglycans Leading To Increased Tau Phagocytosis And Seeding	9	41	Seeley
Elizabeth	Pierpont	Diffusion Tensor Imaging Of The Corpus Callosum As An Early Disease Marker In Adrenoleukodystrophy	9	42	Seeley
Sara	Trowbridge	The Role Of Fos And The Baf Complex In Neuronal Activity-dependent Chromatin Remodeling And Gene Expression	9	43	Seeley
Defne	Amado	Improved Survival, Strength, And Neuroinflammation In A Mouse Model Of Sporadic ALS After Novel AAV-mediated Delivery Of RNAi TargetingAtxn2	10	44	Paredes
Philip	Boone	Variants In Cohesin Release Factors Define A Novel Class Of A Cohesin Balance Disorders And Illuminate A Therapeutic Path For Cohesinopathies	10	45	Paredes
Claire	Clelland	Reversal Of C9orf72 Mutation-induced Transcriptional Dysregulation And Pathology In Cultured Human Neurons By Allele-specific Excision	10	46	Paredes
Andrew	Edmondson	Loss Of O-glycosylation Via Neuronal Galnt2 Knock-out In Mice Recapitulates GALNT2-CDG Patient Seizure Phenotype	10	47	Paredes
Kellen	Winden	Increased Degradation Of Fmrp Contributes To Neuronal Hyperexcitability In Tuberous Sclerosis Complex	10	48	Paredes
David	Benavides	Investigations Of Synaptic Signaling Targets Of Human Anti-NMDAR Antibodies	11	49	Sansing
Matthew	Brier	Disrupted Cerebral Metabolism In Multiple Sclerosis	11	50	Sansing
Juliane	Gust	Brain Capillary Obstruction By Leukocytes Is Ameliorated By Integrin Blockade In An Immunocompetent Mouse Model Of CAR T Cell Neurotoxicity	11	51	Sansing
Michael	Kornberg	The PKC Modulator Bryostatin-1 Augments Remyelination Through Therapeutic Targeting Of CNS Innate Immunity	11	52	Sansing
Amber	Nolan	Satellite Microglia Have A Role In Regulation Of Neuronal Excitability And Change In Response To Injury	11	53	Sansing
Vishnu	Cuddapah	Homeostatic Sleep Need Increases Seizure Risk	12	54	Lee
Christa	Habela	Impaired Early Neuronal Development In Vitro And Increased Seizure Susceptibility In Vivo In A Model Of 15q11.2 Related Neurodevelopmental Disorders	12	55	Lee
Christopher	McGraw	Zebrafish Models Of Genetic And Chemical Seizures: Opportunities And Challenges	12	56	Lee
Evan	Noch	Cysteine Induces Mitochondrial Reductive Stress in Glioblastoma through Hydrogen Peroxide Production	12	57	Lee
Brian	Theyel	Frequency-responsive Ectopic Action Potentials In Neocortical Regular Spiking Neurons	12	58	Lee