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Presented by
the Mesulam Center
for Cognitive Neurology
and Alzheimer's Disease

29th Annual Alzheimer Day

Thursday, May 11, 2023 | 9:00 AM - 2:30 PM

Feinberg Pavilion Conference Center
251 E Huron, 3rd Floor
Chicago, IL 60611

ABSTRACT BOOK

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Planning Team

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Nicole Hunt	Phyllis Timpo
Ashley Knight	

Thank you to all Mesulam Center staff and faculty who have made this day a success!

The Mesulam Center appreciates your dedication and commitment to making this day possible.

Schedule of Events

29th Annual Alzheimer Day | Thursday, May 11, 2023

Robert Feinberg Pavilion Conference Center
251 E. Huron St, 3rd Floor

9:00 - 10:00 AM

Registration and Vendor Fair

10:00 - 11:30 AM

Welcome and Center Update

Robert Vassar, PhD

Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease; Davee Professor of Alzheimer Research, Northwestern University Feinberg School of Medicine

Presentation of Marie and Carl Duncan Prize in Memory Research

John Disterhoft, PhD

Associate Director, Ernest J. and Hattie H. Magerstadt Memorial Research Professor Emeritus in Neuroscience, Northwestern University Feinberg School of Medicine

Mendelson Lecture: "New Insights into Alzheimer's Disease: Will They Give Us New Treatments?"

William Jagust, MD

Professor of Neuroscience and Public Health at University of California, Berkeley; Faculty Senior Scientist, Lawrence Berkeley National Laboratory

11:30 - 11:45 AM

Break

11:45 AM - 1:00 PM

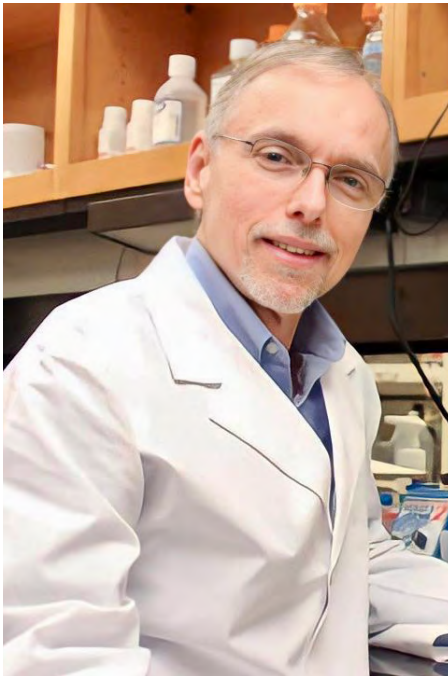
Quality of Life Symposium: "Community-Academic Partnerships in Brain Health and Dementia Research"

Symposium sponsored by the Glen and Wendy Miller Family Foundation.

1:00 - 2:30 PM

Lunch, Research Poster Session, and Vendor Fair

Welcome



Dear Friends and Colleagues:

It is my great pleasure to welcome you to the 29th annual Alzheimer Day. After nearly three decades at the helm, Dr. Marsel Mesulam has stepped down as Director of the Mesulam Center for Cognitive Neurology and Alzheimer's Disease. As of January 1, 2023, I have transitioned to become the new Director of the Mesulam Center. Dr. Mesulam is a giant of the dementia field and has built an extraordinary treasure here at Northwestern. I want to thank him for his leadership of the Center and for his many seminal contributions to the understanding of dementia. I am deeply honored to succeed Dr. Mesulam and lead the Mesulam Center toward its next great achievements. I look forward to working with our faculty, staff, trainees, community, and you all to keep the Center strong and continue its growth into the years ahead.

Mesulam Center Update

You will be pleased to know that the current year has witnessed exceptional growth and progress. Components of the Mesulam Center, including the Alzheimer's Disease Research Center (ADRC), the SuperAging Program, the Primary Progressive Aphasia (PPA) Program, Communication Bridge, the Glen and Wendy Miller Family Buddy Program, the Ken and Ruth Davee Laboratories, the Clinical Trials Program and the Neurobehavior Clinic are all thriving. Communication Bridge, a person-centered, internet-based intervention for individuals with PPA led by Dr. Emily Rogalski, was renewed by the National Institutes of Health (NIH). Additionally, Dr. Borna Bonakdarpour was awarded a grant from the National Endowment for the Arts on the effectiveness of music on anxiety in individuals with mild to moderate Alzheimer's disease.

The ADRC, which Dr. Mesulam founded in 1996 and led for 25 years, continues its sixth cycle of funding for years 25–30 under my leadership and that of Associate Director Dr. Sandra Weintraub. The SuperAging Program, a multi-center consortium under the leadership of Drs. Rogalski and Geula, is advancing our knowledge of superior cognitive aging. The PPA Program, now into years 15–20 (principal investigators: Mesulam and Rogalski), continues progress toward understanding this devastating dementia. We look forward to continuing these iconic research programs of our Center into the years ahead.

The Glen and Wendy Miller Family Buddy Program, that matches persons living with dementia with students and fellows, continues to flourish and expand under the leadership of Dr. Darby Morhardt and her team. The Research Education Component (REC) of our ADRC, led by Dr. Changiz Geula, has continued its mission of training and education. A recent addition to the REC is the Brain Scholars Program, with the goal of training the future research workforce with a concentration on underrepresented groups. In partnership with schools on the Southside of Chicago, this program provides exposure to research and clinical aspects of aging and dementia, and in its short period of operation, has engaged over 60 students from underrepresented groups in activities related to this field. On Saturday, October 8, the Mesulam Center participated in the Alzheimer's Association annual Walk to End Alzheimer's at Soldier Field. We had our largest team yet with 56 participants and raised over \$16,500 to support Alzheimer's and dementia research!

The Mesulam Center Neurobehavior and Memory Clinic on Arkes 13 continues its mandate to serve dementia patients and their families. At the Neurobehavior and Memory Clinic, neurologists, neuropsychologists, psychiatrists, and social workers all work in the same space—a unique situation where care providers can talk to their team members down the hall about patients and get immediate answers. The Neurobehavior and Memory Clinic doubles our space and will enable new and expanded clinical programs.

Recruitments and promotions are central to academic life. I am delighted to report that Dr. Tamar Gefen was named as Clinical Core co-leader of our ADRC. In addition, Dr. Rudolph Castellani was promoted to ADRC Neuropathology Core leader. Both these roles are critical for the Center's research on the causes of dementia. Dr. Borna Bonakdarpour was promoted to Associate Professor of Neurology. Drs. Weintraub and Morhardt were both appointed to the Illinois Supreme Court Commission on Elder Law. Dr. Maureen Daly was named Associate Director of MA and PhD programs in clinical psychology. Dr. Elena Barbieri joined the Mesulam Center as a senior clinical research associate on the PPA team. Last but not least, Dr. Mesulam was honored at the French Society of Neurology Awards with the designation of "Member of Excellence" in recognition of his important contributions to research in neurology.

It is no secret that patient care and basic research on Alzheimer's disease are subject to major social and cultural influences. Health care disparities remain to be addressed more creatively and diversity in research remains a goal to be attained. Phyllis Timpo, senior community engagement coordinator on Dr. Morhardt's team, joined the Center last year to develop relationships in Chicago neighborhoods with high populations of Black older adults. These efforts are critical for participant recruitment into studies to understand why the incidence of dementia is higher among underrepresented groups. Under the guidance of our center administrator, Eskedar Alem, center committees were reactivated and reorganized. These included committees on diversity, equity and inclusion; staff relations; and the Underrepresented Group Recruitment and Retention Taskforce. The Center is committed to addressing diversity and health care disparities into the future.

Alzheimer Day 2023

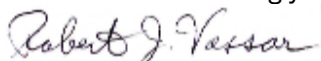
Last year, we returned to an in-person Alzheimer Day event, that over the years has attracted hundreds of participants and featured a procession of world-renowned keynote lecturers. COVID-19 interrupted the tradition in 2020 and 2021, but we have now returned to the excitement of face-to-face interactions and have an action-packed Alzheimer Day event for you, as in years past. This year, Alzheimer Day is also presented as a hybrid event to accommodate those who are unable to attend in person.

Festivities begin with my Welcome and State of the Center Address, followed by the award of the annual Duncan Prize for best Alzheimer Day poster. We then will be honored by Dr. William Jagust from UC Berkely, who will be giving the Mendelson Lecture entitled "New Insights into Alzheimer's Disease: Will They Give Us New Treatments?". Dr. Jagust is a world-leading Alzheimer researcher who uses imaging technologies to understand the changes in the brain that occur during aging and Alzheimer's disease. We are very fortunate to have him with us today to provide his deep insights into this critical question.

Following Dr. Jagust's lecture, we will have our Quality of Life Symposium, "Community-Academic Partnerships in Brain Health and Dementia Research," sponsored by the Glen and Wendy Miller Family Foundation. We have a distinguished panel to discuss topics related to developing a shared vision for Mesulam Center community engagement, how longitudinal investment in minority engagement is critical for dementia research, and celebrate current Mesulam Center community partnerships. The Quality of Life Symposium will conclude with an award presentation to Robin Tillotson, for her partnership with the Mesulam Center as Director for the Atlas Regional Senior Center.

Next, we invite you to enjoy lunch while you peruse the many posters that describe the exciting research that is being conducted at the Mesulam Center. Our researchers, many of whom are our trainees, will be present in front of their posters and would very much appreciate hearing your questions and comments about their work. Be sure also to investigate the vendor fair and our many sponsors who are represented there. We thank them for their generous support.

I look forward to seeing you in-person at the 29th Alzheimer Day festivities!



Robert Vassar, PhD

Davee Professor of Alzheimer Research

Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Thank You



(Left to Right): Sandra Weintraub, PhD, Robert Mendelson, Linda Mendelson, Marsel Mesulam, MD

Mendelson Family

The Mesulam Center for Cognitive Neurology and Alzheimer's Disease would like to thank the Mendelson Family for their generous support of this event.

In honor of Robert and Linda Mendelson's 50th wedding anniversary, David and Blythe Mendelson, Sharon and Scott Markman, and Debbie Mendelson Ponn established the Mendelson Lectureship, which brings a keynote speaker to the Mesulam Center's annual Alzheimer Day.

Miller Family

The Mesulam Center for Cognitive Neurology and Alzheimer's Disease would also like to thank the Miller Family for their generous support of this event.

Since 2008, Glen and Wendy Miller and their daughter Lauren, have supported the Glen and Wendy Miller Family Buddy Program, which was named in their honor in 2021. In addition, they helped establish the Glen and Wendy Miller Family Post Graduate Social Work Fellowship in Neurocognitive Disorders.



(Left to Right): Glen Miller, Wendy Miller, Marsel Mesulam, MD

Thank You

We would like to thank our Platinum, Gold, Silver, and Bronze Sponsors for their support of this event.

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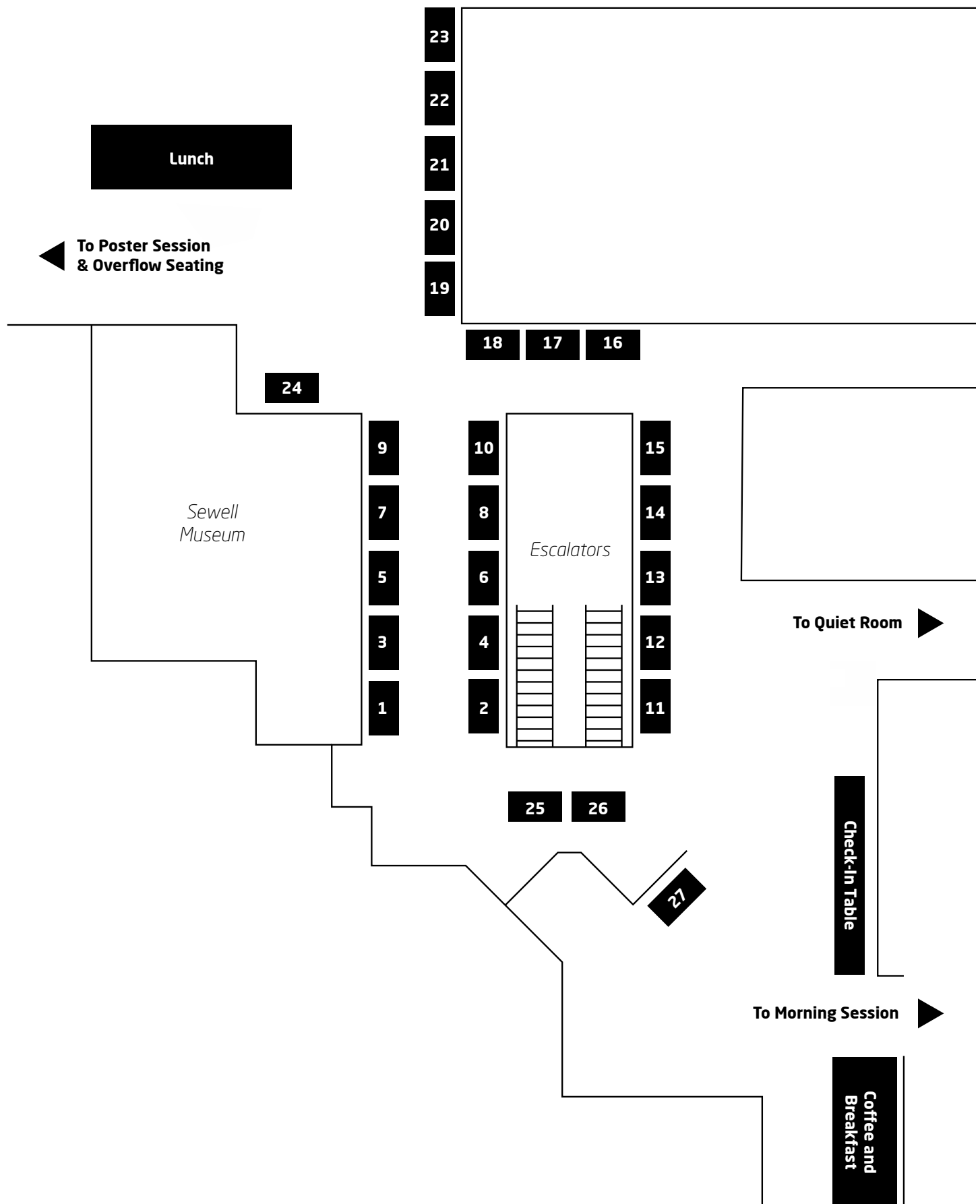
Renewal Memory Partners
Sunrise Senior Living
TheKey
Transitions Care

List of Vendors by Number

The numbers of each vendor correspond to the Map of Vendor Fair on the next page.

- | | |
|--------------------------------------------------------|----------------------------------------------------------------------------------------|
| 1. Peck Ritchey, LLC | 17. TheKey |
| 2. Eli Lilly and Company | 18. Transitions Care |
| 3. Belmont Village Senior Living - Lincoln Park | 19. Illinois Cognitive Resources Network / Dementia Friendly Communities |
| 4. Clarendale Six Corners | 20. South Loop Village, Skyline Village, Edgewater Village |
| 5. Elderwerks Educational Services | 21. Hyde Park Village and Village Chicago |
| 6. Maple Glen | 22. Far South Chicago Coalition |
| 7. Alzheimer's Association IL Chapter | 23. All of Us Research Program |
| 8. Artis Senior Living | 24. Northwestern Music and Medicine Program |
| 9. Centers for Cognitive Wellness | 25. Northwestern Mesulam Center for Cognitive Neurology and Alzheimer's Disease |
| 10. CJE SeniorLife | 26. Northwestern Mesulam Center Research |
| 11. Chicago Methodist Senior Services | 27. Poster Presenter Check-In and CEU Information |
| 12. Home Instead Senior Care | |
| 13. Norridge Gardens | |
| 14. Open Arms Solutions | |
| 15. Renewal Memory Partners | |
| 16. Sunrise Senior Living | |

Map of Vendor Fair



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Welcome & Center Update



Robert Vassar, PhD

Director of the Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Davee Professor of Alzheimer Research

Director of the Northwestern Alzheimer's Disease Research Center

Scientific Director of Behavioral Neurology, Department of Neurology, Northwestern University

Robert Vassar is the Davee Professor of Alzheimer Research, Departments of Neurology and Cell and Developmental Biology at the Feinberg School of Medicine, Northwestern University. He is Director of the Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Scientific Director of the Division of Behavioral Neurology, and Director of the Northwestern NIH-funded P30 Alzheimer's Disease Research Center. He serves on the Cure Alzheimer's Fund Research Strategy Planning Committee, the Board of Directors of the International Society of Molecular Neurodegeneration, the Dominantly Inherited Alzheimer's Network Trials Unit Therapy Evaluation Committee, and he is a member of the Cure Alzheimer's Fund Research Leadership Group.

He has received the MetLife Foundation Award for Medical Research in Alzheimer's Disease, the Potamkin Prize from the American Academy of Neurology, and the Zenith Fellows Award from the Alzheimer's Association. He is a Fellow of the American Association of the Academy of Science and a member of the Dana Alliance for Brain Initiatives. He is on the Scientific Advisory Board of Alector, Inc., and is an Associate Editor of the journal *Molecular Neurodegeneration*.

Dr. Vassar received his PhD in 1992 in molecular genetics and cell biology in the lab of Dr. Elaine Fuchs at the University of Chicago studying transgenic mouse models of human epidermal disease. He did his postdoctoral fellowship in the lab of Dr. Richard Axel at Columbia University, New York, where he investigated the molecular neurobiology of olfaction. His scientific discoveries in Dr. Axel's lab contributed to the Nobel Prize in Physiology or Medicine in 2004 to Dr. Axel.

After his postdoc, he joined the biotechnology company Amgen to start a research group to identify novel drug targets for Alzheimer's disease. Using an expression cloning approach, he and his team co-discovered the beta-secretase enzyme, beta-site amyloid precursor protein cleaving enzyme-1 (BACE1) that is essential for generating the Aβ peptide that makes amyloid plaques, a primary lesion of the Alzheimer's brain.

In 2001, Dr. Vassar moved to the Northwestern University Feinberg School of Medicine, where he invented the 5XFAD transgenic mouse model of amyloid pathology in the Alzheimer's brain. He continues to explore molecular and cellular mechanisms of Alzheimer's disease using genetic, biochemical, and physiological approaches. His trainees in basic neuroscience and neurodegeneration research lead major research academic and industrial programs in the United States and abroad.

Presentation of Duncan Prize



John Disterhoft, PhD

*Associate Director, Ernest J. and Hattie H. Magerstadt Memorial
Research Professor Emeritus in Neuroscience, Feinberg School
of Medicine*

John Disterhoft and his laboratory group are studying the neurobiology of associative learning in the young and aging mammalian brain with in vivo and in vitro techniques using eyeblink conditioning and spatial learning as behavioral model systems.

Many of their ongoing experiments focus on the hippocampus, a paleocortical region involved in transferring information during learning from short- to long-term memory storage. Single-neuron ensemble recording in the conscious animal is used to localize and functionally characterize the cell types involved in laying down the “memory trace” in the hippocampus and associated medial temporal lobe regions. In parallel experiments, biophysical measurements are made from brain slices taken from trained animals to define ionic mechanisms for the conditioning-specific alterations in postsynaptic intrinsic currents that have been observed. Synaptic alterations related to conditioning are also being explored in brain

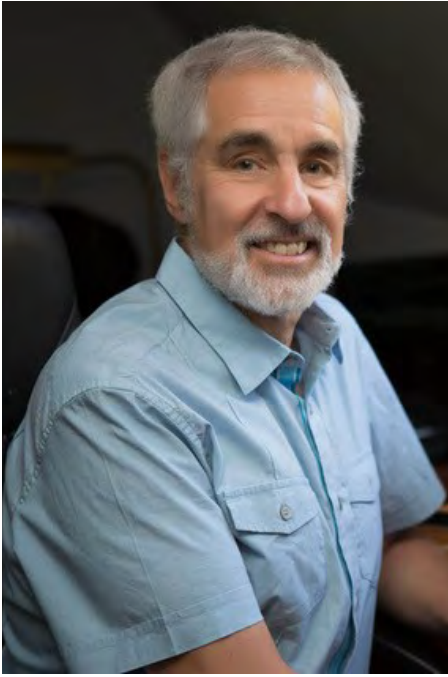
slices. Cellular and systems alterations in aging brain that may underlie learning deficits and agents which may be useful in enhancing learning rates in aging are being studied.

An overall goal of their studies is to understand both the mechanisms of learning and of memory storage and how those mechanisms are altered in cognitively intact “SuperAger” rats as compared to cognitively impaired aging animals. Hippocampus is especially involved in the initial acquisition of associative tasks. More permanent memory storage occurs in other brain regions after a process called memory consolidation. Some of their recent experiments are focusing on the manner that lateral entorhinal cortex and dentate gyrus change during both initial learning and after longer term storage of the eyeblink conditioned response. After regions are defined that store memories of the conditioned response after consolidation, more focused cellular and molecular studies can be done to characterize how this storage occurs at the subcellular level. Collaborative experiments are being done with mass spectroscopy to determine if cognitively intact aging animals show a different pattern of protein expression from cognitively impaired aging animals, as well as from a transgenic rat model of Alzheimer’s Disease.

The portion of Dr. Disterhoft’s research program investigating slow outward currents during learning in aging received two consecutive MERIT award designations from the National Institute on Aging (NIA). His laboratory is collaborating with Dr. Joel Voss’ laboratory at the University of Chicago to investigate the mechanisms of learning enhancement after transcranial magnetic stimulation in both humans and a preclinical animal model.

Dr. Disterhoft is Associate Director of the Northwestern University Alzheimer’s Disease Research Center, Executive Director of the Northwestern University Behavioral Phenotyping Core and Director of the Northwestern University Postbaccalaureate Research Education Program (PREP).

Mendelson Lecture



"New Insights into Alzheimer's Disease:
Will They Give Us New Treatments?"

William Jagust, MD

Professor of Neuroscience and Public Health at University of California, Berkeley

Faculty Senior Scientist, Lawrence Berkeley National Laboratory


William Jagust is a professor of public health and neuroscience at the University of California, Berkeley, and a faculty senior scientist at Lawrence Berkeley National Laboratory. He was previously the Chair of the Department of Neurology at the University of California, Davis and founding director of the UC Davis Alzheimer's Disease Center.

Dr. Jagust's career has been focused on understanding the aging brain, and particularly the borderland between normal cognitive aging and Alzheimer's disease. His laboratory has pioneered the use of multimodal imaging to understand brain aging and Alzheimer's disease, employing positron emission tomography (PET) to measure β -amyloid and tau proteins in the brain, and magnetic resonance

imaging (MRI) to investigate how these protein aggregates affect neural function and structure.

He has served on editorial boards of major journals, advisory boards to the National Institute on Aging, and to the pharmaceutical industry. His laboratory leads the PET component of numerous multi-center studies including the Alzheimer's Disease Neuroimaging Initiative, the POINTER imaging study, SCAN, and the HEAD project.

He is a recipient of the 2013 Potamkin Prize for Research in Pick's, Alzheimer's and Related Diseases.



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Quality of Life Symposium

"Community-Academic Partnerships in Brain Health and Dementia Research"

Welcome and Introduction

Darby Morhardt, PhD, LCSW

Panel Discussion

Moderator: Darby Morhardt, PhD, LCSW

Panelists: Jen Brown, MPH; Tonya Roberson, PhD, MPH, DTR; Emily Rogalski, PhD; Phyllis Timpo, MS; Janie Urbanic, MA, LPC

Community Conversation

Honoring Mesulam Center Community Partner Robin Tillotson, AM

Darby Morhardt, PhD, LCSW and Sandra Weintraub, PhD



Robin Tillotson, AM

Former Director, Francis J. Atlas Regional Senior Center; Regional Director, Chicago Department of Family and Support Services

Robin Tillotson has a diverse background in training and development, advertising and public relations. However, it was her role as Regional Director at the Chicago Department of Aging and through the Chicago Department of Family Support Services, that she truly found her passion.

During her tenure, specifically at the Atlas Senior Center, she oversaw center operations, programming, community engagement, information and assistance, along with nutrition programs and overall service delivery. She is extremely proud that she has worked with the Mesulam Center during her time with the city.

She has always maintained a particular interest in intergenerational programs and policies, and she has served on a number of committees and co-chaired conferences centered around this important element of work with seniors. Her work in this practice area was nurtured and honed through her mentors at Generations United in Washington, D.C.

Robin is a proud graduate of Englewood High School, Oberlin College (Ohio), and The University of Chicago Crown Family School of Social Work, Policy and Practice.

Robin is an avid traveler; she has been on every continent except Antarctica, and she can assure you that she will not be going there.

Robin is now actively engaged in developing travel programs for women age 50+, through the creation of an exciting business called *This I Do For Me*. She will also be embarking on creating travel experiences for marginalized youth where seniors will serve as mentors. She is proud that these endeavors allow her to utilize her clinical social work skills.

Robin lives by a quote from Erica Jong — "I haven't been everywhere, but it's on my list."

Quality of Life Symposium



Jen Brown, MPH

Co-Founder & Co-Director of the Alliance for Research in Chicagoland Communities (ARCC), Northwestern University

Jen Brown is the Co-Founder & Co-Director of the Alliance for Research in Chicagoland Communities (ARCC) at Northwestern University. She is passionate about ARCC's work to grow and support authentic community-academic research partnerships that honor, are driven by, and share power with communities to improve health and equity.

Jen has over two decades of experience building and supporting community and patient engagement in research at project, institutional, and multi-institutional levels through infrastructure development, partnership brokering, capacity-building, seed grants, and advocacy. She is on faculty at Northwestern's Feinberg School of Medicine Department of Preventive Medicine and affiliate faculty of the Center for Native American & Indigenous Research.

Jen currently serves as Co-Chair of the Patient Engagement Advisory Panel for the Patient-Centered Outcomes Research Institute, and as member of the Chicago Consortium for Community Engagement, Partnership for Healthy Chicago, 2020 inductee into the Gold Humanism Honor Society, and was a Chicago United for Equity 2019 Racial Justice Fellow.



Darby Morhardt, PhD, LCSW

Research Professor, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Darby Morhardt, PhD, LCSW is a Research Professor, Mesulam Center for Cognitive Neurology and Alzheimer's Disease and Department of Preventive Medicine (Public Health Practice), Northwestern University Feinberg School of Medicine. Dr. Morhardt directs the Mesulam Center's Outreach, Recruitment and Engagement Core, Clinical Social Work Services, Quality of Life Initiatives, and the Miller Post-Graduate Social Work Fellowship in Neurocognitive Disorders.

Areas of research include the experience of families living with dementia; the process of tailoring care to specific needs and symptoms; and the development and evaluation of quality-of-life enrichment interventions, including the Buddy Program, an experiential learning program for first year medical students and persons living with dementia which has been replicated internationally.

Dr. Morhardt has a long history of community engaged research partnerships to address inequities in dementia education, awareness, research participation and quality of life enhancing programs throughout Chicago especially with underrepresented groups.

Dr. Morhardt has been appointed to the State of Illinois Alzheimer's Disease Advisory Committee since 2000 and has contributed to the writing of the Illinois Alzheimer's Disease State Plan. She was a founding leader of the Illinois Cognitive Resources Network which is currently coordinating state-wide efforts for workforce development in cognitive disorders and the creation of dementia friendly communities. Dr. Morhardt was recently appointed to the Illinois Supreme Court Commission on Elder Law, tasked with helping the Illinois Supreme Court more effectively address the needs and legal issues of older adults, particularly those living with dementia, and their families.

Quality of Life Symposium



Tonya Roberson, PhD, MPH, DTR

President, Far South Chicago Coalition & Director of Community Engagement, Program Development and Academic Success / Adjunct Faculty in the College of Health and Human Services, Governor's State University

Dr. Tonya S. Roberson is a Community Psychologist currently working in the role of Director of Community Engagement, Program Development and Academic Support at Governors State University in the College of Health and Human Services. She is also and the CEO/Founder of Helping Communities Help Themselves and the Community Investigator with Dr. Rachel O'Connor of It's a Family Affair: Development of a Family-Centered Dementia Caregiving Program which is supported by Alliance for Research in Chicagoland Communities.

Dr. Roberson's work is deeply rooted in the overall health and well-being of communities and has made important contributions to the field. She has vast knowledge in biomedical research, culturally tailoring initiatives, community

engagement, health education, and disease prevention.

Dr. Roberson has a particular expertise in methods to address social determinants of health inequities to achieve better population health of Blacks in the urban centers. Dr. Roberson is well connected and trusted in the Chicagoland and Southland communities and many other large US cities. She is committed to giving generously of her time and talents through her community organizing efforts and outreach work to educate, empower, and inspire individuals to be their own advocate for their health.

Dr. Roberson is the caregiver of her 85-year-old mother who has Vascular Dementia and her 86-year-old father who has Alzheimer's disease.



Emily Rogalski, PhD

Associate Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease; Ann Adelman Perkins and John S. Perkins Professor of Alzheimer's Disease Prevention

Dr. Emily Rogalski is a clinical and cognitive neuroscientist, the Ann Adelman Perkins and John S. Perkins Professor of Alzheimer's Disease Prevention, and Associate Director of the Mesulam Center for Cognitive Neurology and Alzheimer's Disease at Northwestern University's Feinberg School of Medicine. She serves as Neuroimaging Biomarker Core Leader of Northwestern's NIA-funded Alzheimer's Disease Research Center (ADRC) and Co-Chair for the Imaging Steering Committee for the national ADRC Network.

Her research falls under the broad umbrella of aging and dementia. Using a multimodal approach, she focuses her investigations on two aging perspectives: primary progressive aphasia (PPA) in which neurodegenerative

disease invades the language network and SuperAging in which individuals are seemingly resistant to the deleterious changes in memory associated with "normal" or more typical cognitive aging. Her PPA research has helped to characterize the clinical and anatomical features of PPA including drivers of disease progression, identification of risk factors, and refinement of our understanding of language network organization. She has also pioneered a line of research concentrated on maximizing care and quality of life for individuals living with PPA and related dementias. She operationalized the SuperAging phenotype and has helped to establish the unique biologic, molecular, genetic, and psychosocial features associated with SuperAging. She currently leads the multisite SuperAging Research Initiative which holds promise for identifying protective factors for avoiding Alzheimer's disease, optimizing health span, and reducing stigma and negative expectations associated with aging.

Quality of Life Symposium



Phyllis Timpo, MS

Senior Community Engagement Coordinator, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Phyllis Timpo, MS is the senior community engagement coordinator at Northwestern University Feinberg School of Medicine's Mesulam Center for Cognitive Neurology and Alzheimer's disease, with 15 years of experience engaging under resourced and disenfranchised communities to achieve health equity. She currently works to diversify research cohorts in National Institute of Aging funded research programs and clinical trials. She works to promote awareness about brain health, healthy aging, and dementia to minoritized populations.

Specializing in facilitating partnerships between minority communities and academic research institutions, Phyllis works to promote health equity among minority older adults who are at risk for age related disease due to social determinants of health such as unequal access to health care, lack of education, stigma, and racism.



Janie Urbanic, MA, LPC

Founding Director, South Loop Village

Janie Urbanic, MA, LPC is the founding director of the South Loop Village, a 501(c)(3) organization with the mission of helping older adults age in community.

After a 30+ year career in marketing and advertising, Ms. Urbanic earned a Master of Gerontological Psychology degree, and started a second career in the research & support of persons living with dementia and their care partners. She spent 12 years at Rush University Medical Center in this field, retiring in 2019 to start the South Loop Village.

The South Loop Village is committed to brain health. In partnership with the Mesulam Center for Cognitive Neurology and Alzheimer's Disease of Northwestern University, the South Loop Village offers activities and educational programs in support of brain health to older adults living in under

resourced communities on Chicago's Southside. To date, this brain health initiative has reached over 600 residents of the South Loop and Bronzeville.

Mesulam Center for Cognitive Neurology and Alzheimer's Disease Faculty Members

Robert Vassar, PhD

Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Davee Professor of Alzheimer Research

Emily Rogalski, PhD

Associate Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Ann Adelman Perkins and John S. Perkins Professor of Alzheimer's Disease Prevention

M. Marsel Mesulam, MD

Founding Director Emeritus, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Ruth Dunbar Davee Professor in Neuroscience and Neurology

Borna Bonakdarpour, MD, FAAN

Assistant Professor of Neurology

Rudolph Castellani, MD

Professor of Pathology

Maureen Daly, PhD

Assistant Professor of Psychiatry and Behavioral Sciences

John Disterhoft, PhD

Research Professor Emeritus in Neuroscience, Feinberg School of Medicine

Ernest J. and Hattie H. Magerstadt Memorial Research Professor of Physiology

Tamar Gefen, PhD

Assistant Professor of Psychiatry and Behavioral Sciences

Changiz Geula, PhD

Research Professor, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Ian Grant, MD

Assistant Professor of Neurology

Adam Martersteck, PhD

Assistant Professor of Radiology

Darby Morhardt, PhD, LCSW

Research Professor, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Fred Osview, MD

Clinical Professor of Psychiatry and Behavioral Sciences

Alfred Rademaker, PhD

Professor Emeritus of Preventive Medicine

Deborah Reed, MD

Assistant Professor of Psychiatry and Behavioral Sciences

Sandra Weintraub, PhD

Professor of Psychiatry and Behavioral Sciences, Psychology, and Neurology

Jana Wingo, PhD

Assistant Professor of Psychiatry and Behavioral Sciences

Hui Zhang, PhD

Professor of Preventive Medicine

Executive Committee

Robert Vassar, PhD

*Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease
Davee Professor of Alzheimer Research*

Emily Rogalski, PhD

*Associate Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease
Ann Adelman Perkins and John S. Perkins Professor of Alzheimer's Disease Prevention*

M. Marsel Mesulam, MD

*Founding Director Emeritus, Mesulam Center for Cognitive Neurology and Alzheimer's Disease
Ruth Dunbar Davee Professor in Neuroscience
and Neurology*

Eskedar Yirga Alem, BS, MSC

Administrator, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

John Disterhoft, PhD

*Research Professor Emeritus in Neuroscience, Feinberg School of Medicine
Ernest J. and Hattie H. Magerstadt Memorial Research Professor of Physiology*

Tamar Gefen, PhD

*Assistant Professor of Psychiatry
and Behavioral Sciences*

Changiz Geula, PhD

Research Professor, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Darby Morhardt, PhD, LCSW

Research Professor, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Sandra Weintraub, PhD

Professor of Psychiatry and Behavioral Sciences, Psychology, and Neurology

Hui Zhang, PhD

Professor of Preventive Medicine

Advisory Board

We would like to graciously thank our Advisory Board, founded and led from 1998 to 2008 by the late Jerome Rosenstone.

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Craig C. Grannon, Co-Chair
David Moscow, Past Chair (2014-2016)

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Jerome Rosenstone
Kay Van Cleave

The Mesulam Center Advisory Board was formed to increase public awareness and knowledge of the Center, and to help garner ongoing philanthropic support for the Mesulam Center's programs and facilities. The Board helps promote the Center both locally and nationally, and assists in securing the funding necessary to position the Center among the premier Alzheimer's research and patient care facilities in the United States.

If you are interested in learning more about the Mesulam Center Advisory Board, please contact Eskedar Alem at 312.503.2832 or visit our website: brain.northwestern.edu/about/advisory-board.html.

Marie and Carl Duncan Prize in Memory Disorders Research

Professor Carl Duncan is widely regarded as the first to demonstrate the existence of memory consolidation, showing the vulnerability of recently stored memories. His landmark work is cited more than half a century later. Upon his passing in 1999, his wife, Dr. Marie Duncan, who received her medical degree from Northwestern, set up the Duncan Fund to encourage research and discussion on issues related to memory.

In addition to an annual lecture on fundamental research on memory in the name of Professor Duncan, the Duncan Fund inaugurated in 2006 the Marie and Carl Duncan Prize in Memory Disorders Research to award accomplishments in clinically relevant arenas of inquiry. **Previous winners are listed below.**

2022: Allegra Kawles

Concordance between Neocortical Distribution of Pick's Disease and the Salience of Distinct Dementia Phenotypes

2022: Rachel Keszycki

Characterization of Distinct Neuropsychiatric Trajectories in FTLD-tauopathies

2021: Erfan Taefi

Cultured Microglia from Cognitive SuperAgers Show High Rates of Proliferation

2020: Chloe Parker

The role of astrocytes in the propagation of tau45-230-induced neuronal degeneration.

2020: Adam Martersteck

Age prediction and amyloid deposition in SuperAgers

2019: Kyla Guillaume

Impaired Turnover of Synaptic Vesicle Machinery Contributes to Amyloid Pathology in Mouse Models of Alzheimer's Disease

2019: Timothy J Hark

Decreased Resting Connectivity of Language Network with Exrasylvian Regi

2018: Melvin Thompson & Darby Morhardt

REACH to Faith 2.0: Building the Dementia Friendly Woodson Library

2017: Borna Bonakdarpour

Altered Language Network Connectivity in Primary Progressive Aphasia

2016: Ashlee E. Rubino

Internalized Tau45-230 Aggregates Can Spread Tau Pathology and Neuronal Degeneration in Alzheimer's Disease and Related Disorders

2015: Dina Simkin

Calbindin-D28K Restores the Intrinsic Excitability Properties of Aged CA1 Pyramidal Neurons to Young-Like State

2014: Daniel M. Curlik II

Ameliorating Age-Related Cognitive Impairments by Reducing Expression of L-Type Calcium Channels in Area CA1 of the Hippocampus

2013: Diana Schwab Himmelstein

Characterization of the Oligomeric Form of Tau

2012: Tharinda Rajapaksha

The Alzheimer's β -Secretase Enzyme BACE1 is Required for Accurate Olfactory Sensory Neuron Axon Guidance and Normal Glomerulus Formation in the Olfactory Bulb

2011: Carmen Westerberg

Electrically Enhancing Memory Consolidation During Sleep: A Novel Method for Reducing Age-Related Memory Decline

2010: Nicolas Kanaan

Phosphorylation in the N-Terminal Region of Tau Can Regulate Tau-Mediated Inhibition of Anterograde Fast Axonal Transport in the Squid Axoplasm

2009: Katherine Sadleir

The Role of EIF2- α Phosphorylation in A β 2 Induced BACE1 Elevation

2008: Carmen Westerberg

Relationships Between Poor Sleep and Poor Memory in Mild Cognitive Impairment



The Mesulam Center for Cognitive Neurology and Alzheimer's Disease

of Northwestern University Feinberg School of Medicine

Who We Are

Mission

The Mesulam Center for Cognitive Neurology and Alzheimer's Disease (Mesulam Center) is a multidisciplinary organization dedicated to the following pursuits:

- Conducting research to discover how the brain coordinates cognitive functions such as memory, language, attention, and emotion.
- Discovering causes and treatments for diseases that disrupt these functions, such as Alzheimer's disease and related dementias.
- Transferring the benefits of this research to patients and their families.
- Training researchers and clinicians who want to work in this field.

Research Areas

- Treatment and Prevention of Alzheimer's Disease
- Causes and Treatments of Primary Progressive Aphasia, Frontotemporal Degeneration, and other Younger Onset Dementias
- Nature of Cognitive and Behavioral Changes in Alzheimer's Disease
- Human Cognitive Brain Mapping
- Experimental Treatments
- Chemistry of Memory
- Maintenance of Cognitive Functions in Aging
- Genetics
- Impact of Non-Pharmacological Interventions on Quality of Life

The Mesulam Center has a number of research studies for which we are seeking volunteer participants. If you are interested in participating in memory research and/or would like to be placed on our mailing list, please contact us at 312-926-1851 or join a study at brain.northwestern.edu/join

300 E. Superior Street
Tarry 8th Floor
Chicago, IL 60611
Phone: 312-908-9339
Fax: 312-908-8789
mesulam-center@northwestern.edu



The Mesulam Center for Cognitive Neurology and Alzheimer's Disease

of Northwestern University Feinberg School of Medicine

Neurobehavior and Memory Clinic

Care for Patients and Families

The Neurobehavior and Memory Clinic is designed to meet the needs of persons experiencing memory loss or other symptoms of dementia, and their families.

Services Include

- Evaluation and follow-up care by behavioral neurologists who specialize in the diagnosis and treatment of dementia syndromes
- Evaluation of memory and other thinking abilities with the use of specialized tests given by a clinical neuropsychologist
- Management of medication for memory disorders
- The opportunity to participate in clinical research and clinical drug trials
- Psychiatric evaluation and treatment for mood and behavior disorders associated with neurological disease
- Education and counseling for patients and families
- Symptom specific interventions and strategies
- Information and referral to other supportive services

Our dedicated clinical team includes behavioral neurologists, neuropsychiatrists, neuropsychologists, and social workers.

Call for an appointment:
312-695-9627

676 North Saint Clair Street
Suite 1310
Chicago, Illinois 60611
Phone: 312-695-9627
Fax: 312-695-6072

Neurobehavior and Memory Clinic

A dedicated clinical team

Behavioral Neurologists

M.-Marsel Mesulam, MD, Director

Borna Bonakdarpour, MD

Joshua Cahan, MD

Ian Grant, MD

Allison Lapins, MD

Malik Nassan, MD

Neuropsychiatrists

Fred Ovsiew, MD

Deborah Reed, MD

Neuropsychologists

Maureen Daly, PhD

Tamar Gefen, PhD

Jana Wingo, PhD

Sandra Weintraub, PhD, ABPP-CN

Social Workers

Lauren Dowden, MSW, LCSW

Kate O'Neil, MSW

Darby Morhardt, PhD, LCSW

Clinic Manager

Kevin Reyes, BA

Resource Coordinator

Nicole Wright, BA, CSP

Patient Liaison

Anthony Nowaske

Sandra Zuniga

Technician, Neuropsychology

Gregory Tesnar



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Information Center

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The Importance of Brain Donation

Help us combat dementia and better understand healthy aging.

To win the fight against Alzheimer's disease and other brain diseases that cause dementia we need more research. Brain donation at the time of death from individuals who have been well-studied during life is one of the most important and generous gifts a patient who has lived with dementia and their family can make. Brain donations from individuals who do not suffer from dementia are also critical for comparison and to learn why some people do not develop Alzheimer's and other dementias.

Brain donation is one of the most important contributions to research.

The study of brain tissue from individuals with and without disease who have been carefully studied during their lifetime allows scientists to understand the mechanisms of disease, and how those with and without disease differ in their genes and molecules. While major advances have already been made possible through the generosity of brain donation, there is still much more to be learned.



Brain donation provides valuable information to families.

A comprehensive autopsy is performed on the brain of donors. The family of the donor receives a full report detailing the neuropathologist's findings. At present, neurodegenerative diseases that cause dementia can only be diagnosed with 100% certainty through a brain autopsy, so families are provided with a definitive diagnosis. Such information is useful if other family members develop a dementia in the future or if there is a known strong family history. Making this generous donation provides the family with a way to potentially help others, which can create a sense of hope and power over the illness that affected their loved one.

Unfortunately, we cannot accept every brain donation.

If someone interested in brain donation was never seen as part of research, we will not be able to accept the brain donation. However, we can determine on a case-by-case basis if the individual should be enrolled in our research and thus donate their brain.

Brain donation is a decision that individuals and their families can make only after thoughtful consideration. The decision has important emotional and practical implications.



Members of the professional staff at the Mesulam Center for Cognitive Neurology and Alzheimer's Disease at Northwestern University are available to talk with you and answer your questions.

Phone: 312.908.9339

Email: adc@northwestern.edu



ALLFTD Longitudinal Study



ALLFTD is a multisite research project aimed at understanding the changes in brain function that occur as a result of frontotemporal lobar degeneration (FTLD) syndromes. FTLD syndromes can include bvFTD, bvFTD with ALS, PPA, PSP, or CBD. Some forms of FTLD are genetic, while others are not. ALLFTD is interested in all forms of FTLD.

We can learn about changes in your brain in a variety of ways, including a clinical examination, memory and thinking tests, and MR imaging of your brain. We also measure different proteins in your blood or cerebrospinal fluid (CSF) that we think change in response to disease progression.

If you are interested in helping us learn more about FTLD and you've been diagnosed with an FTLD syndrome or are at risk due to your family history, please consider participating in our ALLFTD Longitudinal Study.

Why am I being asked to participate in the ALLFTD Longitudinal Study?

You're being asked to participate in the ALLFTD Longitudinal Study because you've either:

1. Been diagnosed with an FTLD syndrome like bvFTD, bvFTD with ALS, PPA, PSP, or CBD
2. Are from a family with a mutation in a gene known to cause FTLD (such as *C9orf72*, *MAPT*, and *GRN*)
3. Have a significant family history of FTLD suggesting a familial genetic mutation.

If you are from groups 2 or 3, you don't have to have symptoms to participate and you don't need to know your mutation status to participate.

What happens in the ALLFTD Longitudinal Study?

The ALLFTD Longitudinal Study is an annual visit to the clinic, each lasting 2–3 days. You will complete some questionnaires and memory and thinking questions, meet with a clinician for a neurological exam, and have your blood drawn and an MRI.

Where can I find more information about the study?

You can find more information about the study on our website at www.allftd.org.

I am interested in participating. What do I do next?

Please tell your neurologist that you would like to participate in the ALLFTD Longitudinal Study. You can also find contact information for ALLFTD site study coordinators at www.allftd.org and can also email a coordinator to say that you would like to join. We suggest you choose the site most convenient for you.

Study Sites

Case Western Reserve University, Cleveland
Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas
Columbia University in the City of New York
Houston Methodist Hospital, Nantz National Alzheimer Center
Indiana University
Johns Hopkins University, Baltimore
Massachusetts General Hospital, Boston
Mayo Clinic, Jacksonville
Mayo Clinic, Rochester
Northwestern University, Chicago
University of Alabama at Birmingham
University of British Columbia, Vancouver
University of California, Los Angeles
University of California, San Diego
University of California, San Francisco
University of Colorado Denver
University of Michigan
University of North Carolina at Chapel Hill
University of Pennsylvania, Philadelphia
University of Toronto
University of Washington, Seattle
Vanderbilt University
Washington University in St. Louis

Contact your site:

Find more information at www.allftd.org/sites.

Frequently Asked Questions



What is the AHEAD Study?

The AHEAD Study tests whether intervening **AHEAD** of symptoms may help prevent future memory loss and dementia caused by Alzheimer's disease.

The study looks at an investigational treatment aimed at delaying memory decline in people up to 20 years before the symptoms of Alzheimer's disease appear. Discovering a treatment that targets brain changes early means doctors may be able to one day prevent memory loss.

The AHEAD Study needs participants of every race and ethnicity to help find a treatment for Alzheimer's disease that works for everyone.

Who is eligible?

Individuals eligible for the AHEAD Study:

- › Are healthy, non-smoking adults, ages 55–80.
- › Have not been diagnosed with Alzheimer's disease.
- › Have elevated or intermediate levels of amyloid in their brains (a protein shown by brain imaging, as part of the study screening process).

- › Have a close friend or relative who the participant sees or talks to every week who can serve as their study partner.

What makes this study unique?

It is made up of two different clinical trials testing the same investigational medication BAN2401 (lecanemab), which can remove amyloid, a protein that builds up in the brains of people who can go on to have memory problems because of Alzheimer's disease.

Study participants will receive tailored dosing of the investigational treatment, depending on which study they qualify for, instead of a one-size-fits-all approach.

- › **AHEAD A-3 Trial:** participants with intermediate amyloid levels will receive BAN2401 (lecanemab) once every four weeks for four years. The AHEAD A-3 trial aims to intervene at the very earliest signs of Alzheimer's disease.
- › **AHEAD A-45 Trial:** participants with elevated amyloid levels will receive BAN2401 (lecanemab) once every two weeks for about two years, in an effort to clear amyloid from the brain, then once every four weeks for the remainder of the study.

AL001-3: A STUDY TO EVALUATE EFFICACY AND SAFETY OF AL001 IN FTD

AL001

Alector, Inc. is studying AL001 as a new experimental drug for frontotemporal dementia (FTD) caused by mutations in the progranulin gene. These mutations reduce progranulin levels in the body and may lead to symptoms of FTD. The purpose of the phase 3 study is to learn whether increasing progranulin levels with treatment with AL001 will delay onset of symptoms or slow disease progression, when compared to a placebo (a solution that contains no active AL001 drug).

ELIGIBILITY

Each individual will be evaluated to determine eligibility. You may be eligible if:

You have a progranulin gene mutation and are at risk of developing FTD symptoms as evidenced by a biomarker

OR

You are diagnosed with FTD and have a progranulin gene mutation

MORE INFORMATION

AL001 or placebo will be administered every 4 weeks by an intravenous (IV) infusion. Assessments will include regular medical examinations, blood tests, brain imaging, and completion of questionnaires.

For all participants:

- You will be in the study about 2 years.
- You will need to visit the study site at least 1 time per month for 2 years.

Optional open-label extension (OLE):

- Participants who complete the study and who meet the criteria will be eligible to continue to the OLE.
- All participants will receive AL001.
- OLE duration is about 2 years.

AL001 has not been approved by the US Food and Drug Administration (FDA) or any other health authority around the world.

For more information about participating in this study at <Institution Name>, please contact <Name> at <phone #/email address> or visit www.alectorftdtrial.com

HELP SPARK NEW POSSIBILITIES IN FTD



ABOUT TRC-PAD

To facilitate Alzheimer's clinical trial enrollment and speed up the pace of discovery, the University of Southern California Alzheimer's Therapeutic Research Institute (ATRI) and other leading research institutions are using an innovative, two-pronged approach, known as TRC-PAD (Trial-Ready Cohort for the Prevention of Alzheimer's Dementia), to identify, evaluate, and enroll volunteers in Alzheimer's prevention trials. TRC-PAD consists of two parts:

apt webstudy

Alzheimer Prevention Trials (APT) Webstudy

The APT Webstudy uses internet-based memory testing to identify people who are at increased risk for developing Alzheimer's disease in the future and interested in helping researchers develop ways to prevent it.

The webstudy requires volunteers to sign an online informed consent form, provide basic demographic information and take two short memory tests online every three months. Altogether, the tests take approximately 20 minutes to complete. Researchers use the results to track volunteers' memory and, based on their risk level, select participants who may be candidates for Alzheimer's prevention trials. These participants are invited for further evaluation at a nearby research clinic to determine eligibility for the Trial-Ready Cohort (TRC).

To learn more, visit www.APTWebstudy.org. The APT Webstudy is available in both English and Spanish.

▶ trc-pad

Trial-Ready Cohort (TRC)

TRC is an observational study that advances Alzheimer's research by matching healthy people with clinical trials to prevent Alzheimer's disease. It is the next phase of the online-only APT Webstudy.

Select volunteers from the APT Webstudy are invited to in-person research evaluations at one of the TRC research facilities across the United States. These assessments include a positron emission tomography (PET) brain scan, cerebrospinal fluid collection, tests of memory and thinking, questionnaires about daily functioning, mood and behavior, genetic testing, and routine blood and urine tests. Participants who meet certain criteria and are identified as being at potential increased risk for future memory loss caused by Alzheimer's disease may be invited to participate in TRC.

People who are in the TRC are routinely assessed at twice yearly in-person visits until they are found to be eligible for a clinical trial.

Clinical studies connected to TRC-PAD differ by research location, but all the participating clinical trials share the same goal: to prevent Alzheimer's disease.



To learn more about this research effort, visit trcpad.org or email trc-participate@usc.edu.



communication BRIDGE

Speech Therapy Study

Who?

Individuals with a diagnosis of Primary Progressive Aphasia and their Communication Partners

Why?

To help us better understand the effects of speech language therapy on communication abilities in individuals with PPA

Where?

All components of the study take place remotely via video-conferencing

How Long?

Over the course of one year, participants in our study will be involved in:

- 5 evaluations with a certified speech language therapist
- 15 therapy sessions with a certified speech language therapist
- Exercises through our web-application

There are no costs to participate in this study. Compensation will be provided.

If interested, contact us for more information

Phone: (312) 503-4012

Email: communicationbridge@northwestern.edu

Website: www.brain.northwestern.edu

Study funded by: National Institute on Aging, IRB#STU00206086, PI: Dr. Emily Rogalski
Study Title: Communication Bridge: Using Internet-Based Speech Therapy to Improve Quality of Life and Access to Care

Northwestern Medicine
Feinberg School of Medicine

Mesulam Center for Cognitive
Neurology and Alzheimer's Disease



LANGUAGE IN PRIMARY PROGRESSIVE APHASIA

Observational Research Study

Funded in part by the National Institute on Aging

Principal Investigators: Marsel Mesulam, MD & Emily Rogalski, PhD; STU00026372

Currently
Recruiting!

PURPOSE

The Language in Primary Progressive Aphasia (PPA) research program seeks to enroll and follow individuals living with PPA over time using neuropsychological testing and advanced imaging techniques to:

1. better understand progression in PPA and its link to brain changes,
2. increase awareness of PPA and educate those living with PPA, their families, clinicians, and the community,
3. identify biomarkers that will lead to earlier and effective diagnosis and intervention.

STUDY ACTIVITIES

At study visits, participants will be asked to:

- Have an examination by a neurologist
- Answer questions about their health and family history
- Have brain scans
- Take paper and pencil tests that evaluate memory and thinking



DETAILS

Study visits last four days total, for about seven hours each day, including breaks.

Participants are asked to return every two years to compare changes between visits.

The study takes place at Northwestern University in downtown Chicago, IL.

Travel arrangements are provided for both the person with PPA and study partner at no cost.

Participants will be compensated for their time and effort.

Eligibility Requirements:

- Diagnosed with PPA
- Right-handed
- Native English speaker
- Have a study partner who can accompany them to visits
- Not claustrophobic
- Safe for an MRI Scan

Individuals not seen at the Mesulam Center Neurobehavior and Memory Clinic will need to send medical records and have a phone interview before being approved to participate.

FOR MORE INFORMATION please contact:

Seyi Adeolu, Research Coordinator
PPA.Research@northwestern.edu

312-503-2398

www.brain.northwestern.edu



OVER 80 AND STILL GOING STRONG

Are you 80+ and still actively engaged in life?
Does this sound like you or someone you know?



Why are YOU important?

You can help us better understand and identify factors that contribute to exceptional cognitive aging

Who are we?

We are the Northwestern University SuperAging Team and we would love to hear from you!

What is involved?

- Visiting our Center every two years
 - Pen & paper cognitive tests
 - MRI/PET brain scans
- Surveys and questionnaires

Compensation will be offered for your time.
Travel to the Center will be covered.

If Interested Please Contact us for more Information

Phone: (312) 503-2716

Email: agingresearch@northwestern.edu

Website: brain.northwestern.edu

Mesulam Center for Cognitive Neurology
and Alzheimer's Disease of Northwestern University



Study Funded by: National Institute on Aging and The Davee Foundation
Principal Investigator: Emily Rogalski, PhD
Grant #: 1R01AG067781-01/ 2R56AG045571-06, IRB# STU00027225
Study Title: Super Aging Study: Correlates of Active Engagement in Life in the Elderly

The VIVA-MIND trial is designed to determine if the study drug, varoglutamstat, can stabilize or slow memory and thinking problems that increase in early AD.

The VIVA-MIND clinical research trial is designed specifically for people who are age 50-89, and experiencing significant memory concerns, or who have already been diagnosed with Mild Cognitive Impairment (MCI) or mild Alzheimer's disease (AD). This stage of the disease, MCI through mild AD disease, is also known as early AD.

Basic Eligibility Criteria

- Age 50-89
- Diagnosed Mild Cognitive Impairment (MCI) due to AD or probable Mild AD
- Taking the following Alzheimer's medication(s) for at least four months: Donepezil (Aricept®) or rivastigmine (Exelon®) or galantamine (Razadyne®) with or without memantine (Namenda®)
- Have a study partner who can accompany the participant to clinic visits
- Willing to participate in the VIVA-MIND study for up to 20 months



What happens during the VIVA-MIND Study?

Participation in the study will take up to 20 months. A potential participant will first go through a screening process to see if they are eligible to take part in the clinical trial. Half of the participants are given the study drug, Varoglutamstat, and half are given an inactive pill (called a placebo), which is taken orally two times daily.

Screenings include: Memory and thinking tests, EKGs (a look at your heart rhythms), and MRI scans (a picture of your brain that shows changes related to AD).

For more information or to volunteer, please contact:



NORTHWESTERN
UNIVERSITY

Caila Ryan

Study Coordinator

Phone: (312) 503-5674

Email: caila.ryan@northwestern.edu

www.VIVA-MIND.org



The Mesulam Center Presents **The Glen and Wendy Miller Family Buddy Program**

The Buddy Program is a unique opportunity for **persons living with dementia** to mentor first-year medical students.

As a Buddy Program Mentor, you will:

- Be paired with a first-year medical student to visit with on a regular basis throughout the academic year (October – May).
- Engage in activities hosted by the program throughout the year including a Match Day, Valentine's Day Lunch, and End of the Year Celebration.
- Help to inform a future physician's understanding of how dementia affects a person and their family.

“*I found the experience to be fantastic: I felt I had a 'friend' in my disease. I felt privileged and grateful to learn from him. I felt the mutual empathy was inspiring.*”

2021 Buddy Program Mentor

Contact

Darby Morhardt, PhD, LCSW
d-morhardt@northwestern.edu



The Mesulam Center for Cognitive Neurology and Alzheimer's Disease

of Northwestern University Feinberg School of Medicine

Care Partner Support Groups

The Mesulam Center offers three monthly support groups for family members and care partners of persons living with dementia. Currently, we are offering these groups through Zoom.

New care partners are always welcome to join the group.

There is no fee to participate. If you have not been to the group before and would like to join, please reach out to the contact listed on the group to set up a brief telephone screening.

For Care Partners of Individuals Living with PPA

This monthly support group is for family members and care partners of people living with primary progressive aphasia (PPA).

Time: first Monday of each month from 4:30 to 6 p.m. CT.

Contact: Darby Morhardt, PhD, LCSW, d-morhardt@northwestern.edu, 312.908.9432

For Care Partners of Individuals Living with FTD

This monthly support group is for family members and care partners of people living with frontotemporal dementia (FTD).

Time: third Monday of each month from 4:30 to 6 p.m. CT.

Contact: Lauren Dowden, LCSW, lauren.dowden@northwestern.edu, 312.503.5559

For Care Partners of Individuals Living with Younger-Onset Dementia

This monthly support group is for family members and care partners of people living with younger-onset (under age 65) dementia.

Time: second Monday of each month from 4:30 to 6 p.m. CT.

Contact: Darby Morhardt, PhD, LCSW, d-morhardt@northwestern.edu, 312.908.9432

Counseling, Education, and Support

Clinical Social Work Consultation:

A Customized Approach to Care



The Northwestern Neurobehavior and Memory Clinic offers a multidisciplinary team approach. Your care team includes neurologists, psychiatrists, neuropsychologists and social workers. Clinical social workers are available to discuss your questions and work with you to develop a personal and customized approach to care. Following are some questions you may have:

- **“Do I understand the diagnosis?”**

Your social worker will:

- Review the diagnosis and provide the opportunity to ask questions and get up-to-date disease information.
- Discuss changing behaviors and other diagnosis-related symptoms, and offer helpful communication strategies.

- **“How do I cope with this now and as it progresses?”**

Your social worker can:

- Provide counseling regarding changing roles as the disease progresses.
- Help you to assure your own self-care and to strengthen your support network.
- Provide referrals for individual, couples, and/or family counseling.

- **“How can I plan for future care?”**

Your social worker can:

- Connect you to trusted elder law attorneys for estate planning and to establish powers of attorney for health care and finances.
- Provide counseling regarding advance directives.
- Help you to explore long-term care options and funding sources.

- **“What services are available at Northwestern or in my own neighborhood?”**

Your social worker can guide you to:

- Specialized support and education groups for newly diagnosed individuals and families.
- Quality-of-life programs designed to offer meaningful and purposeful activity.
- Other community programs in which you can find enriching opportunities.

Please call the Northwestern Neurobehavior and Memory Clinic, 312-695-9627 or ask your doctor for a referral for a clinical social work consultation.



Become a Dementia Friend

Dementia Friends USA is part of a global movement that is changing the way people think, act, and talk about dementia. Anyone can be a Dementia Friend – we all have a part to play in creating dementia friendly communities!

A Dementia Friend is someone who, through viewing a series of online videos or attending a live interactive session, learns about what it's like to live with dementia and then turns that understanding into action. From telling friends about the Dementia Friends program to visiting someone who is living with dementia, every action counts.

Get started today at **www.DementiaFriendsUSA.org**!

From there you can become a Dementia Friend by committing to an activity that will help someone in your community with dementia.



ICRN QR CODE



Dementia Friendly QR CODE

Poster Session Map

Lunch Buffet

**To Vendor Tables
and Lecture**

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82	44	41	2
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Poster Session

Cell & Molecular Biology

- 1. TLR4 Antagonists as A Potential Therapeutic for Alzheimer's Disease-Associated Neuroinflammation**
Deebika Balu, Ana C. Valencia-Olvera, Jason York, Francesco Peri, Frank Neumann, Leon M. Tai, Mary Jo LaDu
- 2. Anti-CD49d Antibody Treatment Improves Survival and Attenuates Neurocognitive Deficits after Traumatic Brain Injury in Aged Mice**
Zhangying Jennie Chen, Kacie Ford, Mecca Islam, Booker Davis, and Steven Schwulst
- 3. Targeting TDP-43 loss-of-function induced mis-splicing in ALS-FTD**
Wanhao Chi, Jonathan K. Watts, Evangelos Kiskinis
- 4. Bone morphogenetic protein signaling is exacerbated in Alzheimer's Disease**
Sara Rose Dunlop, Callen Spencer, Margaret Flanagan, John Kessler
- 5. DISE Contributes to Neurotoxicity in Alzheimer's Disease**
Bidur Paudel, Si-Yeon Jeong, Ashley Haluck-Kangas, Elizabeth T. Bartom, Amira Affaneh, John A. Kessler, Joseph R. Mazzulli, Andrea E. Murmann, Emily Rogalski, Adriana Ferreira, Bradlee L. Heckmann, Douglas R. Green, Katherine R. Sadleir, Robert J. Vassar, and Marcus E. Peter
- 6. Single cell transcriptomics reveals cerebrospinal fluid immune dysregulation during healthy brain aging and cognitive impairment**
Natalie Piehl, Lynn van Olst, Abhirami Ramakrishnan, Victoria Teregulova, Brooke Simonton, Ziyang Zhang, and David Gate
- 7. Peripheral immunomodulatory effects of Apolipoprotein E4 in Alzheimer's disease**
Abhirami Ramakrishnan, Natalie Piehl, Lynn van Olst, Brooke Simonton, Ziyang Zhang, Brian Druciak, and David Gate
- 8. Annexin A6 in membrane resealing in Alzheimer's disease**
Katherine Sadleir, Ammaarah Khatri, Regan Andringa-Seed, Alexis Demonbruen, Elizabeth McNally, Robert Vassar
- 9. Increased production of Reactive Oxygen Species by Human Microglia in SuperAgers in Response to Soluble Oligomeric and Fibrillar Amyloid- β Peptide**
Erfan Taefi, Kevin Shen, Cameron Swope, Atousa Bahrami, Regina Taefi, Margaret E. Flanagan, Tamar Gefen, Emily Rogalski, M.-Marsel Mesulam, and Changiz Geula

Clinical Best Practices

- 10. Evaluation of the 10-item Communicative Participation Item Bank for Persons with Primary Progressive Aphasia and their Communication Partners**
Ollie Fegter, Sara Shaunfield, Matthew Bona, Angela Roberts, Emily Rogalski
- 11. Suitability of Goal Attainment Scaling in Older Adult Populations with Neurodegenerative Disease Experiencing Dementia or Cognitive Impairment: A Systematic Review**
Ollie Fegter, Haylie Santos, Alfred Rademaker, Angela Roberts, Emily Rogalski

Poster Session

Clinicopathologic Studies

12. Trajectories of Neurocognitive Decline in Aphasic versus Behavioral Dementia Syndromes due to Pick Disease

Kawles A, Keszycki R, Minogue G, Zouridakis A, Kochheiser M, Riley M, MS, Coventry C, RN MS, Emily Rogalski, PhD, Weintraub S, PhD, Mao Q, MD PhD, Flanagan M.E, MD, Bigio, E.H, Mesulam M.M, MD, Geula C, PhD, Gefen T, PhD

13. Amygdala pathology in early neuropsychiatric phenotypes due to 3R-Pick disease

Rachel Keszycki, Allegra Kawles, Grace Minogue, Antonia Zouridakis, Alyssa Macomber, Vivienne Lubbat, Christina Coventry, Emily Rogalski, Sandra Weintraub, Margaret E. Flanagan, Rudolph J. Castellani, M.-Marsel Mesulam, Changiz Geula, Tamar Gefen

14. Spatial extent and intensity of Alzheimer associated tau PET burden is greater in agrammatic than logopenic primary progressive aphasia

Adam Martersteck, Jaiashre Sridhar, Christina Coventry, Sandra Weintraub, M.-Marsel Mesulam, and Emily Rogalski

15. Epicenters of cortical atrophy in primary progressive aphasia differ by underlying neuropathology

Adam Martersteck, PhD, Jaiashre Sridhar, MS, Christina Coventry, MS, RN, Daniel Gutstein, MS, Sandra Weintraub, PhD, M.-Marsel Mesulam, MD, and Emily Rogalski, PhD

16. Stereological densities of corticobasal degeneration neuropathology are anatomically distinct in PPA vs bvFTD

Grace Minogue, Allegra Kawles, Antonia Zouridakis, Rachel Keszycki, Christina Coventry, Nathan Gill, Hui Zhang, Emily Rogalski, Sandra Weintraub, Qinwen Mao, Margaret Flanagan, Rudolph Castellani, M-Marsel Mesulam, Changiz Geula, Tamar Gefen

17. Burden of pathology in hippocampal subregions can distinguish amnestic dementia with comorbid Alzheimer's and TDP-43 pathology from pure Alzheimer's and FTLD-TDP

Grace Minogue, Allegra Kawles, Antonia Zouridakis, Rachel Keszycki, Nathan Gill, Makayla Kochheiser, Vivienne Lubbat, Kaouther Ajroud, Callen Spencer, Jaclyn Lilek, Qinwen Mao, Rudolph J. Castellani, Margaret E. Flanagan, Hui Zhang, Eileen H. Bigio, M.-Marsel Mesulam, Changiz Geula, Tamar Gefen

18. Spatial transcriptomics reveals long-term neuropathological effects of amyloid- β immunization

Lynn van Olst, Brooke Simonton, Ziyang Zhang, Abhirami Ramakrishnan, Victoria Teregulova, Nathalie Piehl, Jeanette Norman, James AR Nicoll, Delphine Boche, and David Gate

19. Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4)

Jelena Pejic, Ali Raja, Kailey Basham, Loreece Haddad, MS, Caila Ryan, MS, Phyllis Timpo, MS, Joshua Cahan, MD, Allison Lapins, MD, Malik Nassan, MD, Sandra Weintraub, PhD, Ian Grant, MD, Darby Morhardt, PhD, Emily Rogalski, PhD

20. Longitudinal Early-onset Alzheimer's Disease Study (LEADS)

Ali Raja, Jelena Pejic, Loreece Haddad, MS, Kailey Basham, Caila Ryan, MS, Joshua Cahan, MD, Allison Lapins, MD, Malik Nassan, MD, Darby Morhardt, PhD, Sandra Weintraub, PhD, Ian Grant, MD, Emily Rogalski, PhD

Poster Session

21. Inhibition of ACAT as a Therapeutic Target for Alzheimer's Disease is Independent of ApoE4-lipidation

Ana C. Valencia-Olvera, Deebika Balu, Naomi Faulk, Jason M. York, Gregory R. J. Thatcher, and Mary Jo. LaDu

22. Anatomic Selectivity of Neuronal and Glial Tau in Primary Progressive Aphasia with 4R FTLD-tauopathies

Antonia Zouridakis, Allegra Kawles, Grace Minogue, Rachel Keszycki, Vivienne Lubbat, Christina Coventry, Matthew McCord, Sandra Weintraub, Emily Rogalski, Rudolph J. Castellani, Margaret E. Flanagan, Qinwen Mao, Eileen H Bigio, M-Marsel Mesulam, Changiz Geula, and Tamar Gefen

Neuroanatomy

23. Shades of Grey in Human White Matter

Antonia Zouridakis, Ivan Ayala, Grace Minogue, Allegra Kawles, Rachel Keszycki, Alyssa Macomber, Eileen Bigio, Changiz Geula, M.-Marsel Mesulam, Tamar Gefen

24. White matter tract disruption predicts cognitive disfunction in patients with glioma

Mia Andreoli, Melissa-Ann Mackie, PhD, David Aaby, MS, Matthew Tate, MD, PhD

Community Engagement

25. Mesulam Center Brain Scholars Program: Empowering Diverse Next Generation of Neurologist and Neuroscientists

Paige Barenthin, Ivan Ayala, Janelli Rodriguez, Antonia Zouridakis, Sarah Simon, Grace Minogue, Chernise Bayley-Turner, Phyllis Timpo, Melvin Thompson, Eskedar Alem, Darby Morhardt and Changiz Geula

26. Race-Based Corrections in Cognitive Function Scores May Obscure Disparities: The Disparities in Sleep and Cognitive Outcomes (DISCO) study

Thanh-Huyen T. Vu, Alana V Hernandez, Mandy Wong, Shaina J Alexandria, Diana A Chirinos, Kristen L Knutson, Mercedes R Carnethon

27. It's a Family Affair: Addressing the Needs of Black Caregivers Through a Community Based Dementia Caregiver Program

Dianne Oladejo, Joyce Chapman, Tonya S. Roberson, PhD, MPH, Rachel O'Connor, PhD MPH

28. The Mesulam Center Underrepresented Groups (URG) Recruitment and Retention Taskforce: connecting with, recruiting, and retaining diverse research participants through community engagement.

Phyllis Timpo, Nicole Hunt, Emily Rogalski, Darby Morhardt

29. Using Community-University Partnership to Increase Brain Health Awareness in Community-Dwelling Black Older Adults on the South Side of Chicago

Janie Urbanic, Phyllis Timpo, Nicole Hunt, Emily Rogalski, Darby Morhardt

30. Introducing the MidCog Study: a prospective, observational cohort study investigating modifiable risk factors to cognitive decline in middle-aged adults

Pauline Zheng, Han Luu, Patrick Cecil, Prophecy Agyare, Rudy Zuleta, Fangyu Yeh, Laura Curtis, Minjee Kim, Michael Wolf

Poster Session

Health Services

31. Primary Care Detection of Cognitive Impairment Leveraging Health & Consumer Technologies in Underserved Communities: The MyCog Strategy

Morgan Bonham, BS, Julia Yoshino Benavente, MPH, Laura Curtis, MS, Zahra Hosseinian, MA, Michael Bass, MS, Maria Diaz, MSCS, Stephanie Batio, MS, Mary Kwasny, ScD, Rebecca Lovett, PhD, Andrea Russell, PhD, Minjee Kim, MD, Yusuke Shono, PhD, Jeffrey Linder, MD, MPH, Cindy Nowinski, MD, PhD, Richard Gershon, PhD, Michael Wolf, PhD, MPH, MA

32. Length of stay relates to inpatient antipsychotic use in Alzheimer's type dementia at a large US-based tertiary care hospital.

Joshua G. Cahan MD, Borna Bonakdarpour MD

33. Lorenzo's House, an international nonprofit empowers families living with younger-onset dementia through our holistic model.

Diana Cose

34. Communication Bridge: A person-centered Internet-based intervention for individuals with Primary Progressive Aphasia

Eunbi Kwon, Matthew Bona, MPH, Zoe Sweeney, Marissa Esparza, Aimee Mooney, MS, Emily Cummings, MS, Ollie Fegter, Darby Morhardt, PhD, Angela Roberts, PhD, and Emily Rogalski, PhD

Neuroscience

35. Primary Progressive Aphasia Research Program at the Mesulam Center for Cognitive Neurology and Alzheimer Disease

Lauren Ables-Torres, Hayley Olson, Oluwaseyi Adeolu, Elena Barbieri, Christina Coventry, Sarah Simon, Jaishree Sridhar, Fatima Eldes, Daniel Gutstein, Marissa Esparza, Zoe Sweeney, Eunbi Kwon, Joshua Pasaye, Shruti Chandra, Matthew Bona, Adam Martersteck, Darby Morhardt, Angela Roberts, Cynthia Thompson, Sandra Weintraub, Emily Rogalski, M.-Marsel Mesulam

36. Cognitive SuperAgers are Protected from Phosphorylated Tau Accumulation in Basal Forebrain Cholinergic Neurons

Ivan Ayala, Tamar Gefen, Margaret E. Flanagan, Emily Rogalski, M.-Marsel Mesulam, Changiz Geula

37. Detection of MAP2K3 Immunoreactivity in the Human Cerebral Cortex and Primary Human Microglia, and Loss in Frontotemporal Lobar Degeneration with TDP-43 Proteinopathy

Atousa Bahrami, Cameron B Swope, Erfan Taefi, Ivan Alejandro Ayala, Margaret E. Flanagan, Regina Taefi, Emily Rogalski, M.-Marsel Mesulam, Tamar Gefen, and Changiz Geula

38. Neural basis of word and sentence comprehension in PPA: a deficit-based neuroimaging approach

Elena Barbieri, Lauren Ables-Torres, Sandra Weintraub, Emily Rogalski, M.-Marsel Mesulam

39. Neuropathology-specific neural pathways underlying agrammatism in PPA

Elena Barbieri, Ken Li, Sandra Weintraub, Emily Rogalski, Borna Bonakdarpour, M.-Marsel Mesulam

40. Regional Relationship between Brain Hypometabolism and Atrophy in Semantic Primary Progressive Aphasia

Jordan Q. Behn, Elena Barbieri, Sandra Weintraub, Emily Rogalski, Marsel Mesulam, Borna Bonakdarpour

Poster Session

- 41. Chronic Levetiracetam Treatment Alters Synaptic Protein Turnover in Alzheimer's Mouse Model and Reduces Production of A β ₄₂**
Olivia DeGulis, Nalini R. Rao, Jeffrey N. Savas
- 42. Functional Connectivity within Two Large-Scale Memory Systems in SuperAgers**
Bram Diamond, Adam Martersteck, Jaiashre Sridhar, Emily Rogalski
- 43. Molecular mechanisms of apathy and affective symptoms in Alzheimer's disease**
Jeffrey T. Dunn, Rachel Keszycki, Daniel W. Fisher, Guadalupe Rodriguez, David A. Bennett, Robert S. Wilson, Hongxin Dong
- 44. Validation of the NIH Toolbox Odor Identification Test across Normal Cognition, Amnestic Mild Cognitive Impairment, and Dementia due to Alzheimer's Disease**
Shiloh L. Echevarria-Cooper, Emily H. Ho, Richard C. Gershon, Sandra Weintraub, Thorsten Kahnt
- 45. Not All Tauopathies are Created Equal**
Donte Lorenzo Garcia, Sara Rose Dunlop, Yasushi Nishihira, Ivan Ayala, Eileen Bigio, Margaret E. Flanagan, Tamar D. Gefen, M.-Marsel Mesulam, Changiz Geula
- 46. Using AAV-mediated overexpression of Nrf2 to prevent Alzheimer's neuropathology**
Karen P. Gomez, Katherine R. Sadleir, Yunlu Sawyer Xue, Connie Cepko, Robert J. Vassar
- 47. Noradrenergic dysregulation, sleep and cognition in older adults with insomnia**
Daniela Grimaldi, Kathryn Reid, Sabra Abbott, Phyllis Zee
- 48. Structural brain network degeneration associated with agitation in dementia**
Lisanne M. Jenkins, Sonya Gupta, Maryam Kouchakidivkolaie, Jaiashre Sridhar, Emily Rogalski, Sandra Weintraub, KartEEK Popuri, Howie Rosen, Lei Wang
- 49. Amyloid beta oligomers, inflammatory astrogliosis, and the therapeutic action of NU-9 in the 5xFAD model**
Kranz DL, Silverman RB, Klein WL
- 50. Northwestern Alzheimer's Disease Research Center (MADRC) Clinical Core**
Kathryn LaFroschia, MPH, Janelli Rodriguez, BS, Christopher Mazurek, BA, Elizabeth Haynes, BS, Grace Minogue, BA, Joshua Pasaye, BS, Deborah Zemlock, BS, Antonia Zouridakis, BS, Hui Zhang, PhD, Ian Grant, MD, Borna Bonakdarpour, MD, Joshua Cahan, MD, Changiz Geula, PhD, Darby Morhardt, PhD, Emily Rogalski, PhD, M.-Marsel Mesulam, MD, Robert Vassar, PhD, Tamar Gefen, PhD, Sandra Weintraub, PhD
- 51. Neural Mechanisms Underlying Confrontation and Generative Naming in behavioral variant Frontotemporal Dementia**
Grace Lee, Elena Barbieri, Mehraveh Garjani, Emily Rogalski, Sandra Weintraub, Marsel Mesulam, Borna Bonakdarpour
- 52. Evaluating the Causal Association Between Genetically Proxied Psychiatric Disorders and SuperAging**
Malik Nassan, Ignazio Piras, Changiz Geula, M-Marsel Mesulam, Matt Huentelman, Emily Rogalski
- 53. Proteome fidelity during aging**
Nalini R. Rao, Arun Upadhyay, and Jeffery N. Savas

Poster Session

54. The SuperAging Research Initiative: A multisite consortium focused on identifying factors promoting extraordinary cognitive aging

Emily Rogalski, PhD, Matt Huentelman, PhD, Angela Roberts, PhD, Bill McIlroy, PhD, Karen VanOoteghem, PhD, Elizabeth Finger, MD, Andrew Lim, MD, Ozioma Okonkwo, PhD, Felicia Goldstein, PhD, Todd Parrish, PhD, Nathan Gill, Denise Scholtens, PhD, Gabriella Amador, Elena Do, Sophia Moore, Molly Mather, PhD, Nicole Hunt, Phyllis Timpo, Janessa Engelmeyer, Adam Martersteck, PhD, Sandra Weintraub, PhD, Changiz Geula, PhD, M.-Marsel Mesulam, MD, Amanda Cook Maher, PhD

55. Investigating the role of rare genetic variants in Angiotensin-1-Converting Enzyme in Alzheimer's Disease pathogenesis

Miranda A Salvo

56. Alterations in Basal Ganglia Connectivity in Individuals with Primary Progressive Aphasia due to Alzheimer's Disease and Frontotemporal Degeneration

Daniel Seog, Jordan Behn, Elena Barbieri, Emily Rogalski, Marsel Mesulam, Borna Bonakdarpour

57. Northwestern Alzheimer's Disease Research Center Neuroimaging Biomarker Core

Ulises Sosa, Joshua Pasaye, Daniel Gutstein, Jaiashre Sridhar, Eunbi Kwon, Sarah Simon, Shruti Chandra, Karthik Sreenivasan, Ajay Kurani, Allison Lapins, Malik Nassan, Ryan Avery, Adam Martersteck, Robert Vassar, Sandra Weintraub, Todd Parrish, M.-Marsel Mesulam, Emily Rogalski

58. High Levels of the Dendritic Spine Protein Spinophilin in Cognitive SuperAgers

Regina Taefi, Kenton Haynes, Ivan Ayala, Atousa Bahrami, Margaret E. Flanagan, Tamar Gefen, Emily Rogalski, M.-Marsel Mesulam, and Changiz Geula

59. Elevated Carotid Pulse Wave Velocity is associated with Cognitive Impairment and Cerebral Amyloid Deposition: A Phase-Contrast MRI Study

Jianing Tang, Soroush H Pahlavian, Elizabeth Joe, Jamie Turner, Meredith Braskie, Vasilis Z Marmarelis, Helena Chui, Lirong Yan

60. Strain-Dependent Disease Progression in a Conditional Wild-Type Human TDP-43 Transgenic Mouse Model

Yekaterina Taylor, Amber Chiodini, Ivan Ayala, Katherine R. Sadleir, Robert Vassar, Hongxin Dong, M.-Marsel Mesulam, and Changiz Geula

61. Quantitative Proteomics Based Identification of Novel AD Therapeutic Targets

Arun Upadhyay, Nalini R. Rao, Robert Vassar, Jeffrey N. Savas

62. Alterations in Auditory and Language Network Connectivity in Primary Progressive Aphasia

Kate Vidano, Jordan Behn, Emily Rogalski, Marsel Mesulam, Borna Bonakdarpour

63. Proteomic Characterization of a Novel Antibody for FTLD-TDP Pathologic TDP-43

Anika Wilen, Qinwen Mao, Jeffrey Savas

Poster Session

Pharmacology

64. The VIVA-MIND Study

Kailey Basham; Loreece Haddad, MS; Jelena Pejic; Ali Raja; Caila Ryan, MS; Ian Grant, MD; Joshua Cahan, MD; Allison Lapins, MD; Malik Nassan, MD

65. The AHEAD Study

Loreece Haddad, MS; Kailey Basham; Jelena Pejic; Ali Raja; Caila Ryan, MS; Ian Grant, MD; Joshua Cahan, MD; Allison Lapins, MD; Malik Nassan, MD

Physiology

66. Study design and concepts for heart-brain MRI evaluation in aging and hypertension

Kelly Jarvis, PhD, Adam Martersteck, PhD, Sara Bradley, MD, Ann Ragin, PhD, Sandra Weintraub, PhD, Emily Rogalski, PhD

Recruitment Science

67. Using Community Engaged Research Strategies to Promote of Sense of Community in the SuperAging Research Initiative

Phyllis Timpo, Nicole Hunt, Darby Morhardt, Gabriella Amador, Elena Do, Sophia Moore, Fatima Eldes, Bobby Bobbitt, Molly Mather, Emily Rogalski

Social & Behavioral Sciences

68. Psychosocial Pathway Seminar Series Training

Lauren Dowden, Kate LaFroscia, Phyllis Timpo, Emily Rogalski, Darby Morhardt

69. Reducing Fear and avoidance of memory loss (REFRAME) study: A pilot randomized control trial to reduce fear and avoidance and improve well-being in older adults

Francesca R Farina, John Regan, Melissa Marquez, Hosanna An, Patricia O'Loughlin, Pavithra Pavithra, Michelle Taddeo, Rachel C. Knight, Marc Bennett, Bert Lenaert, James W Griffith

70. A randomized controlled trial of a positive affect skills intervention to reduce stress in family caregivers of individuals with Alzheimer's disease: Protocol and design for the LEAF 2.0 study

Amanda Summers, MA, Veronika E. Grote, MHI, Caroline Leong, Elizabeth L. Addington, PhD, Judith T. Moskowitz, PhD, MPH

71. Construct Validity Indicators for the Tablet Computer-Based NIH Toolbox Cognition Battery (NIHTB-CB) from the ARMADA STUDY

Emily Ho, Bruno Giordani, Felicia Goldstein, Sandra Weintraub, Richard Gershon

72. Differences in Intra-individual Variability on the NIH Toolbox in Older Adults with Normal Cognition, Mild Cognitive Impairment, and Dementia of the Alzheimer Type

Tatiana Karpouzian-Rogers, Emily Ho, Elizabeth M. Dworak, Sandra Weintraub, Richard Gershon

Poster Session

73. Health-related quality of life in patients with Primary Progressive Aphasia

Eunbi Kwon, Allison Lapins, MD, Nathan Gill, Emily Rogalski, PhD

74. Longitudinal Performance on the NIH Toolbox Cognition Module in a Cognitive Aging Sample

Molly A. Mather, Emma J. Pollner, Emily H. Ho, Richard Gershon, Sandra Weintraub

75. Boosting Positive Emotion in Caregivers: Moderators of a Positive Psychological Intervention

Taylor R. Maynard, BS, Jacquelyn Stephens, PhD, Glenna Dowling, PhD, Judith T. Moskowitz, PhD, MPH

76. PPA Tele-Savvy: Results of an Online Pilot Intervention with Caregivers of Persons with Primary Progressive Aphasia

Darby Morhardt, Kate Maley, Lauren Dowden, Kaitlyn O'Neil, Deborah Dyslin-Kman, Angela Roberts, Allison Lindauer, Tamar Gefen, Sandra Weintraub, Emily Rogalski, Kenneth Hepburn

77. Managing Medications across the Alzheimer's disease spectrum from a Patient-Caregiver Perspective

Rachel O'Connor, PhD, MPH, Dianne Oladejo, BS, Sarah Filec, MPH, Lee Lindquist, MD, MPH, MBA, Darby Morhardt, PhD, Emily Rogalski, PhD, Michael Wolf, PhD, MPH

78. The Alzheimer's Drug, Lecanemab: Patient and Family's Understanding, Perceptions and Experience with Drug Consultation

Kate O'Neil, Allison Lapins, Darby Morhardt

79. Longitudinal Performance on Three Words Three Shapes in Primary Progressive Aphasia

Janelli Rodriguez, Molly A. Mather, Sarah N. Simon, Christina Coventry, Emily Rogalski, M.-Marsel Mesulam, Sandra Weintraub

80. Teleconference Group Singing Programs for Well-being of Healthy Older Adults and Persons with Neurocognitive Disorders During the COVID-19 Pandemic

Borna Bonakdarpour, MD, Rhiana Schafer, BS, Jonathan Miller, PhD, Sandra Siegel Miller, PhD

81. Let's talk: Preliminary results of a conversation-based hearing aid trial for adults with cognitive impairment

Pamela Souza, Kendra Marks, Esther Cha, Angela Roberts

82. Combined Music Enrichment and Verbal Stimulation for Individuals with Neurocognitive Disorders: Preliminary Feasibility Results

Takarabe C., Vidano K., Yu, Y., Morhardt, D., McFadden, A., Bonakdarpour B.

83. Developing a Method for Memory Improvement Overnight in the Home

Erika M. Yamazaki, Nathan W. Whitmore, and Ken A. Paller

TLR4 Antagonists as A Potential Therapeutic for Alzheimer's Disease-Associated Neuroinflammation

Deebika Balu¹, Ana C. Valencia-Olvera¹, Jason York¹, Francesco Peri², Frank Neumann³, Leon M. Tai^{1*}, Mary Jo LaDu¹

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² Dept. of Biotech. and Biosciences, University of Milano-Bicocca, Milan, Italy.

³ Innaxon Biosciences, Tewkesbury, UK

Background: *APOE4* is the greatest genetic risk factor for Alzheimer's disease (AD), with female (♀) *APOE4* carriers having higher risk of developing AD than male (♂) *APOE4* carriers. Overall, *APOE4* is associated with higher levels of neuroinflammation, and in EFAD (5xFAD+/-/*APOE*+/+) mice, neuroinflammation is greater in ♀E4FAD mice compared to ♂E4FAD mice. Treatment with LPS increased microgliosis and pro-inflammatory cytokines with *APOE4* compared to *APOE3* and higher expression levels of Toll-like receptor 4 (TLR4)-related inflammatory markers in E4FAD compared to E3FAD mice. TLR4s are a key component in the innate immune response, expressed in the brain by neurons, microglia, and brain endothelial cells. In vitro, glial cultures from *APOE4*-TR mice demonstrate that soluble oligomeric forms of Ab peptide (oAβ) induce an increase in TNF-α levels that is blocked by IAXO101 (IAXO), a TLR4 antagonist. Our hypothesis is that IAXO101 will reduce the neuroinflammation associated with AD pathology, particularly in ♀E4FAD mice.

Methods: EFAD mice, specifically ♀E3FAD, ♂E4FAD, ♀E4FAD, were treated with vehicle control (VC) or IAXO via sub-cutaneous injection using two treatment paradigms: prevention (PVT) paradigm from 4-6 months (M) or reversal (RVS) paradigm from 6-7M. Learning and memory were tested by Morris Water Maze (MWM). Amyloid deposition, and neuroinflammation were assessed by immunohistochemistry. IL-1β was measured by ELISA.

Results: As a measure of indirect target engagement, IAXO treatment reduced neuroinflammation in ♀E4FAD with both paradigms. For an AD therapeutic, efficacy is defined as enhanced or retained cognition. We operationally defined surrogate efficacy as enhanced MWM learning or memory performance. While the IAXO- and VC- treated ♀E3FAD mice learned in both paradigms, only the IAXO-treated ♀E4FAD mice learned in both the paradigms. IAXO-treated ♀E4FAD mice also showed an improvement in memory with both paradigms. IAXO treatment reduced amyloid pathology in ♀E4FAD mice only in the RVS paradigm.

Conclusion: IAXO is effective in reducing neuroinflammation only in ♀E4FAD mice, either due to severity of AD pathology, a compromised BBB or mechanisms not yet identified. Thus, future anti-inflammatory therapeutics are a potential alternative or a combination therapeutic approach for AD in female *APOE4* carriers.

Lay Language: Increased inflammation in the brain is one of the early events in Alzheimer's disease (AD) progression in humans. Thus, targeting inflammation may decrease AD symptoms. However, anti-inflammatory drugs so far have not been successful, partly due to complexity of AD. People with the E4 variant of APOE gene have increased odds of AD risk compared to E3 variant carriers. Also, women have increased AD risk compared to men. To target early inflammation in the brain in the context of AD, we used a novel drug that inhibits a protein that modulates inflammation in the brain. We tested this drug in a mouse model that has the human variants of APOE3 and APOE4 and shows progressive increase in AD pathology with age, mimicking the progression of AD in humans. In this study, the novel drug improved cognition, decreased brain inflammation and decreased AD pathology in female mice that have human APOE4. Thus, the drug may be a potential alternative or a combination medication for the high-risk population, females with *APOE4* gene.

Poster 2

Anti-CD49d Antibody Treatment Improves Survival and Attenuates Neurocognitive Deficits after Traumatic Brain Injury in Aged Mice

Zhangying Jennie Chen^{1,2}, Kacie Ford¹, Mecca Islam¹, Booker Davis¹, and Steven Schwulst¹

¹ Department of Surgery, Division of Trauma and Critical Care, Northwestern University Feinberg School of Medicine, Chicago IL

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Introduction: Patients aged 65 years and older account for an increasing proportion of patients with TBI and aged TBI patients suffer increased morbidity and mortality as compared to young TBI patients. Our prior data demonstrated a marked accumulation of CD8+ T-cells within the injured brain of aged TBI mice as compared to young TBI mice. This may be one of the mechanisms underlying the differential TBI outcomes between aged and younger TBI subjects. Therefore, we hypothesized that blocking infiltration of peripheral T-cells into the injured brain would improve neurocognitive outcomes in aged mice after TBI.

Methods: Young (4-month; N=50) and aged (18-month; N=56) male C57BL/6 mice underwent TBI via controlled cortical impact vs. sham injury. We utilized an anti-CD49d antibody (aCD49d Ab), an FDA approved drug that blocks the $\alpha 4$ integrin, to attenuate infiltration of lymphocytes into the injured brain. 300 μ g of aCD49d Ab, or its isotype control, were administered 2 hours post-TBI. Dosing was repeated every 2 weeks. At 1 week after injury, neurocognitive testing was performed. Zero maze was used as to assess anxiety. Fear conditioning was used to assess associative memory. Novel object recognition was used to assess contextual memory. Gait was evaluated using DigiGait. Mortality was tracked, and plasma was collected for cytokine analysis at the time of sacrifice. High-parameter flow cytometry was employed to phenotype distinct subtypes of lymphocytes within the brains.

Results: aCD49d Ab treatment significantly improved post-TBI survival ($p=0.042$), species-specific anxiety level ($p=0.0302$), spatial memory ($p=0.0175$), recognition memory ($p=0.0034$), associative learning ($p=0.0034$) and post-TBI gait impairment of the left forelimb ($p=0.0375$) and right hindlimb ($p=0.0421$) in aged mice 2 months post-TBI as compared to aged TBI mice that received isotype control Ab. Cytokine analyses indicated an augmented Th2 response after repeated aCD49d Ab treatment with increased IL-4 ($p=0.0144$) & IL-13 ($p=0.0004$) in the plasma aged mice treated with aCD49d Ab as compared to isotype control. Notably, aCD49d Ab treatment significantly reduced overall accumulation of activated CD8+ cytotoxic T-cells ($p=0.0294$) and activated effector CD8+ T-cells ($p=0.0312$) within the injured brains of aged mice after TBI. Meanwhile, no difference in mortality, neurocognitive outcome, or motor function was detected in young mice after aCD49d Ab treatment.

Discussion: We hypothesized that blocking T-cell infiltration into the brain after TBI would improve neurocognitive outcomes in aged mice after TBI. We found that aCD49 Ab treatment blocked the infiltration of T-cells into the injured brain, improved survival, and attenuated neurocognitive and gait deficits. Hence, aCD49d Ab may be a promising therapeutic intervention in aged TBI subjects—a population that is often excluded in clinical trials of TBI.

Lay Language: Traumatic brain injury (TBI) occurs as a result of a severe physical injury or car accident and is a major cause of death and disability, with the highest incidence occurring in older adults. However, there have not been many studies investigating post-TBI treatments in older patients. In this study, we utilize an FDA-approved antibody to prevent T-cells from entering the injured mouse brains and investigate whether blocking T-cells can have improved TBI outcomes in specifically older mice.

Targeting TDP-43 loss-of-function induced mis-splicing in ALS-FTD

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Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease caused by the loss of motor neurons (MNs) from the brain and spinal cord, leading to more than 1 in 500 deaths in adults. ALS is genetically diverse, yet approximately 97% of cases share TDP-43 proteinopathy such that TDP-43 aggregates in the cytoplasm and concomitantly depletes in the nucleus. TDP-43 proteinopathy also occurs in ~45% of frontotemporal dementia (FTD) and 40% of Alzheimer's Disease (AD) cases. TDP-43 is an RNA-binding protein that is critical in RNA metabolism and splicing. Because of its trans-localization and loss-of-function, several dozen genes are mis-spliced in ALS-FTD patient samples, including *UNC13A* and *KCNQ2*. *UNC13A* and *KCNQ2* encode a synaptic protein and an ion channel, respectively, that play fundamental roles in motor neuron physiology. Upon TDP-43 nuclear depletion, a cryptic exon (between exons 21 and 22) in *UNC13A* is spliced in, and a coding exon (exon 5) in *KCNQ2* is spliced out, which ultimately leads to reduced function of both genes because of non-sense mRNA-mediated decay for *UNC13A* and mislocalization for *KCNQ2*. Here we set out to establish a cellular system to study these mis-splicing events using human induced pluripotent stem cells (hiPSCs)-derived motor neurons treated with TDP-43 siRNAs. We confirm that TDP-43 knockdown induces mis-splicing in both genes in human motor neurons. We further design and screen gene-specific antisense oligonucleotides (ASOs) targeting the mis-splicing events in these two genes. Lastly, we multiplex ASOs from each gene using spherical nucleic acids (SNAs) and deliver multiplexed SNAs to hiPSC-derived motor neurons to restore the function of *UNC13A* and *KCNQ2*. Together, this study establishes a cellular system to study TDP-43 nuclear depletion-induced mis-splicing, identifies effective splice-modulating ASOs for *UNC13A* and *KCNQ2*, and develops multiplexed SNAs to target two mis-splicing events upon TDP-43 nuclear depletion as a proof-of-concept experiment of targeting mis-splicing in ALS-FTD.

Lay Language: TDP-43 dysfunction has been found in several neurodegenerative disorders, including amyotrophic Lateral Sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's Disease (AD). TDP-43 dysfunction leads to mis-splicing several dozen genes, compromising their physiological functions. This study aims to develop an innovative approach to suppress mis-splicing collectively. We first establish a cellular system to study TDP-43 dysfunction-induced mis-splicing using human induced pluripotent stem cells (hiPSCs)-derived motor neurons. We then design antisense oligonucleotides (ASOs) targeting two mis-spliced genes and screen ASOs using the cellular system. Lastly, we multiplex ASOs from each gene using spherical nucleic acids (SNAs) and deliver multiplexed SNAs to hiPSC-derived motor neurons to restore genes' function. Together, this study establishes a proof-of-concept experiment of collectively targeting TDP-43 dysfunction-induced mis-splicing.

Poster 4

Bone morphogenetic protein signaling is exacerbated in Alzheimer's Disease

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Purpose: Aging is the greatest risk factor for Alzheimer's disease (AD). Aging causes multiple changes in the brain, one of which is increases in bone morphogenic protein signaling (BMP). We have identified an inverse relationship between higher BMP signaling and hippocampal cognition in aged animals and are looking at BMP as a candidate pathway to better understand mechanisms underlying risk and resilience to cognitive decline in aging and AD. Here we wanted to explore how levels of BMP may relate to cognitive impairment due to underlying AD.

Methodology: We first wanted to assess levels of BMP signaling and downstream effectors across the Alzheimer's disease pathological cascade. Using postmortem hippocampal tissue obtained from the Northwestern Alzheimer's Disease Research Center brain bank we assessed levels of BMP-4. Cases with low ADNC were treated as controls and high ADNC considered AD cases. Additionally, we compared levels of BMP-4 cognitive dementia rating (CDR) score to establish a possible relationship between BMP and cognitive status.

Findings: Protein analysis of post-mortem tissue samples revealed elevated BMP-4 in AD cases compared to controls. Levels of BMP-4 were not significantly different between control cases and age matched intermediate ADNC despite hippocampal pathological changes in intermediate cases, consistent with BMP levels correlating with cognitive status. This work expands our knowledge about BMP and cognition from animals to humans. Together these data demonstrate that hippocampal BMP-4 is elevated in AD. Further, higher levels of BMP-4 appear to be associated with greater cognitive impairment.

Impact Statement: BMP signaling is exacerbated by biological aging. Here we demonstrate that this signaling pathway is further increased in AD and higher BMP is associated with worse cognition. Understanding the relationship between BMP signaling and cognition may provide insight into the development of disease modifying therapies to lower BMP levels and preserve cognitive decline in patients living with dementia.

Lay Language: Bone morphogenic protein (BMP) is one pathway increased by the aging process. Increased BMP signaling leads to impaired memory in mice. These results show an increase in BMP signaling in the Alzheimer's disease brain and suggests that levels of BMP proteins are related to severity of cognitive decline. This suggests that BMP could be a potential target for AD disease modifying therapies.

DISE Contributes to Neurotoxicity in Alzheimer's Disease

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Alzheimer's disease (AD) is characterized by progressive neurodegeneration, but the specific events that cause cell death remain poorly understood. We recently discovered a powerful mechanism of cell death called Death Induced by Survival gene Elimination (DISE) (2) where toxic short (s)RNAs/miRNAs that are rich in G-rich seeds enter the RNA induced silencing complex (RISC) and kills cells by targeting genes essential for cell survival (1). The RISC of most cells is occupied by miRNAs with nontoxic seeds, which may protect them from DISE by blocking loading of toxic sRNAs. However, during aging miRNA expression decreases and toxic sRNAs may enter the RISC more readily leaving cells primed for DISE. We analyzed RISC bound sRNAs (R-sRNAs) of in vitro, in vivo AD mouse models, aged mice, and AD patients and showed that in mouse models that show neurodegeneration and during aging R-sRNAs shift to more toxic seeds. In contrast, in cells that survived in post-mortem brains of AD patients and "SuperAgers", R-sRNAs shift to more nontoxic seeds, supporting a protective function of miRNAs. We provide evidence that DISE contributes to neuronal loss seen in AD and increasing the levels of protective miRNAs in the brain could lead to a novel way of treating the disease.

Lay Language: Alzheimer's disease (AD) is characterized by progressive neurodegeneration, but the specific events that cause cell death remain poorly understood. We recently discovered a powerful mechanism of cell death called Death Induced by Survival gene Elimination (DISE) (2) where toxic short (s)RNAs/miRNAs that are rich in G-rich seeds enter the RNA induced silencing complex (RISC) and kills cells by targeting genes essential for cell survival (1). The RISC of most cells is occupied by miRNAs with nontoxic seeds, which may protect them from DISE by blocking loading of toxic sRNAs. However, during aging miRNA expression decreases and toxic sRNAs may enter the RISC more readily leaving cells primed for DISE. We analyzed RISC bound sRNAs (R-sRNAs) of in vitro, in vivo AD mouse models, aged mice, and AD patients and showed that in mouse models that show neurodegeneration and during aging R-sRNAs shift to more toxic seeds. In contrast, in cells that survived in post-mortem brains of AD patients and "SuperAgers", R-sRNAs shift to more nontoxic seeds, supporting a protective function of miRNAs. We provide evidence that DISE contributes to neuronal loss seen in AD and increasing the levels of protective miRNAs in the brain could lead to a novel way of treating the disease.

Poster 6

Single cell transcriptomics reveals cerebrospinal fluid immune dysregulation during healthy brain aging and cognitive impairment

Natalie Piehl, Lynn van Olst, Abhirami Ramakrishnan, Victoria Teregulova, Brooke Simonton, Ziyang Zhang, and David Gate

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Cerebrospinal fluid (CSF) contains a tightly regulated immune system. Yet, little is known about how CSF immunity is altered with aging or neurodegenerative disease. Here, we performed single cell RNA sequencing on CSF from 45 cognitively normal subjects ranging from 54-82 years old. We reveal upregulation of lipid transport genes in monocytes with age. We then compared this cohort to 14 cognitively impaired subjects. In cognitively impaired subjects, downregulation of lipid transport genes in monocytes occurred concomitantly with altered cytokine signaling to CD8 T cells. Clonal CD8 T effector memory cells upregulated C-X-C Motif Chemokine Receptor 6 (CXCR6) in cognitively impaired subjects. The CXCR6 ligand, C-X-C Motif Chemokine Ligand 16 (CXCL16), was elevated in CSF of cognitively impaired subjects, suggesting CXCL16-CXCR6 signaling as a mechanism for antigen-specific T cell entry into the brain. Cumulatively, these results reveal cerebrospinal fluid immune dysregulation during healthy brain aging and cognitive impairment.

Lay Language: Cerebrospinal fluid (CSF) contains a tightly regulated immune system. Yet, little is known about how CSF immunity is altered with aging or neurodegenerative disease. Here, we performed single cell RNA sequencing on CSF from 45 cognitively normal subjects ranging from 54-82 years old. We reveal upregulation of lipid transport genes in monocytes with age. We then compared this cohort to 14 cognitively impaired subjects. In cognitively impaired subjects, downregulation of lipid transport genes in monocytes occurred concomitantly with altered cytokine signaling to CD8 T cells. Clonal CD8 T effector memory cells upregulated C-X-C Motif Chemokine Receptor 6 (CXCR6) in cognitively impaired subjects. The CXCR6 ligand, C-X-C Motif Chemokine Ligand 16 (CXCL16), was elevated in CSF of cognitively impaired subjects, suggesting CXCL16-CXCR6 signaling as a mechanism for antigen-specific T cell entry into the brain. Cumulatively, these results reveal cerebrospinal fluid immune dysregulation during healthy brain aging and cognitive impairment.

Poster 7

Peripheral immunomodulatory effects of Apolipoprotein E4 in Alzheimer's disease

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Background: Apolipoprotein E (APOE) is a lipid and cholesterol transport molecule known to influence Alzheimer's disease (AD) risk in an isoform-specific manner. In particular, the APOE E4 allele is the largest genetic risk factor for late-onset sporadic AD. Our recent findings uncovered activated, clonally expanded T cells in AD cerebrospinal fluid (CSF). This T cell phenotype occurred concomitantly with altered expression of APOE in CSF monocytes. Yet, whether APOE variants differentially affect peripheral immunity systems remains unknown.

Method: In this study, we performed targeted immune profiling using single-cell epigenetic and transcriptomic analysis of peripheral blood mononuclear cells (PBMC). We analyzed 55 age-matched healthy control (HC) and AD patients with equal distribution of APOE E3/E3, E3/E4, and E4/E4 genotypes.

Result: We reveal dysregulation in monocytes and clonally expanded T cells that are distinct to AD patients carrying the APOE E4/E4 genotype. Additionally, we find APOE isoform-dependent chromatin accessibility differences that correspond to RNA expression changes.

Conclusion: Cumulatively, these results uncover APOE isoform-dependent changes to peripheral immunity in AD.

Lay Language: Apolipoprotein E (APOE) is a fat transport molecule with several forms (including E3 and E4) known to influence Alzheimer's disease (AD) risk. In particular, the APOE E4 is the largest genetic risk factor for late-onset sporadic AD. Our recent findings uncovered activated immune cells and altered levels of the gene encoding APOE in AD cerebrospinal fluid (CSF). Yet, whether different forms of APOE affect blood immune systems in AD remains unknown. In this study, we analyzed immune cells in the blood using DNA and RNA profiling of 55 age-matched healthy control (HC) and AD patients with an equal distribution of APOE E3 and E4 carriers. We reveal parallel changes in DNA and RNA of immune cell types known as monocytes and activated central memory T cells in AD patients distinct to those carrying APOE E4. These findings reveal that different forms of APOE may affect AD risk via changes in blood immunity.

Annexin A6 in membrane resealing in Alzheimer's disease

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Background/Purpose: The AD brain contains amyloid plaques consisting of the β -amyloid protein and neurofibrillary tangles containing hyperphosphorylated, aggregated tau protein. Amyloid plaques form first and likely give rise to tangles, but the mechanistic link between them is unclear. The local environment around the plaque is toxic to neurons, characterized by synaptic loss, activated microglia, and vesicle-filled dystrophic neurites, which accumulate aggregation-prone, phosphorylated forms of tau. We hypothesize that dystrophic neurites form because axonal contact with plaque β -amyloid causes membrane damage, which leads to calcium influx, kinase activation, tau hyperphosphorylation, microtubule disruption, trafficking impairment, and accumulation of lysosomes, endosomes, and autophagosomes. Since dystrophic neurites generate β -amyloid and impair synapse function, preventing their formation would be beneficial. We hypothesize that preventing or repairing neuronal membrane damage caused by β -amyloid plaques would decrease the formation of dystrophic neurites. In this poster, we demonstrate that overexpressing the membrane repair protein annexin A6 in the 5XFAD mouse model of Alzheimer's disease reduces dystrophic neurites and phospho-tau.

Methodology: To localize annexin A6 in AD mouse model brains and human brains, floating sections were immunostained, then imaged using confocal microscopy. Primary neurons from mice expressing genomic encoded annexin A6-GFP underwent laser injury to induce membrane damage and were imaged on a multiphoton microscope. To overexpress annexin in 5XFAD mouse neurons, AAV8 hSyn-A6-GFP or AAV8 hSyn-GFP (control) was injected into the ventricles of day-old mouse pups. At 4 months of age, the mice were perfused, and half the brain fixed for sectioning and immunofluorescence analysis, the other half frozen and processed for immunoblotting. To quantify dystrophic neurites, coronal sections (3/mouse) were stained with antibodies to A β 42 (plaques) and Lamp1 (dystrophic neurite marker) and imaged on Ti2 widefield microscope. NIS-Elements image analysis software was used to detect each plaque as a region of interest (ROI), and measure the area within the ROI covered by A β 42 or LAMP1 stain to generate a ratio of Lamp1:A β 42 for each plaque. The same method was used to quantify the ratio of ptau-181 to the amyloid stain thiazine red (ThR). To determine if recombinant A6-HIS bound dystrophic neurites, mice received a single stereotaxic injection of A6-HIS purified from *E. coli* into the cortex, then were sacrificed 4 hours later and brain prepared for sectioning and immunofluorescence.

Findings: In wild type mice and cognitively normal humans, annexin A6 localized to the plasma membrane of neurons, but not to astrocytes or microglia. Brains of 5XFAD and NLGF mouse models of amyloidosis, and humans with AD showed A6 localized to membranes of dystrophic neurites. After membrane injury of neurons, genomic and recombinant annexin A6 localized to the site of damage. In mice that overexpress annexin A6-GFP in neurons, LAMP1:A β 42 and ptau-181:ThR ratios were significantly reduced, indicating fewer dystrophic neurites. Microglia and astrocytes around the plaques remain unchanged. Recombinant A6 injected directly into the brain localizes to the membrane of dystrophic neurites.

Conclusions: Annexin A6 is found at neuronal and dystrophic neurite membranes where it can play a role in membrane resealing. Since overexpression of A6 reduced dystrophic neurites and phospho-tau, increasing A6 levels has potential as an Alzheimer's therapeutic. As recombinant A6 binds damaged neuronal membranes from outside the cell, therapeutic effects of recombinant A6 on reducing dystrophic neurites and tau pathology will be explored.

Lay Language: Traumatic brain injury (TBI) occurs as a result of a severe physical injury or car accident and is a major cause of death and disability, with the highest incidence occurring in older adults. However, there have not been many studies investigating post-TBI treatments in older patients. In this study, we utilize an FDA-approved antibody to prevent T-cells from entering the injured mouse brains and investigate whether blocking T-cells can have improved TBI outcomes in specifically older mice.

Increased production of Reactive Oxygen Species by Human Microglia in SuperAgers in Response to Soluble Oligomeric and Fibrillar Amyloid- β Peptide

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Human microglia are responsible for the first line of immune defense in the central nervous system and have been found to have a central role in the pathobiology of cognitive decline. Among various factors associated with cognitive decline is the deleterious effect of the amyloid- β (A β) peptide that can lead to Alzheimer's disease (AD). When A β accumulates in the brain, an inflammatory immune response is triggered in activated microglia. Activated microglia produce reactive oxygen species (ROS) in response to foreign or abnormal substances. Prolonged activation of microglia in chronic conditions such as AD can have adverse effects on neurons. Most studies of microglia response to A β have utilized rodent models. The purpose of this study was to investigate this response in microglia isolated and cultured from postmortem human brains of cognitive SuperAgers in comparison to normal individuals. Cognitive SuperAgers are individuals 80 years of age or older, with episodic memory performance that is equal to or better than those of individuals 20-30 years their junior. Microglia from the gray matter of fresh autopsied prefrontal cortical tissue of eight elderly participants (4 SuperAgers and 4 normal control) were extracted and cultured. Cells from passage 3 - 5 were seeded in 8 chamber slides (3x10 cells/well). Microglial cells were cultured in the presence of microglia medium (SienCell, Inc), supplemented with 5% fetal bovine serum, 100 U/ml penicillin, 100 μ g/ml streptomycin, 1 ml/500ml primocin, 1% microglia growth supplement (ScienCell), and 10 ng/ml GM-CSF (Sigma-Aldrich). After the cells reached 70% confluence, the media was removed and replaced by 100 μ l of 1mg BSA/RPMI. Various concentrations of fibrillar or soluble oligomeric A β (2.5 μ g, 5 μ g, and 10 μ g), prepared using specific aging protocols, or vehicle were added to the wells. After a 30-minute incubation at 37°C, 20 μ l of 6 mg/ml Nitroblue Tetrazolium (NBT) was added to each well and incubated for an additional 90 minutes. The media was then removed, and 100 μ l/well methanol was added (5 minutes) to fix the cells. The slide was rinsed 3 times in xylene and coverslipped with SubX mounting media. Optical density of the blue ROS reaction product (formazan salt) in individual microglia was measured using the Image J software. Dose-dependent increases in ROS production by microglia were observed in all cases in response to stimulation by A β in both oligomeric and fibrillar forms. Oligomeric A β resulted in greater ROS production by human microglia when compared with fibrillar A β , and this effect was more pronounced in SuperAgers. Microglia of SuperAgers produced slightly greater ROS at every dose and at the various conditions. Additionally, higher percent deviation from blank was observed in SuperAgers with a greater distinction at 10 μ g concentration of oligomeric A β . These findings demonstrate that human microglia are activated in the presence of both oligomeric and fibrillar A β , but more so after stimulation by oligomeric A β . They also suggest that microglia from SuperAgers may mount a stronger protective reaction than microglia from cognitively normal individuals. Cultured primary human microglia will be useful in studies of microglia function and inflammation.

Lay Language: Microglia are specialized immune cells of the brain and play an important role in responding to foreign substances and misfolded proteins, such as the amyloid beta (A β) peptide, that can lead to Alzheimer's disease. When these misfolded proteins accumulate, an immune response is initiated and activated microglia release reactive oxygen species (ROS), which are damaging to cells, in an attempt to combat invaders. In this experiment, we measured the levels of ROS production by microglia in SuperAgers and normal controls in the presence of increasing concentrations of A β and found that there is an increased response in SuperAgers. This may indicate a superior protective response to foreign materials by SuperAgers compared to normal individuals.

Poster 10

Evaluation of the 10-item Communicative Participation Item Bank for Persons with Primary Progressive Aphasia and their Communication Partners

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Primary progressive aphasia (PPA) is a clinical dementia syndrome that results from neurodegenerative disease. Clinical symptoms of PPA include difficulties with word finding, comprehension, and expressive language, among other cognitive impairments. Because of the specific language difficulties associated with PPA, it is important to develop and validate outcome measures relevant to the communication experiences of persons with PPA (PwPPA) and their communication partners (CP). The 10-item Communicative Participation Item Bank (CPIB) was validated as a disorder-agnostic measure of communication participation. Respondents rate the degree to which their condition interferes with communication in different contexts (e.g., communicating in a small group of people, giving detailed information, having a long conversation about a book or movie) on a four-point Likert scale ("Not at all" to "Very much"). While the CPIB has been validated in a broad range of acquired communication disorders in adults, it has not been evaluated in individuals with PPA and their CPs. The purpose of this study is to evaluate the face and content validity of the 10-item CPIB for individuals with PPA and their CPs. For this study, we are conducting cognitive debriefing interviews with individuals diagnosed with mild to moderate PPA and their CPs. We will conduct interviews with up to 30 dyads (PwPPA + CP). PwPPAs and CPs each complete one cognitive debriefing interview via Zoom. During the interview, participants complete the CPIB and respond to semi-structured questions to evaluate the measure format, instructions, response options, item comprehension, and relevance of each item to their experiences with PPA. To evaluate content validity, participants are asked open-ended questions to elicit other relevant communication experiences that may be missing from the questionnaire. CPs also complete two additional self-report measures: the Montgomery Burden Interview (MBI) and the Revised Dyadic Adjustment Scale (RDAS). The MBI is a measure of caregiver burden and the RDAS is a measure of relationship quality in the context of a caregiving relationship. Here we will report preliminary data from the initial participant dyads enrolled into this study. Preliminary findings indicate a need for an additional response option (e.g., "Somewhat") to better represent the range of communication difficulties faced by PwPPAs. Participants have stated that shorter items are easier to comprehend and that examples are helpful to understanding the meaning of individual items. Additionally, several participants have suggested that talking on the phone, emailing, and texting are important communication activities missing from this measure. As such, preliminary findings indicate that some modifications to the 10-item CPIB short form may be needed for use with PwPPAs and their CPs. Modifying this measure may allow for more accurate measurement of communication participation in PPA, an important contributor to quality of life in PPA.

Lay Language: Primary progressive aphasia (PPA) is a dementia syndrome that impairs language functions such as speaking and understanding. It is important to measure how much PPA interferes with people's ability to participate in communication activities, such as communicating in a small group of people, asking a question, or having a long conversation about a book or movie. The 10-item Communicative Participation Item Bank (CPIB) is a survey commonly used by speech-language pathologists to measure how much a condition interferes with communication activities but has not yet been evaluated rigorously in persons with PPA. In this study we are interviewing people with PPA and their communication partners as they complete the CPIB, to gather their impressions regarding its clarity, relevance to their experiences with PPA, and if important communication experiences are captured by this survey. This research will help us develop a better questionnaire for individuals living with PPA and their families.

Poster 11

Suitability of Goal Attainment Scaling in Older Adult Populations with Neurodegenerative Disease Experiencing Dementia or Cognitive Impairment: A Systematic Review

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Background: Identification of responsive outcome measurements for assessing functional change related to cognition, communication, and quality of life for those with Primary Progressive Aphasia (PPA) or related dementia is important for intervention design and clinical care. Goal Attainment Scaling (GAS) is an outcome measure used to formally specify goals and measure goal attainment in clinical settings that has been shown to be useful in cognitive rehabilitation. This study conducted a systematic review to evaluate the suitability of GAS as an outcome measure in older adult populations with neurodegenerative disease experiencing dementia or cognitive impairment.

Methodology: A systematic review was registered with PROSPERO and performed by searching ten electronic scientific databases (PubMed, Medline OVID, CINAHL, Cochrane, Embase, Web of Science, PsychINFO, Scopus, OTSeeker, RehabDATA) and four registries (Clinicaltrials.gov, Grey Literature Report, Mednar, Open Grey). 882 eligible articles were identified and screened by two independent reviewers. A summary measure of responsiveness (post-intervention minus pre-intervention mean GAS T-score) was then compared across eligible studies using a random-effects meta-analysis.

Results: Ten of the 882 studies met criteria for final analysis. Responsiveness analyses showed post- and pre-intervention GAS goals were significantly different from zero ($Z=7.48$, $p<0.00001$), with post-intervention GAS scores being higher than pre-intervention GAS scores.

Conclusion: GAS showed an improvement in goal attainment across different dementia patient populations and intervention types. The results support GAS as being highly responsive to functional change and suggest it is suitable for use in older adult populations with neurodegenerative disease experiencing dementia or cognitive impairment.

Lay Language: This project looks at a measurement tool used in speech-language, occupational, and cognitive therapy called Goal Attainment Scaling (GAS). GAS allows people to set specific goals and then measures their progress towards those goals while they are receiving treatment. This project specifically looks at how well GAS measures change in people with neurodegenerative disease who are experiencing cognitive difficulties. We searched 8 databases and found over 500 relevant articles. We searched these articles to make sure they focus on people with cognitive difficulties, include GAS scores, and include people receiving treatment focused on cognition, communication, or quality of life. Ten articles fit these criteria. We analyzed GAS scores from before and after treatment for each of these articles. Our results showed that GAS is an effective way to measure change in this population. As such, it is likely a useful tool in speech-language, occupational, and cognitive therapies.

Poster 12

Trajectories of Neurocognitive Decline in Aphasic versus Behavioral Dementia Syndromes due to Pick Disease

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State of the art: This study compared rates of neurocognitive decline and pathologic burden in two distinct dementia syndromes—primary progressive aphasia (PPA) and behavioral variant frontotemporal dementia (bvFTD)—caused by FTLD 3R-tauopathy of Pick disease (PiD).

Methodology: Eleven cases with postmortem PiD were identified from the Northwestern ADRC brain bank (bvFTD, N=6; PPA, N=5). Uniform composite scores for global cognition, language, executive function, and memory were calculated from yearly visits. Domain-specific rates of decline (i.e., slope) were calculated between initial visit (1-5 years from symptom onset; global CDR=0.5-1) and final visit (1 year prior to 'untestability' due to disease severity). Unbiased stereology was performed using AT-8-stained sections from bilateral neocortical regions [middle frontal, inferior parietal, and superior temporal gyri] per case to quantify Pick body densities. T-tests compared trajectories of decline and pathologic burden between groups.

Results: The bvFTD group showed fastest rates of decline (i.e., steepest slope) in global cognition and executive functioning, whereas PPA cases showed fastest decline in language. As expected, executive functioning declined significantly faster in bvFTD than PPA ($p=0.027$). bvFTD patients were rendered "untestable" significantly sooner than PPA patients ($p<0.05$). Stereological analysis revealed significantly greater bilateral neocortical densities of Pick bodies in bvFTD compared to PPA at autopsy ($p<0.01$).

Conclusion: Preliminary analysis of domain-specific longitudinal performance appears to be concordant with the behavioral versus aphasic phenotype characteristic of bvFTD and PPA, respectively. Compared to PPA, cases with bvFTD demonstrated swifter neurocognitive decline, which appears to be linked with overall greater PiD burden in neocortex.

Lay Language: Two types of atypical dementia syndromes are 1) primary progressive aphasia (PPA), characterized by progressive impairment of language, and 2) the behavioral variant of frontotemporal dementia (bvFTD), characterized by progressive dysfunction in personality. Interestingly, both PPA and bvFTD can be caused by the same pathology known as Pick's disease (PiD). In this study, we investigated rates of decline in cognition and quantified densities of PiD pathology in regions important for language and/or behavior in those with bvFTD or PPA. Our findings suggest that the "defining" deficits at initial stages of bvFTD and PPA are also the ones that decline the fastest, such that bvFTD patients declined fastest in areas related to planning and attention and PPA patients showed fastest decline in language. We also found that bvFTD patients became too impaired to complete neuropsychological testing ("untestable") significantly sooner than PPA patients. When we quantified PiD pathology, we found that bvFTD patients had significantly greater densities of PiD pathology in their overall neocortex. These results suggest that cognitive decline in PiD may be linked to relative abundance of pathology in the neocortex.

Amygdala pathology in early neuropsychiatric phenotypes due to 3R-Pick disease

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Background: Persons with dementia syndromes such as primary progressive aphasia (PPA) and behavioral variant frontotemporal dementia (bvFTD) often develop neuropsychiatric symptoms (NPS). Various neurodegenerative diseases may cause PPA or bvFTD, including frontotemporal lobar degeneration (FTLD) with 3-repeat tau pathology (Pick disease, "PiD"). Limbic regions implicated in mood and behavior, such as the amygdala, are highly impacted in FTLD with PiD. This study quantified Pick bodies and activated microglia in the amygdala of individuals with antemortem diagnosis of PPA or bvFTD and postmortem PiD neuropathology and examined associations with initial NPS.

Methods: We identified 16 right-handed cases from the Northwestern University Alzheimer's Disease Research Center brain bank with bvFTD (N=8) or PPA (N=8) due to PiD with unilateral amygdala tissue (basolateral region) available. Fifteen cases had data on 12 NPS assessed via the Neuropsychiatric Inventory-Questionnaire (NPI-Q) from their earliest visit. We performed AT-8 or HLA-DR immunohistochemistry on amygdala sections to visualize Pick bodies or HLA-DR+ activated microglia, respectively. We quantified the density of Pick bodies per mm³ via modified unbiased stereology and used HALO software (Indica Labs) to quantify percent area of HLA-DR immunopositivity. We assessed differences between clinical groups via Welch's t-test (Pick bodies) or repeated-measures two-way ANOVA (HLA-DR). Pearson clinicopathologic correlations were examined between Pick bodies or HLA-DR immunopositivity and initial endorsement of total (out of 12) or behavioral/comportmental (apathy, disinhibition, motor stereotypies, or appetite disturbance) NPI-Q symptoms.

Results: Amygdala Pick body densities were similar between PPA (M=28,822/mm³) and bvFTD (M=29,114/mm³) cases. Compared to bvFTD, PPA cases trended towards a lower percent area of HLA-DR immunopositivity (5.5% vs. 2.4%, $p<0.10$). There was no significant relationship between Pick Body density and initial NPIQ symptoms endorsed across all cases. However, area of HLA-DR immunopositivity was positively correlated with initial endorsement of total ($r=0.47$, $p<0.10$) and behavioral/comportmental ($r=0.54$, $p<0.05$) NPI-Q symptoms.

Conclusions: Our findings suggest that microglial pathology in the amygdala contributes to early neuropsychiatric presentations in PiD, particularly symptoms reflective of behavioral/comportmental disturbance. Future study will investigate the impact of neuronal size and density in the amygdala on NPS in these dementia syndromes due to PiD.

Lay Language: Primary progressive aphasia (PPA) is a language-based dementia, whereas behavioral variant frontotemporal dementia (bvFTD) is characterized by personality changes. PPA and bvFTD are caused by different brain pathologies, which are discovered at autopsy. Many patients develop PPA or bvFTD when tau protein aggregates and spreads throughout the brain, damaging cells. These processes are associated with inflammation in the brain.

For this study, participants with PPA or bvFTD due to "Pick disease," a form of tau pathology, committed to brain donation. We examined tau and inflammation in participants' amygdala, which is a brain region involved in controlling emotions and behavior. We found that levels of tau pathology were similar between PPA and bvFTD. However, inflammation tended to be higher in bvFTD and was associated with more behavioral changes, such as apathy.

Our findings suggest that disease processes beyond brain pathology, such as inflammation, may impact patients' symptoms, representing an additional treatment target.

Poster 14

Spatial extent and intensity of Alzheimer associated tau PET burden is greater in agrammatic than logopenic primary progressive aphasia

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Background: Primary progressive aphasia (PPA) is a clinical dementia syndrome characterized by selective vulnerability of the language network, with salient deficits in language domains. The most common neuropathologies reported for PPA are one of the forms of frontotemporal lobar degeneration (FTLD; ~60%) or Alzheimer disease neuropathologic change (ADNC; ~40%). PPA can be subdivided into clinical subtypes based on specific language deficits. PPA subtypes have differing probabilistic relationships with underlying neuropathology. Semantic and agrammatic (PPA-G) subtypes have the strongest association with FTLD while the logopenic subtype (PPA-L) is most associated with ADNC.

Objective: Examine the flortaucipir PET differences between PPA-L and PPA-G with evidence of ADNC.

Methods: 21 PPA participants were identified based on (1) an agrammatic or logopenic subtype, (2) 18F-flortaucipir PET and structural MRI, and (3) CSF or amyloid PET indicating ADNC and/or autopsy-confirmed ADNC. FreeSurfer segmentations and surfaces provided MRI-guided PET analysis, referenced by hotspot-removed inferior cerebellar gray, analyzed with and without Müller-Gärtner partial volume correction (PVC). Vertex-wise general linear models tested tau PET uptake on subtype covarying for age and meta-region of interest (ROI) tau. All analyses were corrected for multiple comparisons at Benjamini-Hochberg false discovery rate $q=0.05$.

Results: 4 PPA-G participants (average age=67.9±2.7; average meta-ROI-SUVr=2.06±0.42) and 17 PPA-L participants (average age=68.8±7.6; average meta-ROI-SUVr=2.14±0.43) were included (Figure 1). There were significant differences in flortaucipir uptake between the groups, with greater uptake in left and right motor cortex, paracentral lobule, and V2 of the occipital lobe in PPA-G participants compared to PPA-L (Figure 2). Analyzing the data without PVC and using models without covariates did not alter the results.

Conclusions: This study adds further evidence ADNC can result in a PPA-G phenotype. Further, PPA-G may present with an extended spatial distribution and intensity of Alzheimer's type tau, which may inform prognosis, emergence of additional symptoms, and disease progression.

Lay Language: This study investigated differences in the amount and location of abnormal tau protein in the language-related syndrome called primary progressive aphasia (PPA) using PET imaging. The study found that one subtype of PPA, which has difficulty with grammar (agrammatic PPA), had higher levels of tau protein than the other subtype, which has difficulty with finding words (logopenic PPA). The differences were observed across the parietal and occipital lobe. This suggests that agrammatic PPA caused by Alzheimer's disease may have more severe tau protein build-up in the brain, which could impact how the disease progresses. Further PET studies and participants are needed to validate the results.

Epicenters of cortical atrophy in primary progressive aphasia differ by underlying neuropathology

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Introduction: Primary progressive aphasia (PPA) is caused by neurodegenerative disease that selectively targets the (usually) left hemisphere language network. Recent studies suggest that the epicenter of cortical atrophy can be identified based on healthy resting state networks. With this method, typical amnesic Alzheimer disease dementia (ADD) tends to have posterior network epicenters while frontotemporal dementia (FTD) tends to have anterior epicenters. We hypothesized that individuals with PPA would show differential epicenters based on their underlying neuropathology: frontotemporal lobar degeneration (FTLD) or Alzheimer disease neuropathologic change (ADNC).

Methods: Analysis included PPA participants that had undergone structural T1-weighted MRI and had either autopsy, CSF, or PET imaging that indicated ADNC or FTLD neuropathology. We calculated the most likely epicenter of cortical atrophy for each PPA participant using the Human Connectome Project (HCP) multi-modal parcellation, the average resting state fMRI connectivity from 337 healthy HCP participants, and the PPA participant's FreeSurfer-derived cortical thickness w-scored for age. The frequency of atrophy-epicenters between anterior and posterior networks was compared between the PPA-FTLD and PPA-ADNC groups.

Results: We found a significant difference between the frequency of 64 PPA-FTLD participant's anterior and posterior epicenters (51 anterior, 13 posterior) compared to 53 PPA-ADNC epicenters (15 anterior, 38 posterior) with a 2-sided Boschloo's exact test ($p < 0.0000001$). As expected, cortical epicenters were mostly found in the left hemisphere ($n=109/117$).

Conclusion: This study further demonstrates the selective vulnerability of AD or FTLD pathology in a group of well-characterized PPA participants with overlapping clinical deficits but divergent pathology.

Lay Language: This study is about primary progressive aphasia (PPA), a clinical syndrome which affects the language network of the brain. The researchers used brain scans to study the differences between PPA caused by two different diseases: frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD). They found that the areas of the brain affected by the diseases were different, with FTLD mainly affecting the front part of the brain and AD mainly affecting an area further back. This helps us to better understand the differences between these two diseases that cause PPA.

Poster 16

Stereological densities of corticobasal degeneration neuropathology are anatomically distinct in PPA vs bvFTD

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Objective: Primary progressive aphasia (PPA) is a dementia syndrome characterized by gradual dissolution of language and is associated with asymmetric atrophy in the language-dominant hemisphere (usually left). In contrast, behavioral variant frontotemporal dementia (bvFTD) is characterized by a progressive decline in personality and comportment and is associated with relatively symmetric or rightward predominant bifrontal atrophy. This study analyzed the regional and hemispheric distributions of neuronal tau inclusions characteristic of the corticobasal degeneration variant of FTLD-tau pathology (FTLD-CBD) in individuals with PPA and bvFTD. The goal was to establish clinicopathologic concordance between FTLD-CBD and behavioral/comportment vs aphasic dementia syndromes.

Participants and Methods: Seven participants were clinically diagnosed with PPA and 6 were diagnosed with bvFTD, all of whom showed FTLD-CBD as the principal neuropathologic diagnosis. The following sections were stained immunohistochemically with AT-8 to visualize neuronal tau inclusions: bilateral middle frontal gyrus (MFG), inferior parietal lobule (IPL), superior temporal gyrus (STG); and unilateral occipital cortex (OCC). Bilateral anterior temporal lobe (ATL) was analyzed in PPA cases only. Unbiased stereological analysis was performed to compare regional and hemispheric distribution between and within PPA and bvFTD groups.

Results: Overall neocortical (MFG+STG+IPL) neuronal tau densities were significantly greater in the PPA group compared to the bvFTD group ($p < 0.05$). Within the bvFTD group, the highest densities of neuronal tau inclusions were observed in the right MFG (mean=6,871.17; SD=3,220), whereas the left ATL showed highest densities in the PPA group (mean=9,901.81; SD=6,871). There was leftward hemispheric asymmetry of neuronal tau inclusions in IPL, STG and ATL which trended towards significance in the latter ($p = 0.083$). Cortical distributions were symmetric or rightward predominant within the bvFTD group. The occipital cortex was devoid of inclusions.

Conclusions: Preliminary stereological findings of FTLD-CBD neuronal tau inclusions suggest that distributions of pathology are different across two distinct dementia phenotypes. The presence of left-sided neuronal tau inclusions in PPA is concordant with the aphasic phenotype whereas symmetric and frontal-predominant densities in bvFTD are consistent with compartmental dysfunction.

Lay Language: Primary progressive aphasia (PPA) is a dementia syndrome characterized by progressive impairment of language and primary atrophy of left-sided brain regions. Behavioral variant frontotemporal dementia (bvFTD) is a dementia syndrome characterized by progressive dysfunction in personality, and atrophy in frontal brain regions. Interestingly, both PPA and bvFTD are associated with an underlying neurodegenerative disease found at autopsy known as frontotemporal lobar degeneration caused by the protein tau (FTLD-tau). More specifically, both PPA and bvFTD can be associated with a subtype of FTLD-tau called corticobasal degeneration (CBD). This study investigated the distribution of CBD pathology in various brain regions in bvFTD and PPA to establish important relationships between clinical symptoms demonstrated during life and location of disease at death.

Poster 17

Burden of pathology in hippocampal subregions can distinguish amnestic dementia with comorbid Alzheimer's and TDP-43 pathology from pure Alzheimer's and FTLD-TDP

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State of the Art: We investigated hippocampal tau and TDP-43 positivity in individuals with amnestic dementia due to Alzheimer's disease and TDP-43 (AD/TDP), due to Alzheimer's disease alone (AD), and non-amnestic dementia due to TDP-43 proteinopathy associated with frontotemporal lobar degeneration (FTLD-TDP).

Methodology: Seventeen individuals with AD/TDP, 14 individuals with AD, and 19 individuals with FTLD-TDP were identified from the Northwestern AD Research Center brain bank. AD/TDP and AD cases carried an antemortem diagnosis of amnestic dementia and FTLD-TDP cases carried a clinical diagnosis of primary progressive aphasia or behavioral variant frontotemporal dementia. Paraffin-embedded sections from left hippocampi were stained immunohistochemically with phosphorylated TDP-43 and AT-8 antibodies to visualize TDP-43 and tau-positive immunoreactivity, respectively. HALO software (Indica Labs) was used to generate the percentage area occupied by immunopositivity in the dentate gyrus (DG), CA1, and CA3 subfields of the hippocampal complex. Student t-tests and one-way ANOVAs were used to determine group differences.

Results: As expected, TDP-43 immunoreactivity was significantly greater across CA1, CA3, and DG in FTLD-TDP compared to AD/TDP ($p < 0.05$). In AD/TDP, TDP-43 immunoreactivity was low across all hippocampal subregions with CA1 showing greatest relative TDP-43 burden, whereas in FTLD-TDP the DG was most affected. Interestingly, AT-8 immunoreactivity was significantly greater in DG and CA3 in AD/TDP compared to pure AD ($p < 0.05$).

Conclusion: AD/TDP can be distinguished from AD and FTLD-TDP based on differential regional distribution of tau and TDP-43 pathology in the hippocampus. Findings suggest that the severity of neurofibrillary degeneration in AD/TDP may be influenced by TDP-43 proteinopathy.

Lay Language: Recently, it has been discovered that memory-related (amnestic) dementia is often caused by more than one disease in the postmortem brain. This study aimed to investigate two proteins that appear together in almost 80% of individuals with amnestic dementia: 1) Alzheimer's disease characterized by amyloid plaques and tau-tangles and; 2) an abnormal inclusion in brain cells known as TAR DNA-binding protein 43 (TDP-43). The goal was distinguishing the role each disease plays in amnestic dementia. We focused our analysis on three regions of the memory-center of the brain, the hippocampus. We found important and significant differences between the amount and location of tau vs TDP-43 in regions of the hippocampus, which help us to distinguish and better understand these two diseases as separate entities.

Poster 18

Spatial transcriptomics reveals long-term neuropathological effects of amyloid- β immunization

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Modern Alzheimer's disease (AD) therapeutics include immunization against amyloid- β (A β). Intriguingly, neuropathological examination of the first active A β vaccination trial (Elan Pharmaceuticals' AN1792) showed some patients with evidence of A β clearance 15 years post-vaccination. Yet, these patients progressed to severe dementia before death, possibly due to ongoing tau propagation. The AN1792 trial was halted when some participants developed aseptic meningoencephalitis. Imaging features of meningoencephalitis experienced by AN1792 subjects are pathologically reminiscent of amyloid-related imaging abnormalities (ARIA), a complication that currently hampers clinical trials and the therapeutic use of passive A β immunotherapy for AD. To investigate the long-term effects of A β immunotherapy, we utilized spatial transcriptomics on a unique neuropathological cohort of 14 immunized AD cases and a placebo-control from AN1792. Additional controls included 6 naïve (unimmunized) AD cases and 3 non-neurological disease controls. We discovered genetic signatures that distinguish cortical areas cleared of A β in immunized AN1792 subjects. These areas typically express genes that engage in neuronal regeneration and synaptic remodeling, while inflammatory genes were downregulated. We also further investigated the meningeal response to active A β vaccination and found that meningeal immune cells of immunized AD cases overexpress genes that participate in lipid and amyloid processing. Meningeal vessels of immunized AD cases upregulated genes that take part in amyloid clearance from the brain, but also show loss of genes that maintain blood-brain barrier integrity. In sum, we show that active A β immunotherapy induces long-term neuropathological effects in the AD cortex.

Lay Language: New Alzheimer's disease (AD) therapeutics include immunization against a protein called amyloid- β (A β), which is associated with the disease. In the first active A β vaccination trial, AN1792, AD patients showed evidence of A β clearance 15 years after the treatment, but still developed severe dementia before death. To investigate the long-term effects of this treatment, we used a new technique to analyze brain tissue from patients who had been immunized against A β . We found genetic signatures in areas of the brain where A β had been cleared that suggested nerve cells were being repaired and inflammation was reduced. Immune cells and blood vessels in the protective barrier around the brain of immunized AD patients expressed specific genes that help to clear the A β protein from the brain. However, we also found that some of the genes that help maintain the protective barrier were decreased. Overall, these findings show that active immunization against A β has long-term effects on the brain in AD patients.

Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4)

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The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longstanding project to discover clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease. This work has been carried out in the ADNI1, ADNI-GO, ADNI2, and ADNI3 studies since 2004, and it continues with ADNI4. ADNI4 is a multi-center, non-randomized, natural history, non-treatment study that lasts up to 5 years and enrolls participants across three cohorts: (1) individuals with Alzheimer's disease (AD), (2) individuals with Mild Cognitive Impairment (MCI), and (3) cognitively normal (CN) individuals. Overall, 1,500 participants, age 55 to 90, will be enrolled at 65 sites in the United States and Canada. Approximately, 750 participants will be newly enrolled into the ADNI4 study, while 750 participants will be rollover participants from previous ADNI studies. Participants will undergo longitudinal clinical and cognitive assessments, computerized cognitive batteries, biomarker tests, brain imaging scans (including PET and MRI), and optional cerebral spinal fluid analysis. The data collected from the ADNI project has now contributed to more than 2,500 peer-reviewed publications, continuing to inform the field of Alzheimer's research. The ADNI project is very mindful of the need for diversity, equity, and inclusion in Alzheimer's research. In 2020, the ADNI Diversity Taskforce Initiative was launched to support the accelerated enrollment of individuals from underrepresented groups, including, but not limited to racial and ethnic minoritized populations and individuals with lower socioeconomic standing. Our Northwestern site aims to achieve culturally informed community engaged research; and is currently recruiting for an expected start date in June 2023.

Lay Language: The overall goal of the Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4) Study is to determine the relationships among the clinical, cognitive, imaging, genetic and biochemical biomarker characteristics for early detection of Alzheimer's disease (AD). ADNI4 seeks to understand the entire spectrum of AD, as the pathology evolves from normal aging through very mild symptoms, to mild cognitive impairment (MCI), to dementia.

Poster 20

Longitudinal Early-onset Alzheimer's Disease Study (LEADS)

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The Longitudinal Early-onset Alzheimer's Disease Study (LEADS) is a non-randomized, natural history, non-treatment study designed to examine disease progression in individuals with early onset Alzheimer's disease (AD). To develop sensitive clinical and biomarker measures for future clinical and research use, participants will complete annual visits for 2 to 4 years. The study enrolls participants aged 40 to 64 across three cohorts: (1) individuals with Early-onset Alzheimer's disease (EOAD), (2) individuals with Early-onset non-Alzheimer's disease (EO-nonAD), and (3) cognitively normal (CN) individuals. Overall, 100 CN participants and 600 cognitively impaired (CI), both EOAD and non-EOAD participants will be enrolled at approximately 20 sites in the United States. At Northwestern University, we plan to enroll up to 20 CN participants and up to 40 CI participants. The CI cohort will be followed for 4 years, while the CN cohort will be followed for 2 years. Participants will undergo clinical and cognitive assessments, computerized cognitive batteries, biomarker and genetic tests, brain imaging scans (including PET and MRI), and optional cerebral spinal fluid analysis. Researchers will compare data between cohorts to study AD progression and to better understand the causes and changes associated with early onset cognitive decline.

Lay Language: While the risk of Alzheimer's disease (AD) increases with advancing age, approximately 5% of AD patients develop symptoms before age 65 (~280,000 Americans). Patients with early-onset Alzheimer's disease (EOAD), occurring before the age of 65, are an understudied segment of the patient population with AD. To develop more effective AD treatments, scientists need to understand the genetic, biological and clinical processes involved in EOAD. The Longitudinal Early-onset Alzheimer's Disease (LEADS) study will develop a public resource that will enable future planning and implementation of EOAD clinical trials.

Inhibition of ACAT as a Therapeutic Target for Alzheimer's Disease is Independent of ApoE4-lipidation

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Background: Lipid dysregulation is involved in the pathogenesis and progression of neurodegenerative diseases including Alzheimer's Disease (AD). Accumulation of neutral lipids, particularly cholesteryl esters (CE) and triacylglycerol (TAG) stored as lipid droplets (LD), are found in aged and AD brains. Thus, repurposing drugs targeting lipid pathways may be effective AD therapeutics. APOE4, encoding apolipoprotein E4 (apoE4), is the greatest genetic risk factor for Alzheimer's disease (AD), compared to the common APOE3. While the mechanism(s) underlying APOE4-induced AD risk remains unclear, increasing the lipidation of apoE4 is an important therapeutic target as apoE4-lipoproteins are poorly lipidated compared to apoE3-lipoproteins. ACAT (acyl-CoA: cholesterol-acyltransferase) catalyzes the formation of intracellular cholesteryl-ester droplets, reducing the intracellular free cholesterol (FC) pool. Thus, inhibiting ACAT decreases lipid accumulation and increases the FC pool facilitating lipid secretion to extracellular apoE-containing lipoproteins. Previous studies using commercial ACAT inhibitors, including Avasimibe (AVAS), as well as ACAT-knock out (KO) mice, exhibit reduced AD-like pathology and amyloid precursor protein (APP) processing in familial AD (FAD)-transgenic (Tg) mice. However, the effects of AVAS with human apoE4 remain unknown.

Methods: Male E4FAD-Tg mice (5xFAD+/-/APOE4+/+) were treated by oral gavage with AVAS from 6-8 months. Synaptic proteins were measured by Western blot and learning and memory by Morris Water Maze (MWM). Lipid droplets/cell were analyzed by staining with LipidSpot. Aβ pathology was evaluated by measuring Aβ solubility (3-step sequential extraction followed by ELISA) and Aβ/amyloid deposition (immunostaining). Neuroinflammation (astrogliosis and microgliosis) were evaluated by immunohistochemistry. ApoE levels and lipidation were analyzed by apoE-ELISA and native gels.

Results: AVAS treatment significantly reduced intracellular lipid droplets, demonstrating indirect target engagement, increased MWM measures of memory and postsynaptic protein levels, indicating surrogate efficacy, and reduced pathological changes in Aβ solubility/deposition, and neuroinflammation, all critical components of APOE4-modulated AD pathology. However, there was no increase in apoE4 levels or lipidation, while amyloidogenic processing of APP was significantly reduced.

Conclusion: This study suggests that the AVAS-induced reduction in Aβ via reduced APP processing was sufficient to reduce AD pathology, while apoE4-lipoproteins remained poorly lipidated.

Lay Language: Alzheimer's disease (AD) is characterized by brain accumulation of fats and aggregated proteins that lead to cognitive decline. The greatest intrinsic risk factor for AD is inheritance of the APOE4 gene. To identify therapeutic leads, targets, and strategies for the treatment of AD we generated the mouse model called E4FAD. The E4FAD mice contain the human APOE4 gene and develop cognitive decline linked to the accumulation of fats and aggregated proteins.

In this study we reduced the amount of accumulated fats in the E4FAD brain by using a commercially available drug originally designed to reduce the buildup of fats in cardiovascular tissue. Blocking the buildup of fats in E4FAD brain led to a better cognitive performance and lower accumulation of proteins. The efficacy and potential for disease modification observed in this study with human APOE4 supports further testing of therapies that block brain accumulation of fats for AD treatments.

Poster 22

Anatomic Selectivity of Neuronal and Glial Tau in Primary Progressive Aphasia with 4R FTLD-tauopathies

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Introduction: Primary Progressive Aphasia (PPA) can present with underlying 4R-FTLD-tauopathies such as corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP). This study investigated clinicopathologic concordance between PPA and regional distributions of 4R-FTLD PSP and CBD markers in language-related cortical areas and the dentate gyrus (DG) of the hippocampus.

Methodology: Sections were stained immunohistochemically with AT-8 to visualize neuronal inclusions, tufted astrocytes, and coiled bodies in 8 right-handed PPA cases with PSP. Unbiased stereology was performed in bilateral middle frontal gyrus (MFG), inferior parietal lobule (IPL), and left DG. Tau distributions were also analyzed in cases with CBD (N=4; neuronal inclusions, astrocytic plaques, and coiled bodies). One-way ANOVAs and students' t-tests were used to analyze distributions.

Results: The PSP group displayed left-sided asymmetric neocortical predominance of total tau pathology ($p < 0.05$). All cortical regions in PSP had significantly more glial tau pathology (astrocytes + coiled bodies) compared to neuronal inclusions, with a ~5-fold difference in left MFG ($p < 0.05$). CBD cases had significantly more neuronal inclusions than PSP in all regions, with a ~20-fold difference in DG ($p < 0.01$). PSP cases displayed more glial pathology in all regions compared to CBD, with a ~10-fold difference in coiled bodies in left MFG ($p < 0.05$).

Conclusions: Our finding of leftward neocortical predominance of pathology in PPA with FTLD-PSP is concordant with the aphasic phenotype. In PPA, pathologic burden in CBD is primarily neuronal, while PSP is characterized by considerably higher glial tau, offering insights into the selective vulnerability of distinct cell populations within 4R-tauopathies.

Lay Language: Our lab studies the relationship between clinical symptoms of dementia during life and the underlying pathologic disease in the brain found at death. Interestingly, one clinical syndrome can be caused by multiple diseases, so there is no direct correlation between pathology and clinical disorder. To better characterize these complex relationships, we examine the amount and location of specific misfolded proteins in various diseases to see how location of pathology may correlate to clinical presentation.

In this project, we analyzed the brains of people with Primary Progressive Aphasia (PPA), a language-based dementia, that also showed a disease known as Progressive Supranuclear Palsy (PSP), which is characterized by abnormalities in the protein "tau." We examined the distribution of PSP disease markers in several brain regions to distinguish PSP from other diseases that can also present with PPA and found several features unique to those with PPA due to PSP. Further study of this clinicopathologic relationship will lead to earlier and more accurate diagnoses as well as better treatment outcomes.

Poster 23

Shades of Grey in Human White Matter

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Background: Anatomists have long expressed interest in neurons of the white matter, which is by definition supposed to be free of neurons. Hypotheses regarding their biochemical signature and physiological function are mainly derived from animal models.

Methods: Here, we investigate fifteen whole-brain human postmortem specimens, including cognitively normal cases and those with pathologic Alzheimer's Disease (AD). Quantitative and qualitative methods were used to investigate differences in neuronal size and density, and the relationship between neuronal processes and vasculature. Double-staining was used to evaluate co-localization of neurochemicals.

Results: Two topographically distinct populations of neurons emerged: one appearing to arise from developmental subplate neurons and the other embedded within deep, subcortical white matter. Both populations appeared to be neurochemically heterogeneous, showing positive reactivity to acetylcholinesterase (AChE) but not choline acetyltransferase (ChAT), neuronal nuclei (NeuN), nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d), microtubule associated protein (MAP-2), somatostatin (SOM), non-phosphorylated neurofilament protein (SMI-32), and calcium-binding proteins calbindin-D28K, calretinin, and parvalbumin (PV). PV was more richly expressed in superficial as opposed to the deep white matter neurons; subplate neurons were also significantly larger than their deeper counterparts.

Conclusions: NADPH-d, a surrogate for nitric oxide synthase, allowed for the striking morphological visualization of subcortical white matter neurons. NADPH-d-positive subcortical neurons tended to embrace the outer walls of microvessels, suggesting a functional role in vasodilation. The presence of AChE positivity in these neurons, but not ChAT, suggests that they are cholinceptive but non-cholinergic. WMNs were also significantly smaller in AD compared to control cases. These observations provide a landscape for future systematic investigations.

Lay Language: Brain tissue is traditionally separated into two categories: gray matter, which contains the neurons (the cells that send and receive messages between the brain and rest of the body), and white matter, which is found deeper in the brain and made up of other non-neuronal cells and nerve fibers. It was discovered in 1867 that some neurons exist in the white matter in humans; however, their characteristics and functional role in the nervous system have not yet been extensively studied. In this project, we studied white matter neurons (WMNs) in the brains of cognitively normal people as well as people with Alzheimer's disease (AD), a dementia characterized by progressive memory loss. We analyzed features of these WMNs, such as size and distribution, in several brain regions to characterize them in the healthy versus disease state. Additionally, we visually explored the relationship with these neurons and neighboring blood vessels, as it is believed that WMNs modulate blood flow in the brain in some way, potentially impacting cortical circuitry and signaling. Further study of the functional role of these neurons will help us understand their impact on cognition and thus potential role in disease pathogenesis.

Poster 24

White matter tract disruption predicts cognitive dysfunction in patients with glioma

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Introduction: The functional organization of white matter (WM) tracts is not well characterized, especially in patients with intrinsic brain tumors where complex patterns of tissue injury, compression, and neuroplasticity may be present. Patients with infiltrative brain tumors often face a poor prognosis and cognitive deficits, which negatively impact quality of life. This study uses diffusion tensor imaging (DTI) to investigate the relationships between WM tract disruption and cognitive deficits in glioma patients.

Methods: Seventy-nine patients with glioma underwent preoperative DTI and neuropsychological testing. Thirteen WM tracts were reconstructed bilaterally. Fractional anisotropy and streamline number were obtained for each tract as indices of connectivity. Univariate regression models were used to model the association between neuropsychological outcomes and WM tracts.

Results: Glioma patients exhibited variable injury to WM tracts and cognitive deficits on validated neuropsychological tests. We identified 16 age-adjusted associations between WM tract integrity and neuropsychological function. The left IFOF predicted list learning and dominant hand fine motor dexterity. The right IFOF predicted non-dominant hand fine motor dexterity and visuospatial index scores. The left ILF predicted immediate memory list learning and index scores. The right ILF predicted non-dominant hand fine motor dexterity and backwards digit span scores. The left SLF I predicted processing speed. The left SLF III predicted list learning, immediate memory index scores, phonemic fluency, and verbal abstract reasoning. The left cingulum predicted processing speed. The right anterior AF predicted verbal abstract reasoning.

Conclusions: WM tract disruption predicts cognitive dysfunction in glioma patients. This analysis may provide valuable information for neuroscientists to better understand the mechanisms of functional organization of the human brain. Additionally, it may guide maximum surgical resection and functional preservation in glioma patients.

Lay Language: White matter tracts are pathways that connect different regions of the brain and transmit essential information for various cognitive processes. A number of neurological diseases may disrupt these functional networks, including brain tumors. It is important to gain a better understanding of the functions of different white matter tract in patients with brain tumors in order to maximize cognitive preservation throughout treatment. Our findings demonstrate that specific white matter pathways predict memory, motor dexterity, attention, visuospatial ability, processing speed, speech fluency, and abstract reasoning. Additionally, large white matter tracts are associated with multiple functions. These findings highlight important white matter tracts to aim to preserve during surgery. They also may help physicians counsel patients regarding the anticipated cognitive impairments associated with the location of their tumor.

Poster 25

Mesulam Center Brain Scholars Program: Empowering Diverse Next Generation of Neurologist and Neuroscientists

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The Brain Scholars Program is a new initiative of the Mesulam Center for Cognitive Neurology and Alzheimer's Disease (Mesulam Center) committed to providing meaningful, positive scientific and professional experiences in the health sciences for students from underrepresented groups at all levels, with a focus on brain health. This goal will be achieved through several planned activities. First, middle, and high school students from the South Side of Chicago will be invited for day-long visits to the Mesulam Center and exposed to various aspects of brain function and health, including manifestations of cognitive decline in dementias. These visits will include a tour of facilities, mentoring by Center staff in brain sciences, professional development activities such as shadowing scientists and researchers, discussion of potential paid internships and fellowships, and visits to laboratories for exposure to scientific experiments and examination of human brains. Second, university students and junior faculty from underrepresented groups will be paired with the Mesulam Center faculty and staff for mutual learning and exchange. Students who show interest in further exposure to scientific and professional aspects of brain health are invited for more regular visits to the Center, potentially including internships.

To date, the Brain Scholars Program has forged partnerships with a middle school, a high school, and a four-year university on the South Side of Chicago. A 7th grade and an 8th grade middle school class visited the Mesulam Center on separate dates and participated in a variety of activities, including those outlined above. In addition, in partnership with Northwestern Medicine's Discovery Program, a group of high school students from across Chicago visited the Center and took part in discussions with professionals working on various aspects of brain health and dementia, took tests assessing cognitive abilities, observed a neurologic exam, and took a tour of the Center. Overall, so far over 60 students have participated in activities offered by the Brain Scholars Program.

Continuing and expanding its efforts, the Brain Scholars Program hopes to empower increasing numbers of students from underrepresented groups to pursue education and professional careers in the health sciences, including clinical and research efforts related to brain aging and dementia.

Lay Language: The Brain Scholars Program is a new initiative of the Mesulam Center for Cognitive Neurology and Alzheimer's Disease (Mesulam Center) committed to providing meaningful, positive scientific and professional experiences in the health sciences for students from underrepresented groups at all levels, with a focus on brain health. So far over 60 students have participated in activities offered by the Brain Scholars Program through visits to the Mesulam Center. Continuing and expanding its efforts, the Brain Scholars Program hopes to empower increasing numbers of students from underrepresented groups at all levels, from middle school to university, to pursue education and professional careers in the health sciences, including clinical and research efforts related to brain aging and dementia.

Poster 26

Race-Based Corrections in Cognitive Function Scores May Obscure Disparities: The Disparities in Sleep and Cognitive Outcomes (DISCO) study

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Background: Cognitive function is lower in Black adults as compared with non-Hispanic White adults of a similar age. Differences by race in level of education attainment is a central factor in disparities in cognitive function scores. In response to these racial disparities, cognitive assessment toolkits used in population screening studies provide corrected scores that account for race, ethnicity, sex and education. However, corrected scores can obscure differences in cognitive function that are present by race even at the same age and with similar levels of educational attainment. Our objective was to describe differences in uncorrected cognitive function scores between Black and White community dwelling older adults and to test whether the presence of other correlates of cognitive function attenuate those differences.

Methods: We included 229 adults aged 65 years+ (152 white and 77 Black, 67% female) who participated in a cross-sectional study of the role of sleep on disparities in cognitive function using random sampling, through community engagement events and advertisements. Sociodemographic characteristics and medical history were self-reported and blood pressure and body mass index (BMI) were measured. Participants completed the NIH Toolbox assessment of the following cognitive domains: processing speed, working memory, episodic memory, and executive function (inhibition and attention). Fully corrected t-scores account for age, race, ethnicity, sex and educational attainment. We used multivariable linear regression to test the association of race with age corrected and fully corrected t-scores following adjustment for marital status, BMI, and hypertension.

Results: The mean age of study participants was 71.2 years old (SD=4.3), on average participants reported completing 16.4 (SD=2.5) years of education, 46.5% of participants were married, the prevalence of hypertension was 56% and average BMI was 29.1 kg/m² (SD=6.0). As expected, there were no differences by race in the fully corrected t-scores of cognitive function in any of the domains. However, when comparing age corrected scores, Black participants had significantly lower t-scores than White participants for processing speed ($\beta = -12.9$, SE = 4.0, $p < 0.01$), working memory ($\beta = -9.0$, SE = 2.5, $p < 0.01$), episodic memory ($\beta = -8.9$, SE=2.96, $p < 0.01$), and executive functioning ($\beta = -9.8$ SE=2.0, $p < 0.01$).

Conclusions: At a similar age, Black older adults had worse cognitive functioning scores than White participants across all of the NIH toolbox domains. Relying on fully corrected cognitive test scores that account for race may obscure these differences, and in doing so, miss opportunities to initiate additional screenings for cognitive impairment and to launch supportive interventions designed to extend independent living.

Lay Language: Older adults who self-identify as Black or Hispanic/Latino ethnicity are reported to have worse scores on cognitive function tests at a similar age as White or non-Hispanic adults. However, these differences are often hidden when scores from cognitive function include race (e.g., race-corrected). Our goal was to describe the actual differences in scores by race and ethnicity to highlight the higher burden of cognitive decline in Black and Latino older adults.

Poster 27

It's a Family Affair: Addressing the Needs of Black Caregivers Through a Community Based Dementia Caregiver Program

Dianne Oladejo, Joyce Chapman, Tonya S. Roberson, PhD, MPH, Rachel O'Connor, PhD, MPH

Background: Racial disparities exist in dementia diagnosis, co-morbid health conditions, and socioeconomic characteristics between older Black and White adults, compounding caregiving responsibilities for Black families; yet few dementia caregiving programs offer culturally competent, family-centered dementia caregiving programs for Black individuals. In a collaboration between two community-based organizations (CBO) and an academic medical center, we sought to establish a culturally tailored, family-centered, dementia caregiving program for Black individuals on Chicago's Far South Side.

Methods: A team of stakeholders identified by the CBOs was convened to discuss the need for the proposed program and co-designed a key informant interview guide. The team conducted virtual key-informant interviews among Black caregivers of family members with dementia who are residents of the far south side of Chicago.

Results: We conducted 30 interviews. Caregivers were an average of 57 years old, predominantly female (85%), and primarily caring for parents or grandparents. Many shared caregiving responsibilities with other family members. Caregivers recommended the program focus on five top concerns related to their caregiving experience: 1) feelings of stress and burden while being committed to their family member with dementia, 2) education on the progression of dementia and discussion of cultural beliefs, 3) personal experiences with racism and intersectional identities, 4) kinship responsibilities and managing dementia-specific changes that occur with loved ones, and 5) a need for respite and local medical and community-based resources. Anticipated barriers to participation in this program included time, an accessible location to members of the far south, and care for family members during participation.

Conclusion: This feedback will help elevate Black dementia caregiver experiences to better understand the influence that race and culture has on Black caregivers, cultivate a family-centered caregiver program, and contribute to the field because minimal research has focused on Black family-centered dementia caregiving to build capacity in routine caregiving and reduce caregiver stress.

Lay Language: Our research aims to address the unique challenges faced by Black families caring for loved ones with dementia. We collaborated with community-based organizations to create a culturally tailored, family-centered dementia caregiving program for Black individuals on Chicago's Far South Side. We conducted interviews with Black caregivers of family members with dementia and found that they faced high levels of stress and burden, needed education on dementia progression and cultural beliefs, and required respite and access to local resources. By understanding the experiences of Black caregivers, we hope to build capacity in routine caregiving and reduce caregiver stress, ultimately improving the lives of both caregivers and those with dementia.

Poster 28

The Mesulam Center Underrepresented Groups (URG) Recruitment and Retention Taskforce: connecting with, recruiting, and retaining diverse research participants through community engagement

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Background: While the rate of dementia in the United States is expected to double overall by 2060 rates for Blacks are anticipated to double those for Whites (Alzheimer's Association, 2019). Deeply rooted historical race-based mistreatment in research and the health care system at large along with ineffective recruitment approaches persist as barriers to the low participation of Black participants in dementia and brain health studies. Given this persistent disparity, it is critical to develop effective recruitment strategies to reach Black people living with dementia and their families in addition to healthy older adults and encourage their participation in dementia and brain health research. The Mesulam Center Underrepresented Groups (URG) Recruitment and Retention Taskforce was developed to strengthen and cultivate meaningful engagement opportunities with individuals from underrepresented groups in collaboration with community partners; share opportunities for participating in research at the Mesulam Center; and nurture existing research relationships to promote diverse research representation that is more reflective of the community. Here we report on the expanded efforts of the URG Taskforce Recruitment and Retention Taskforce over the past year.

Methods: Leveraging funding from the NIH funded SuperAging and ADNI studies the URG Recruitment and Retention Taskforce expanded its efforts through the addition of two new Community Engagement Coordinators (Timpo and Hunt) and increased community events, partnerships, and educational activities. Utilizing principles of community engaged research (CER) which requires the development of mutually beneficial partnerships that require time, skill and mutual respect, we implemented the strategy of investing in the development of partnerships with key community stakeholders; i.e., community organizations (South Loop Village, Peer Plus Health Advocates, Dementia Friendly Washington Heights, Far South Chicago Coalition), government institutions (Fifth District State Representative Lamont Robinson's office), affordable senior housing independent living facilities, Chicago Public Library System and religious institutions (Progressive Baptist Church, Kingdom Baptist Church, Glorious Light Church). Finally, in light of Northwestern Memorial Hospital's announcement of a planned new advanced outpatient care center in the Bronzeville community we partnered with the NMH community engagement team to coordinate our partnership building efforts in line with their community activation initiative in Bronzeville.

Results: Members of the community engagement team organized and/or attended 65 local community events, 80 meetings with community organizations/members, 15 webinars and trainings and presented at 2 academic conferences. Through these efforts 77% of URG Clinical Trials participants and 62% of SuperAging participants were recruited by way of community engagement efforts. 105 diverse older adults were recruited to be potential participants.

Conclusion: The URG Recruitment and Retention Taskforce team is committed to diversifying our research cohorts through community engagement strategies. As we continue to grow our CER strategies, we will continue to develop new partnerships and strengthen our existing partnerships, develop programming and dissemination strategies to retain existing diverse participants, create culturally tailored study materials and begin to understand the feasibility of developing a participant advisory board.

Poster 29

Using Community-University Partnership to Increase Brain Health Awareness in Community-Dwelling Black Older Adults on the South Side of Chicago

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The older adult population in the United States is rapidly growing and becoming increasingly diverse. With these changes, the onset of Alzheimer's Disease and related dementias (ADRD) is projected to expand, with a disproportionate burden on Black and African American communities (Barnes and Bennett, 2014). Researchers have found evidence to indicate a relationship between lifestyle factors and cognitive decline (Eubank, 2022). Physical activity, dietary intake, and social engagement have been found to be possible protective factors for cognitive decline in older adults.

The Mesulam Center for Cognitive Neurology and Alzheimer's Disease at Northwestern University Feinberg School of Medicine and South Loop Village, a community-based organization, have partnered to address lifestyle factors that promote brain health in diverse older adults, through physical activity, social support, and education programming. We are working collaboratively to increase knowledge and awareness of the connection between physical health and brain health while presenting opportunities to participate in innovative ADRD research to residents of affordable housing senior buildings on Chicago's under-resourced Southside, in particular the Near Southside and Bronzeville. Efforts to date include monthly brain health programming in several affordable housing senior buildings across the South Loop and Bronzeville. These programs include discussions on brain health, diet, dementia, dementia friendly communities, research opportunities and often include an instructor-led fitness or dance session.

To date, we have held over 50 sessions in senior living facilities across Chicago's South Side reaching approximately 500 older adults. Through this partnership, we have discovered Black older adults are undereducated about topics related to cognitive functioning and brain health, lack opportunities to engage with community organizations and research institutions and express a strong interest to learn more about these topics.

The South Loop Village and Northwestern Mesulam Center is a community-university partnership to build trust in communities that are traditionally underrepresented in research by meeting communities where they are to address health disparities and promote health equity in ADRD disease prevention and research. Next steps include continued program development and data collection on specific outcomes, such as participant health behaviors, brain health knowledge, social interactions, and emotional wellbeing.

Poster 30

Introducing the MidCog Study: a prospective, observational cohort study investigating modifiable risk factors to cognitive decline in middle-aged adults

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Introduction: The lack of definitive means to prevent or treat cognitive impairment or dementia is driving intense efforts to identify causal mechanisms. Recent evidence suggests clinically meaningful declines in cognition might present as early as middle age. Studying cognitive changes in mid-life adulthood could elucidate modifiable factors affecting later life cognition and health outcomes, yet few cognitive aging studies include this age group. The purpose of the MidCog Study is to begin investigations of less-studied, potentially modifiable, mid-life determinants of later life cognitive outcomes.

Methods and analysis: MidCog is a prospective cohort study of adults ages 35-64 followed every 2.5 – 3 years. The study is currently enrolling adults into the cohort. Individuals are eligible if they are 1) ages 35-64; 2) English-speaking, 3) receive primary care at a participating clinic within the Access Community Health Network or Northwestern Medicine internal medicine practices in the last 1.5 years or have an upcoming visit in the next 6 months, and 4) without severe, uncorrectable vision, hearing, or cognitive impairments. Data are collected from interviews, actigraphs, and electronic health records. Measurements include health literacy, self-management skills, cognitive function, lifestyle, physical and mental health, healthcare use, health status, psychosocial factors, sleep, and chronic disease outcomes. Associations of health literacy and self-management skills with health behaviors and cognitive/clinical outcomes will be examined in a series of regression models, and moderating effects of modifiable psychosocial factors. Finally, MidCog data will be linked to an ongoing, parallel cohort study of older adults (LitCog; N=900), to explore associations between age, health literacy, self-management skills, chronic diseases, health status, and cognitive function among adults ages 35 to 90.

Ethics and dissemination: The Institutional Review Board at Northwestern University has approved the MidCog study protocol (STU00214736). Results will be published in peer-reviewed journals and summaries will be provided to the funders of the study as well as patients.

Lay Language: The world is rapidly aging, with increasing number of older adults living with Alzheimer's disease and related dementia. Recent evidence suggests clinically meaningful declines in cognition might present as early as middle age. Studying cognitive changes in mid-life adulthood could elucidate modifiable factors to Alzheimer's disease pathology, yet few cognitive aging studies include this age group. The purpose of the MidCog study is to begin investigations of less-studied, potentially modifiable, midlife determinants of later life cognitive outcomes. The MidCog study is actively recruiting participants who are 1) ages 35-64; 2) English-speaking, 3) a patient receiving primary care at Access Community Health Network or Northwestern Medicine internal medicine practices, and 4) without severe, uncorrectable vision, hearing, or cognitive impairments. Participants are compensated up to \$125.

Poster 31

Primary Care Detection of Cognitive Impairment Leveraging Health & Consumer Technologies in Underserved Communities: The MyCog Strategy

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Purpose: Early identification of cognitive impairment (CI), including Alzheimer's disease (AD) and related dementias (ADRD), is a top public health priority. Yet in primary care settings that manage the health of most community-dwelling older adults, less than half of patients with any CI are detected and/or diagnosed. Among community health centers that serve marginalized patients, rates of detection may be far lower. To address this, we sought to test a primary care-based strategy ('MyCog') to improve CI detection as part of an NIH-sponsored consortium (DetectCID).

Methods: The MyCog strategy includes a brief iPad-based, self-administered, electronic health record (EHR)-linked cognitive assessment that leverages two well validated measures from the NIH Toolbox Cognition Battery and has easily interpretable results with 'turnkey' recommendations to enhance clinical decision making. Clinician and practice administrator feedback was sought via cognitive interviews and focus groups to ensure the assessment could properly function in typical workflows. Based on this feedback a self-administered tool was built, with a simple interpretable result (yes or no, cognitive impairment detected). It was then validated in one academic geriatrics practice among 111 older adults.

Findings: The refined self-administered tool was further validated in a geriatric clinical population, with interviewer and self-administered MyCog versions strongly correlated (Spearman $r=0.75$) and similar average response time per trial (0.914 sec. vs. 0.958 sec.). Use of the two tests demonstrated acceptable AUC values separately for detecting CI (0.84 and 0.79, respectively). But combined, these measures provide incremental diagnostic utility (AUC=0.95). We will launch the MyCog Trial at 24 practices from a national network of primary care centers for older adults on Medicare that will be randomized to MyCog or usual care. Clinics receiving MyCog will utilize a protocol to implement the intervention during Medicare Annual Wellness Visits and whenever a cognitive concern is expressed. Findings from the DetectCID consortium and MyCog Trial will directly inform future standards in primary care settings, especially those that serve health disparate patient populations.

Lay Language: Cognitive deficits and impairment, including Alzheimer's disease and related dementias (ADRD), are highly prevalent among older adults - with higher rates among Black and Hispanic/Latino individuals - and have devastating consequences to families and entire communities. Responding to increasing calls for early detection of cognitive impairment in everyday clinical settings, the MyCog Trial is testing a promising, and highly scalable way to identify older adults with a possible cognitive impairment, or even dementia, in busy, resource-constrained primary care settings serving communities of color who are experiencing higher rates of undetected or delayed diagnoses of Alzheimer's disease.

Poster 32

Length of stay relates to inpatient antipsychotic use in Alzheimer's type dementia at a large US-based tertiary care hospital

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Background: Antipsychotic(AP) medications carry a black box warning for increased risk of death in the elderly and should be used judiciously in a dementia population. Studies have shown that encounters with healthcare facilities increase the risk of AP exposure¹. We wanted to know how admissions at our institution impacted antipsychotic use in patients with Alzheimer's disease. Here we describe the results of a retrospective analysis of inpatient antipsychotic use in patients with Alzheimer's disease at Northwestern Memorial Hospital(NMH), Chicago, IL.

Method: Our cohort was generated using NMH's Enterprise Data Warehouse, including patients over 65 with a chart diagnosis of AD admitted to the hospital for over 48hrs between May 2005 and March 2018. We excluded patients with schizophrenia, schizotypal disorder, bipolar disorder, or psychotic illness due to primary psychiatric disease, hospice enrollment, presence of tracheostomy or PEG-tube, and pervasive developmental disorder.

Result: 1712 patients were admitted for a total of 4603 admissions amounting to 25,721 hospital days during the period of analysis. Demographic information is provided in Table 1. A higher proportion of admissions were four days or longer in encounters with an antipsychotic(Figure 1). Though longer LOS becomes progressively less common, this trend continued through a LOS of 20 days. When comparing LOS for encounters with an AP in the home medication list to encounters without, there was no impact on LOS. However, when comparing encounters with an AP prescribed while inpatient to encounters without, inpatient AP administration was associated with a longer length of stay(Table 2).

Conclusion: These findings indicate that a longer LOS is associated with antipsychotic use. Because a longer length of stay was associated with new antipsychotic use but not the continuation of a home antipsychotic, our findings suggest that length of stay may contribute to behavioral and psychological symptoms of dementia requiring pharmacological treatment.

Lay Language: Behavioral issues like agitation are a frequent problem in older adults with Alzheimer's disease when admitted to the hospital, often necessitating antipsychotic medications. Antipsychotics carry an FDA black box warning for increased risk of death in the elderly and are important to monitor as a result. Looking at 4,603 admissions of patients with Alzheimer's disease to Northwestern Memorial Hospital, we explored the relationship between the length of stay and antipsychotic use. Our study shows that the length of stay was longer in patients who received an inpatient antipsychotic, but not for patients that had a home antipsychotic prescription prior to admission. This data suggests that longer hospitalizations may increase antipsychotic use in patients with Alzheimer's disease and does not suggest that antipsychotics prolong hospital length of stay.

Poster 33

Lorenzo's House, an international nonprofit empowers families living with younger-onset dementia through our holistic model.

Diana Cose

Lorenzo's House

Younger-onset dementia does not just impact the person diagnosed, it impacts a whole family. Families are too often undiagnosed, under-resourced and misunderstood in the dementia community. With this diagnosis comes a dramatic shift in a family's dynamic and they are alienated from popular dementia resources geared towards people who are diagnosed later in life. Younger-onset strikes people in their 30s, 40s, and 50s. There is an urgency for support as there has been a 200% increase between 2013-2017 in this age range, according to a 2020 report by BlueCross BlueShield. This gap in appropriate services and alarming uptick leaves families on an isolated path, searching for resources, support, and basic understanding.

Younger carepartners are in a uniquely important and difficult position as they are responsible for being the primary carepartner to their loved one, breadwinner for the household, and for parenting independently - all while navigating the complexities of the diagnosis. There is a need for personal connection and resource exchange, and the best guidance often comes from people walking a similar path. Youth are often affected by a parent's diagnosis at a neurobiologically vulnerable time in their lives. Youth whose parents have younger-onset dementia frequently don't know how to explain their experience as a carer with their peers, leaving them isolated and managing the ongoing change by themselves. By creating spaces specifically catered towards these young carers, Lorenzo's House has radically shifted the journey of what younger-onset dementia looks like for children and young adults.

At Lorenzo's House we ensure carepartner paths cross. Our *Healing Spaces*, *Carepartner Connections* and *Youth Initiatives* offer this innovation of personalized connection and resource exchange. Our *Healing Spaces* unite a community of carepartners from across the globe. These are spaces of bravery, understanding and respite exclusively designed for younger families navigating dementia. Through our gender based Bright Brunch and Light Lounge sessions, carepartners listen deeply, exchange resources and build community. *Carepartner Connections* is a proven model designed to create one-on-one carer matches with a framework that emphasizes social emotional wellness, practical information and resourcefulness. Our three innovative *Youth Initiatives* empower young carers with strategies and a community that understands. Our *Youth Summit*, a virtual experience designed by young carers and trusted professionals builds an alliance by sharing stories, exchanging carer techniques and expanding brain health knowledge. Our *Light Club*, a virtual bi-monthly youth carer hangout offers peer support, mindfulness practices, and laughter. Our *Young Professionals Board* magnifies our mission and works to break stigma through advocacy, education, and outreach. By building a digital and in-person international network of carepartners, we unite journeys.

Lay Language: Lorenzo's House, an international nonprofit empowers families living with younger-onset dementia through our holistic model.

Poster 34

Communication Bridge: A person-centered Internet-based intervention for individuals with Primary Progressive Aphasia

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The Communication Bridge (CB) Research Program is focused on developing interventions that maximize communication participation, quality of life, and access to care while also minimizing burden for persons with Primary Progressive Aphasia (PPA) and their communication partner(s). The research program was initiated approximately ten years ago, with continued development today. The Phase 1 pilot study (CB1) of 57 participants with PPA demonstrated the feasibility of remote speech language intervention and indicated that functional gains and increased confidence in communication after eight weeks of speech-language therapy (SLT) were possible.

Phase 1 provided rationale for CB2, the first randomized controlled trial (RCT) of speech language intervention for individuals with PPA and their communication partners. This trial launched in 2018 and enrolled 95 participants with PPA and their communication partners. The study was completed in March 2023 and final analyses are underway. A pilot phase of Communication Bridge 3 (CB3-Pilot) was initiated in 2021 and is critical for refining the intervention, including assessing the feasibility of using an iPad for intervention and incorporating social work into the program. Four dyads enrolled in the study thus far. We anticipate the launch of the next RCT in the upcoming year.

Lay Language: The Communication Bridge program is focused on developing interventions that maximize communication participation, quality of life, and access to care while also minimizing burden for persons with PPA and their communication partner(s). This poster describes the history and projected next steps of this research program.

Poster 35

Primary Progressive Aphasia Research Program at the Mesulam Center for Cognitive Neurology and Alzheimer Disease

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Mesulam Center for Cognitive Neurology & Alzheimer's Disease, Northwestern University

Primary progressive aphasia (PPA) is a neurodegenerative dementia syndrome characterized by a progressive loss of language function. PPA has a low prevalence in clinical practice compared to Alzheimer's dementia. The Mesulam Center for Cognitive Neurology and Alzheimer's Disease seeks to advance PPA research through a collaborative program aimed at studying, educating, and improving treatment for individuals living with PPA and their families.

Over the past decade, more than 250 participants from 38 US states, Canada, Singapore, and Spain have enrolled in PPA studies at the Mesulam Center. Participants in the observational PPA Program visit Chicago every 1-2 years to complete neuropsychological assessments that precisely measure language, memory, and cognition. Additionally, participants undergo multiple brain imaging examinations with MRI and PET scanners in our state-of-the-art imaging facilities. Researchers combine neuropsychological testing with these advanced neuroimaging techniques to better understand the underlying mechanisms of language decline in the PPA brain. Most Mesulam Center PPA research participants also agree to take part in our brain donation program to allow for further scientific investigation of the neuropathologic causes of the illness.

Some participants also take part in the Mesulam Center's web-based non-pharmacologic randomized controlled trial, Communication Bridge, support groups, or other educational research programs, which are tailored to the needs of people living with PPA. These life-enrichment interventions use innovative technology to improve access and quality of specialized care.

Collectively, these studies allow us to improve the diagnosis, prognosis, and quality of life for individuals living with PPA, as well as understand the biological basis of language in the brain.

Funding from the National Institutes of Health, Illinois Department of Public Health, Run4Papa campaign, Association for Frontotemporal Degeneration, and generous personal donations have provided the opportunity for the Mesulam Center to research novel diagnostic and therapeutic initiatives in PPA. Through its multidisciplinary approach to both research and patient care, Northwestern University's Mesulam Center remains one of the top referral centers in the world for PPA. We are grateful for the time and dedication of our research participants.

Lay Language: Primary progressive aphasia (PPA) is a neurodegenerative dementia syndrome characterized by a progressive loss of language function. The Mesulam Center seeks to advance PPA research through a collaborative program aimed at studying, educating, and improving treatment for individuals living with PPA and their families. Participants in the observational PPA program visit Chicago every 1-2 years to complete neuropsychological assessments that measure language, memory, and cognition, along with undergoing multiple brain imaging examinations with MRI and PET scanners. Researchers combine neuropsychological testing with neuroimaging to better understand the underlying mechanisms of language decline in the PPA brain. At the same time, participants can take part in the web-based speech therapy program Communication Bridge, support groups, or other research programs that are designed to improve access and quality of specialized care for individuals with PPA and their families.

Poster 36

Cognitive SuperAgers are Protected from Phosphorylated Tau Accumulation in Basal Forebrain Cholinergic Neurons

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Decline in memory has been well documented as a normal phenomenon of “typical” human aging. However, some elderly appear to avoid this age-related cognitive decline. We have coined the term ‘SuperAger’ to refer to individuals over the age of 80, whose performance on tests of episodic memory is at least equivalent to healthy 50-65 year-olds, and on tests of other cognitive domains at least equivalent to their cognitively normal aged peers. In a previous study, we described the presence of age-related alterations in the basal forebrain cholinergic system in the form of abnormalities in cortical cholinergic axons and accumulation of phosphorylated tau in basal forebrain cholinergic neurons (BFCN). Our preliminary findings indicated significantly lower abnormalities in cortical cholinergic axons in SuperAgers when compared with cognitively average elderly. In the present study, we investigated accumulation of phosphorylated tau in the BFCN in SuperAgers using the PHF1 antibody, which recognizes tau phosphorylated at Ser396/404 / Thr181. The magnocellular BFCN containing PHF1 immunoreactivity were counted in sections spanning the basal forebrain using a counting box at 10X magnification and were expressed as average counts per section. BFCN containing PHF1 immunoreactivity were present in all SuperAger (N=6) and age-matched, cognitively average control (N=5) participants. However, significantly lower numbers of BFCN per section in SuperAgers contained PHF1 immunoreactivity when compared with cognitively average elderly ($p = 0.03$). Combined with our previous observations of lower numbers of abnormalities in cortical cholinergic axons, our findings indicate maintained integrity of the basal forebrain cholinergic system in SuperAgers. These observations are consistent with other reports indicating an overarching resistance of SuperAger brains to involutional processes that characterize normal human brain aging. Given the known involvement of the basal forebrain cholinergic system in cognitive processing of memory, the preserved integrity of this system is a likely contributor to the greater memory capacity of SuperAgers.

Lay Language: This study provides confirmation of the resistance displayed by SuperAger brains to accumulation of proteins and axonal abnormalities. This resistance is observed in the basal forebrain cholinergic system of the brain which is involved in the cognitive processing of memory. Understanding factors that contribute to superior memory in SuperAgers will assist in devising treatments for Alzheimer's disease in which memory decline is the primary abnormality, and to help cognitively normal elderly preserve memory capacity.

Detection of MAP2K3 Immunoreactivity in the Human Cerebral Cortex and Primary Human Microglia, and Loss in Frontotemporal Lobar Degeneration with TDP-43 Proteinopathy

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Mitogen Activated Protein Kinase Kinase 3 (MAP2K3) is a dual specificity serine/threonine cell-signaling kinase activated by stress. The MAP2K3 pathway has been implicated in processes such as embryonic development, cell proliferation, β -Amyloid (A β) deposition associated with Alzheimer's Disease (AD), and learning and memory. Evidence from the mouse brain indicates high MAP2K3 expression in microglia, which is associated with production of inflammatory proteins. Consistent with the role of MAP2K3 in learning and memory, expression of different gene variants of this kinase distinguish cognitive SuperAgers, individuals 80 years or older with memory performance equal to or better than individuals 20-30 years their junior, when compared with age-matched cognitively normal peers. Previous studies have investigated MAP2K3 protein and downstream target abundance in mouse brain tissue. However, detection and measurement of MAP2K3 protein in the human brain has not been described. The purpose of this study was 1) to detect MAP2K3 protein in cultured primary human microglia and inducible pluripotent stem cell (iPSC) derived human cortical neurons and in the human cerebral cortex, and 2) to investigate potential changes in participants diagnosed with behavioral variant frontotemporal dementia due to TDP-43 proteinopathy of frontotemporal lobar degeneration (FTLD-TDP). Two antibodies against human MAP2K3 (Proteintech, 1/500 and Abcam, 1:2000) were used. Western blot analyses of levels in the middle frontal gyrus of FTLD-TDP participants (N=5), age-matched cognitively normal participants (N=5), primary human microglia isolated and cultured from postmortem frontal cortices, and iPSC derived cortical neurons. We detected and measured MAP2K3 in all brain specimens, cultured microglia and iPSC derived neurons. Proteintech antibody detected MAP2K3 primarily in iPSC derived neurons whereas the Abcam antibody detected MAP2K3 primarily in cultured microglia, with only faintly in neurons in frontal cortex of human participants, the Proteintech antibody detected significantly lower levels of MAP2K3 in FTLD-TDP when compared to cognitively normal controls, which is consistent with loss of neurons in the former. The Abcam antibody, on the other hand, detected virtually the same levels of MAP2K3 in FTLD-TDP and normal participants, consistent with loss of protein in neurons and proliferation and activation of microglia resulting in no net change. These findings indicate that MAP2K3 protein can be reliably measured in the human brain, that similar to the mouse brain its levels are high in microglia, and that its levels are altered in FTLD-TDP. It remains to be determined if the different gene variants of MAP2K3 observed in cognitive SuperAgers result in alterations in the levels of the protein.

Lay Language: MAP2K3 is a signaling protein that is activated by different forms of stressful stimuli and inflammatory signals in the brain and resides in a pathway linked to memory. For the first time, we were able to detect this protein in cultured human brain immune cells (microglia), stem cell derived human cortical neurons and brain samples of cognitively normal controls and participants with frontotemporal lobar degeneration (FTLD) with TDP-43 pathology. Consistent with its role in inflammation, MAP2K3 was found in high levels in microglia when compared with neurons, its levels were reduced in neurons in FTLD, but appeared to be increased in neurons. Thus, MAP2K3 can be detected in human brain cells and its relationship with cognitive abnormalities tracked.

Neural basis of word and sentence comprehension in PPA: a deficit-based neuroimaging approach.

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Background: Classical models based on stroke aphasia located word comprehension primarily in Wernicke's areas (left posterior superior temporal gyrus, L pSTG), whereas evidence from Primary Progressive Aphasia (PPA) underscores the role of the L anterior temporal lobe (ATL; Mesulam et al., 2015). Data from stroke aphasia also point to L posterior perisylvian regions as the primary source of sentence comprehension deficits (Lukic et al., 2021; Matchin et al., 2022), whereas evidence from PPA underscores the importance of left inferior and middle frontal gyri (L IFG/MFG; Mesulam et al., 2021; Wilson et al., 2016). As stroke aphasia is caused by a sudden vascular event that often simultaneously affects multiple regions in the language network, language deficits often encompass multiple language domains. Conversely, PPA is a neurodegenerative disease that in the early stages affects only parts of the language network, providing the opportunity to study the neural bases of deficits affecting selective language domains. This study aims to investigate regions of atrophy uniquely associated with word or sentence comprehension deficits in PPA.

Methods: Forty-seven individuals diagnosed with PPA by expert neurologists were assigned to one of three groups: Group 1 (n=19) included individuals with impaired word (but not sentence) comprehension; Group 2 (n=10) included individuals with impaired sentence (but not word) comprehension; Group 3 (n=18) included participants with impaired sentence (but not word) comprehension and impaired repetition. All participants underwent structural MRI. Structural scans were first preprocessed using CAT12 (Gaser et al., 2022); then, smoothed gray matter (GM) volume maps were entered into two-sample t-tests that compared 1) each of the three groups to a group of age-matched healthy individuals (n=33), and 2) the groups to each other.

Results: GM volume comparisons between each of the three PPA groups and healthy participants (atrophy maps) showed the largest overlap along the L superior temporal sulcus (STS), as well as in the L planum polare and in the R posterior STS. Comparisons between PPA groups yielded areas uniquely associated with word comprehension (Groups 2+3 minus Group 1) in the L/R ATL, the L posterior middle and inferior temporal gyri, and the left insula. Sentence comprehension (Group 1 minus Groups 2+3) was uniquely associated with atrophy in the L IFG, parts of the L MFG and L/R superior frontal gyrus (SFG), and the anterior cingulate. Deficits in both sentence comprehension and repetition (Group 1 minus Group 3) were associated with a region encompassing the L planum temporale and L pSTG, at the temporo-parietal junction.

Discussion: This study employed a deficit-based approach to shed light on the regions that support word and sentence comprehension in PPA. In line with previous evidence in PPA, the results underscore the importance of bilateral (L>R) ATL for word comprehension (Mesulam et al., 2015; 2022), and of L frontal (IFG/MFG/SFG) regions for sentence comprehension. Data point to the L pSTG as being primarily involved in processes that support both sentence comprehension and repetition and that are not crucial for word comprehension. We suggest auditory (phonological) short-term memory as a possible candidate, as also suggested by the complete overlap between regions associated with performance on the Digit Span Forward test and those at the root of deficits that encompass sentence comprehension and repetition.

Lay Language: Primary Progressive Aphasia (PPA) is a dementia syndrome caused by neurodegenerative brain disease in which language deficits slowly progress over time initially before other cognitive and behavioral difficulties arise. The study of language disorders can inform our knowledge regarding the regions of the brain that support language in a healthy brain, a step that is crucial to better understand the mechanisms underlying language deficits in PPA and to develop treatment approaches (e.g., speech therapy, noninvasive brain stimulation) for this disease. In this study, we attempt to uncover the role that different regions of the brain play in comprehending words and sentences. This is important since some individuals can understand sentences better than single words and vice versa.

Neuropathology-specific neural pathways underlying agrammatism in PPA

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Background: Primary Progressive Aphasia (PPA) is a neurodegenerative disease defined by a slowly progressive impairment of language functions. In the agrammatic subtype (PPA-G), which can be caused by either Alzheimer's Disease pathology (PPAG-AD) or frontotemporal lobar degeneration in the form of tauopathies (PPA-FTLD-Tau, see Mesulam et al., 2022), deficits in production and comprehension of complex sentences are prominent. Previous studies have reported associations between agrammatism and atrophy in left inferior and middle frontal gyri (L IFG/MFG, see Mesulam et al., 2021; Wilson et al., 2016). However, some individuals with PPA-G exhibit little to no cortical atrophy for quite some time after onset (Bonakdarpour et al., 2019; Thompson et al., 2021), and progressive atrophy of the basal ganglia is common in PPA-G due to FTLD-Tau (Mandelli et al., 2016). In the present study, we explored the role of the basal ganglia in sentence production deficits in PPAG-FTLD-Tau and PPAG-AD.

Methods: Thirty-two right-handed individuals with PPA-G were included in the study. Diagnosis of PPA was made by expert neurologists and presence of agrammatism was established based on impaired (<80% correct) sentence production on the Northwestern Assessment of Verbs and Sentences (NAVS; Thompson, 2012) and on the Northwestern Anagram Test (NAT; Thompson et al., 2011). Assignment to FTLD-Tau and AD groups was based on either neuropathology or in vivo biomarkers. All participants underwent structural MRI. Structural scans were first preprocessed using CAT12 (Gaser et al., 2022); then, smoothed gray matter (GM) volume maps were entered in a full factorial model that included group, sentence production accuracy on the NAT/NAVS, and their interaction, as factors.

Results: The PPAG-AD group showed greater atrophy than the PPAG-FTLD-Tau group in the L middle and inferior temporal gyri (MTG and ITG), the L posterior superior temporal gyrus (pSTG), and the L superior parietal lobule (SPL), as well as in small portions of the R pSTG and MTG. The interaction group*sentence production revealed that sentence production was associated with GM volume in the left putamen (extending to encompass small portions of the amygdala and hippocampus) only in the PPAG-FTLD-Tau group. A small cluster in the R pSTG was the only area where sentence production accuracy was associated with GM volume in PPAG-AD.

Discussion: The results of this study point to the L putamen, as a primary region underlying sentence production deficits in PPA-G due to FTLD-Tau pathology, in line with previous studies reporting atrophy in PPAG-FTLD-Tau (Mandelli et al., 2016; Santos-Santos et al., 2016), sometimes associated with reduced fluency (Whitwell et al., 2017). In line with this observation, we found lower fluency during connected speech in the PPAG-FTLD-Tau group than in the PPAG-AD group. The association between agrammatic production and damage to the L putamen is also in line with the stroke literature (Faroqi-Shah et al., 2014). In PPAG-AD, sentence production deficits were uniquely associated with the R pSTG, a finding that may have been driven by the greater amount of atrophy in this region in the PPAG-AD (versus PPAG-FTLD-Tau) group.

Results of this study suggest that agrammatic deficits in PPA – albeit of similar severity across groups – may stem from damage to different parts of the language network, depending on the underlying pathology.

Lay Language: Primary Progressive Aphasia is a dementia syndrome caused by neurodegenerative brain disease. In PPA, language deficits slowly progress over time, especially in the initial stages of illness, and other cognitive changes become apparent with a few years. This study shows that two different disease proteins collect in different brain regions but yet cause the same kind of language difficulty. This fact challenges what we have learned about aphasia from studying individuals with stroke and supports the need for novel intervention techniques in PPA.

Poster 40

Regional Relationship between Brain Hypometabolism and Atrophy in Semantic Primary Progressive Aphasia

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Background: Semantic primary progressive aphasia (PPA-S) is a subtype of PPA characterized by significant deficit in naming and word comprehension. PPA-S has been shown to be associated with both hypometabolism and atrophy in the left anterior temporal lobe (ATL). However, the relationship between these neurological abnormalities is not yet well-characterized, and differences between the two may provide additional insights into the underlying mechanisms of PPA-S. This study aimed to examine the differences between brain regional metabolic activity and cortical atrophy in people with PPA-S.

Methods: Participants included 9 right-handed individuals with PPA-S and 10 healthy controls. T1-weighted structural magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) scans were collected for each participant. Single word comprehension ability was assessed with the Peabody Picture Vocabulary Test (PPVT). PET and MRI images were preprocessed using SPM12 software to create standardized uptake value ratio (SUVR) and gray matter volume (GMV) whole-brain maps. SUVR maps were detangled from GMV by voxel-wise partial atrophy correction using the PETPVE SPM toolbox. PPA group maps were compared to controls using a t-test and visualized. PPA-S data were pooled with an additional 25 subjects across other PPA subtypes (15 agrammatic, 5 logopenic, 5 mixed PPA). Voxel-wise correlation values between SUVR and GMV values to PPVT score were calculated with multiple regression analysis and thresholded (FWE cluster corrected @ $p < 0.05$). Resulting T-maps were then used to mask out regions common across PET and MRI to visualize differences.

Results: Two sample t-test revealed significant hypometabolism and atrophy in left ATL stretching posteriorly. Hypometabolism was uniquely present in the medial orbitofrontal and anterior cingulate cortex, and the left posterior middle temporal gyrus (MTG), insula and caudate. Regions unique to atrophy encompassed, left inferior and superior temporal gyri (ITG, STG), the fusiform gyrus and Heschl's gyri. The right MTG, and bilateral amygdala and parahippocampal cortices. Based on regression analysis, both SUVR and GMV values in left ATL correlated with PPVT scores. However, there were unique findings for PET and MRI modalities as above.

Discussion: This study identified regions with cortical atrophy and spared cortical metabolism as well as regions of cortical hypometabolism without a corresponding atrophy. These findings suggest a more complex relationship between structural and metabolic abnormalities in PPA-S, with both contributing to symptomatology. The observed differences in regional hypometabolism and atrophy have potential to inform the development of targeted therapeutic interventions by highlighting brain regions that may be more or less responsive to particular treatments. For example, a treatment that upregulates neuronal activity may prove more efficacious in hypometabolic regions with less atrophy.

Lay Language: Primary progressive aphasia (PPA) is a language disorder that is caused by neurodegenerative disease. This study looked at the brains of individuals with semantic PPA (PPA-S), a type of PPA characterized by a person's difficulty naming and understanding single words. In this study, we found a region of the brain that may play a particularly important role in these symptoms, the left anterior temporal lobe (ATL). This region is affected both by atrophy (a decrease in brain volume) and hypometabolism (a decrease in brain cell activity). We also found regions outside the ATL that were affected by only one of the two abnormalities, which points toward a more complex relationship between these changes in the brain. Brain cells can have decreased activity without the cells shrinking or dying, and conversely, a decrease in brain volume doesn't necessarily mean that the cells that remain are dysfunctional. These results suggest that both changes in the brain contribute to symptoms. By better understanding these differences, researchers can develop more targeted therapies to help individuals with PPA-S.

Chronic Levetiracetam Treatment Alters Synaptic Protein Turnover in Alzheimer's Mouse Model and Reduces Production of A β ₄₂

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Alzheimer's disease (AD) is defined as dementia with the presence of intracellular tau tangles and extracellular amyloid beta plaques. Toxic A β ₄₂ species, that are the foundation for plaques, are produced because of sequential proteolytic cleavage of the amyloid precursor protein (APP). When beta-secretase cleaves APP, beta-CTFs are released which, if then cleaved by gamma secretase, release A β ₄₂ peptides. These proteins accumulate throughout the brain and lead to cognitive decline. Levetiracetam (Lev) is an atypical antiepileptic drug. It has been generically prescribed for a decade for epilepsy treatment. It is understood that Lev works to stabilize neuronal networks in epileptic patients; therefore, there is a possibility the drug can help patients with dementia. While the explicit mechanism of action of Lev has not yet been discovered, it is known that Lev binds to SV2a, a synaptic vesicle protein. In AD, we previously discovered that Lev selectively normalized synaptic vesicle endocytosis machinery abundance and restored non-amyloidogenic processing of APP.

We set out to investigate if chronic Lev treatment induces A β clearance or impedes the production of A β . To do this, we created a metabolic labelling paradigm which allowed for differentiation between N15 incorporated proteins while receiving Lev treatment and the older N14 labelled proteins. This for a high-level quantitative mass spectrometry-based analysis to determine how Lev affects A β ₄₂ deposition. We found that chronic Lev treatment lowers beta-CTF levels while the levels of full-length APP remain unchanged, illuminating the possibility that Lev alters the cleavage process of APP. We also isolated amyloid fibrils to investigate if Lev alters production or clearance of A β . Using a targeted mass-spectrometry methodology, we determined a trend of lowered newly synthesized A β in the Lev-treated animals, suggesting Lev lowers A β production. Overall, Lev provides a potential mechanism for therapeutic target that could minimize A β AD pathology.

Lay Language: Alzheimer's disease (AD) is defined as dementia with the presence of tau tangles and amyloid beta plaques. Toxic A β ₄₂ protein pieces, that are the foundation for these plaques, are produced because of sequential processing of the amyloid precursor protein (APP). These cut up protein fragments are highly likely to clump together and form the plaques, or aggregations. These proteins accumulate throughout the brain and lead to cognitive decline.

Levetiracetam (Lev) is an anti-epileptic drug. It has been prescribed for a decade for epilepsy treatment. But the mechanism of action of Lev has not yet been discovered.

We set out to investigate if Lev treatment in Alzheimer's mouse models can induce A β clearance to prevent the spread of these toxic peptides, or even prevent the production of them in the first place. We found a trend of lowered newly made A β in the Lev-treated animals, suggesting that this drug is lowering production of these toxic peptides seen in AD. Overall, Lev provides a potential mechanism for therapeutic target that could minimize AD pathology.

Functional Connectivity within Two Large-Scale Memory Systems in SuperAgers

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Objective: Memory decline in late life is a hallmark of aging, yet there are older individuals that have maintained youthful memory abilities. SuperAgers are 80+ year-olds with episodic memory performances at least as good as cognitively average 50- to 60-year-olds. The current study explored whether relatively strong functional connectivity within two large-scale memory systems support SuperAgers' exceptional memory abilities. Stronger functional connectivity within the anterior temporal (AT) and posterior medial (PM) memory systems are associated with greater performance on memory tasks involving information familiarity and episodic memory recall, respectively. Given their exceptional episodic memory abilities, we hypothesize that SuperAgers will have stronger functional connectivity within the PM memory system compared to cognitively average older-aged controls (Controls).

Methods: Intra-network functional connectivity of the AT and PM memory systems were compared between 25 SuperAgers and 16 Controls using resting state functional MRI (rs-fMRI) scans. Classification of SuperAgers or Controls was determined based on measures of episodic memory, executive functioning, verbal fluency, and picture naming (for details see Harrison et al., 2012). In addition, inclusion criteria for this study required stable cognitive status across two visits (on average 1.76 years apart). T1-weighted structural and rs-fMRI (Siemens Trio 3T) scans from a single visit were used in our analysis. Four regions-of-interest (ROIs) were chosen: the (1) anterior hippocampus (aHipp), (2) posterior hippocampus (pHipp), (3) AT, and (4) PM. The aHipp and pHipp ROIs were segmented within each participant's structural MRI. AT and PM were predefined (de Flores et al., 2022) and excluded the hippocampal ROIs. Intra-network functional connectivity of the AT and PM systems were defined as the correlation between rs-fMRI signal of AT-to-aHipp and PM-to-pHipp, respectively. Functional connectivity was compared across groups using two-sample independent t-tests.

Results: Group differences in functional connectivity of the AT-to-aHipp and PM-to-pHipp were nonsignificant. Furthermore, group differences were nonsignificant using two complementary methods to measure hippocampal rs-fMRI for our intra-network functional connectivity calculations.

Conclusion: Intra-network functional connectivity of the AT and PM memory systems were not significantly different in SuperAgers and Controls. Our findings may reflect methodological limitations and/or that large-scale memory systems are not entirely responsible for SuperAgers' exceptional memory abilities. Methodological limitations include a conservative sample size and the use of predefined AT/PM maps. Alternatively, SuperAgers' cognitive resilience may be supported by multiple large-scale rs-fMRI networks. Results from this study support the complex relationship between functional connectivity and cognitive resilience and inform future analyses.

Lay Language: Complaints of memory decline in late life are common but not universal. SuperAgers are adults 80-years or older with exceptional memory abilities. In fact, SuperAgers have memory performance at least as good as adults in their 50's and 60's. The Northwestern SuperAging Study is exploring what factors contribute to SuperAgers' superior memory performance. The secret to SuperAgers' memory may involve a small region of their brain called the hippocampus. The front and back of the hippocampus communicate with different parts of the brain and the back-half is more involved in remembering. We investigated if communication from the back-half of the hippocampus to other regions of the brain was stronger for SuperAgers than normal agers but did not find a significant difference. SuperAgers' exceptional memory abilities may instead be supported by multiple regions communicating throughout the brain. This work helps inform future analyses investigating unique brain features of successful cognitive aging.

Molecular mechanisms of apathy and affective symptoms in Alzheimer's disease

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Background: Approximately 90% of Alzheimer's disease (AD) patients experience at least one neuropsychiatric symptom (NPS) over the course of disease progression. However, little is known about the neural mechanisms underlying NPS in AD, leaving treatment options for these symptoms underdeveloped. Here we use a translational approach to refine hub gene candidacy for the two most common NPS domains in AD (i.e., apathy, affective) and identify targets for investigation of causal relationships between genes and behavior.

Method: Weighted gene co-expression network analysis (WGCNA) was performed on RNA-sequencing data from human postmortem anterior cingulate cortex of 60 individuals with AD and antemortem clinical evaluations of NPS. Human and mouse protein-protein interaction networks (PPIs) were constructed from WGCNA modules that significantly correlated with NPS domains. Expression levels of potential hub genes discovered in humans were measured in the prefrontal cortex (PFC) of 16-month-old wild type (WT) and 5xFAD mice by RT-qPCR and correlated with composite z-scores for representative apathy- and affective-like behaviors.

Result: WGCNA revealed that a microglial phagocytic pathway and complement cascade module was uniquely correlated with apathy. PPI analyses refined the list of 43 WGCNA potential apathy hub genes to 21 candidate hub genes suitable for translational investigation. Further, human and mouse PPI analyses identified *TYROBP* as the highest-ranking apathy hub gene. Expression levels of *Tyrobp* were significantly higher in the PFC of 5xFAD mice than in WT controls and positively correlated with apathy z-scores. Only two genes retained affective domain hub gene candidacy (*Tgfb1* and *Nfkb1a*) in mice. Whereas *Tgfb1* expression was elevated in the 5xFAD PFC, *Nfkb1a* was not differentially expressed. Z-scores for affective-like behavior did not significantly correlate with either *Tgfb1* or *Nfkb1a* expression levels.

Conclusion: Our results suggest that the complement system is uniquely implicated in cases of AD with apathy; *Tyrobp* is a strong candidate gene for the regulation of that relationship. 5xFAD mice are an appropriate model for future investigation of *Tyrobp*-complement-apathy mechanisms in AD. Further study is needed to evaluate *Tgfb1* and *Nfkb1a* as possible regulators of affective behavior in models that exhibit other AD pathology(s) (e.g., tau) alone or in conjunction with pathologic amyloid-beta.

Lay Language: Although great research effort has focused on discovering the mechanisms of memory deficits and cognitive decline in Alzheimer's disease (AD), relatively little is known about the specific causes of the neuropsychiatric symptoms that are also experienced by millions of individuals with AD. Apathy and affective (i.e., anxiety and depression) symptoms are the two most common neuropsychiatric symptoms in AD. To improve understanding of these symptoms, we have analyzed the expression levels and unique relationships between genes in a region of the brain known as the anterior cingulate cortex. Our results indicate that apathy and affective symptoms are related to changes in different aspects of the brain's immune response. These findings have the potential to help advance the development of more effective medications for the AD population by identifying new targets for the treatment of apathy and affective symptoms in AD.

Poster 44

Validation of the NIH Toolbox Odor Identification Test across Normal Cognition, Amnesic Mild Cognitive Impairment, and Dementia due to Alzheimer's Disease

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Purpose: Olfactory impairments have been associated with aging, amnesic mild cognitive impairment (aMCI) and Alzheimer's disease dementia (ADd). Olfactory identification tests have been proposed as a cost-effective measure that may be able to distinguish between normal cognition and aMCI or ADd, aiding in early diagnosis and targeting preventative treatments to those most at risk of disease progression. The present study, as part of the Advancing Reliable Measurement in Alzheimer's Disease and Cognitive Aging (ARMADA) (Weintraub et al., 2021) parent study, was conducted to validate the NIH Toolbox Odor Identification Test (NIHTB-OIT; Dalton et al., 2013) across a sample (N=389) of cognitively normal controls over age 65, participants with aMCI, and participants with ADd.

Methodology: We evaluated associations between NIHTB-OIT scores and age, sex, and diagnostic group using multiple linear regression. We then evaluated the ability of the NIHTB-OIT to distinguish between control participants and participants with aMCI or ADd using logistic regression. Finally, for a subset of participants with available data, we evaluated associations between NIHTB-OIT scores and AD biomarker status and APOE genotype.

Findings: We determined that NIHTB-OIT scores significantly decreased with age ($p < 0.001$) and were significantly lower for aMCI ($p < 0.001$) and for ADd ($p < 0.001$) participants compared to controls after correcting for age and sex. Importantly, we found that the rate of decline in NIHTB-OIT scores with age was similar across all groups, suggesting that this decline may begin earlier in life for those who go on to develop aMCI and ADd. We determined that the NIHTB-OIT reliably distinguishes between controls and participants with aMCI (sensitivity and specificity, 49.4% and 88.8%) and participants with ADd (sensitivity and specificity, 56.5% and 89.5%). Additionally, we found that Odor Identification Scores were significantly lower in participants with a positive AD biomarker test compared to those with a negative AD biomarker test ($p < 0.005$). Odor Scores were not found to differ significantly based on APOE $\epsilon 4$ allele carrier status.

Lay Language: Olfactory (sense of smell) impairments are known to be common in Alzheimer's disease dementia (ADd), and its precursor disorder, amnesic (affecting memory) mild cognitive impairment (aMCI). This impairment in smell may occur earlier in the disease process than more serious cognitive and memory symptoms. Simple multiple-choice scratch-and-sniff odor identification tests, such as the NIH Toolbox Odor Identification Test, may be useful for screening who is at highest risk of developing aMCI or ADd. This study evaluates scores on the NIH Toolbox Odor Identification Test across healthy controls, participants with aMCI, and participants with ADd. We found that scores on this test can reliably distinguish healthy controls from participants with aMCI or ADd. We suggest that this quick and cost-effective test may be included in annual senior wellness exams, and that (in the absence of other nasal or sinus explanations) those with low scores should be referred for further neuropsychological testing.

Not All Tauopathies are Created Equal

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Cortical Basal Degeneration (CBD), a subtype of Frontotemporal Dementia, is a neurodegenerative disease in which pathology and neuronal loss is seen in the frontal and temporal lobes and subcortical brain structures. This results in progressive loss of verbal communication ability, other cognitive deficits, and motor abnormalities such as those in walking. While clinical and behavioral symptoms differentiate CBD from other neurodegenerative diseases and dementias, the unique underlying pathology and biological cause of CBD is not fully understood. This lack of insight in the underlying biology of CBD has led to a lack of disease modifying therapeutic treatment options and poor preventative mechanisms. To help resolve these issues, we studied basal forebrain cholinergic neuron (BFCN) vulnerability to the hallmark tau protein pathology in human CBD postmortem brain tissue. In Alzheimer's Disease (AD), one of the most prevalent neurodegenerative dementias, the BFCNs are a primary target for tau protein inclusions which lead to neurofibrillary tangles and cell death. Accordingly, treatments that enhance cholinergic transmission have proven partially effective for symptomatic improvement in AD. Using immunohistochemistry and unbiased stereology to quantify cholinergic neuronal density and tau protein inclusions, we investigated whether the BFCN are also vulnerable to degeneration in CBD. We found that while cholinergic neurons in CBD displayed tau protein inclusions, these inclusions did not seem to lead to degeneration of BFCN, in contrast to that seen in AD. Despite presence of tau inclusions, the cholinergic neurons and their cortical axons showed no significant reduction in density and were virtually identical to those in normal healthy individuals. This suggests that cholinergic neurons in CBD may be resilient to tau protein induced neurodegeneration, and that the species of pathologic tau may be different in AD when compared with CBD and is the determinant of BFCN vulnerability. This also implies that cholinergic based therapies used for treatment of AD and other dementias are likely to be ineffective in treating CBD and further research is needed to understand the characteristics of tau pathology in CBD and identify new therapeutic targets.

Lay Language: Cortical Basal Degeneration (CBD) is a neurodegenerative disease that causes abnormalities in cognition and movement. In Alzheimer's Disease (AD), certain cells called the basal forebrain cholinergic neurons are affected by a protein called tau which causes them to die. To better understand CBD pathology, we looked to see if these same neurons affected in AD are also affected in CBD. In human CBD postmortem brain tissue, we found that the neurons we were interested in did have tau protein inclusions but did not seem to die like they do in AD. This is important because it suggests differences in these disease developments, and that treatments for AD may not be effective for treating CBD.

Poster 46

Using AAV-mediated overexpression of Nrf2 to prevent Alzheimer's neuropathology

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Background: Neurons are specialized cells in the nervous system that transmit information. In Alzheimer's disease, neurons can stop functioning, lose connection with other neuronal networks, and die at faster rates. Other common markers of Alzheimer's include amyloid plaques and dystrophic neurites. Amyloid plaques are aggregates of beta-amyloid proteins that cluster together and often disrupt cell function. Dystrophic neurites are swollen neurons near A β plaques with accumulations of different cellular organelles. Nrf2 is a protein in the body that regulates antioxidant function and prevents oxidative damage by boosting the expression of various detoxifying and anti-inflammatory genes. Prior research found that Nrf2 mediated neuroprotective effects in photoreceptors and retinal ganglion cells, suggesting it may be an effective treatment for multiple cell types in diseases that involve oxidation. Additionally, other studies showed that deletion of Nrf2 increased cognitive deficits in AD model mice. Few studies have tested Nrf2 activation by gene delivery via viral vectors in animal models, which may prevent early pathogenic processes in Alzheimer's. We hypothesized that neuronal AAV-mediated Nrf2 overexpression would exhibit neuroprotective effects.

Methodology: To overexpress Nrf2 in 5XFAD and non-Tg mouse brains, we had four conditions: an uninjected group, GFP, GFP+low Nrf2, and GFP+ high Nrf2. The three injection groups received a ventricular injection within 24 hours of birth. The mice were perfused at 9.5 months of age, where half of the brain was fixed for sectioning and immunofluorescent analysis, while the other half was processed for immunoblotting. Coronal sections were stained with antibodies to quantify neuronal loss (NeuN), neuroinflammation (Iba1), plaque load (MeXO4), BACE1 expression, and dystrophic neurites (Lamp1/A β 42). Sections were imaged on a TI2 widefield microscope and analyzed using NIS-Elements image analysis software.

Findings/Future Directions: We found that high Nrf2 overexpression had adverse effects as it increased plaques and neuronal loss. On the contrary, the low dose of Nrf2 overexpression showed beneficial effects as it reduced BACE1 in the hippocampus and dystrophic neurites. Future experiments include performing bulk mRNA seq from hippocampi to confirm activation of known Nrf2 target mRNAs, measure mRNA levels of Nrf2, and look for activation of candidate pathways to explain the reduction of dystrophic neurites.

Lay Language: A common feature of neurodegenerative diseases is oxidative stress leading to the dysfunction of neuronal cells. Oxidative stress occurs when there are too many unstable molecules, called reactive oxygen species, that can damage organs and tissues. Oxidative stress has been observed in degenerative conditions and normal aging, leading to damaged proteins, nucleic acids, and lipids. Nrf2 is a protein in the body that increases the expression of genes that protect against oxidative stress. We are interested in exploring the connection between Nrf2 expression and Alzheimer's disease. In this study, we overexpressed Nrf2 in a mouse model of Alzheimer's disease, hoping to protect against oxidative stress and protect neurons.

Noradrenergic dysregulation, sleep and cognition in older adults with insomnia

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Study objectives: Insomnia disorder is prevalent among middle and older-aged adults with detrimental consequences on health and quality of life. Notably, insomnia and sleep fragmentation may increase the risk of cognitive decline and Alzheimer's disease-related dementias (ADRD), but the mechanisms underlying these associations remain poorly understood. The noradrenergic (NA) system plays a key role in the regulation of cognition, arousal and sleep homeostasis, and its function significantly declines with aging. However, the potential mechanistic relevance of NA system's dysregulation in insomnia and insomnia-related cognitive impairment has never been investigated, particularly in older adults. The main object of this study was to examine the relationship between the NA system with indices of objective and subjective sleep quality and cognitive function in older adults with insomnia.

Methods: Forty-three adults with chronic insomnia (75% women) and 16 age and sex-matched good sleeper controls were studied in the laboratory for 4 consecutive days. NA system activity was assessed by measuring 24-h plasma norepinephrine (NE), subjective sleep quality by using the Pittsburgh Sleep Quality Index (PSQI), objective sleep quality by electroencephalographic (EEG) spectral components derived from polysomnography, and cognitive function by using the Automated Neuropsychological Assessment Metrics (ANAM).

Results: The insomnia group showed lower 24-h plasma NE levels compared to the control group ($p < 0.001$), which was mainly evident during the wake period. Participants with insomnia displayed lower EEG slow oscillatory (SO: 0.5 – 1.25 Hz) activity in the 1st cycle of sleep compared to the control group ($p < 0.001$), indicative of reduced sleep homeostasis. In controls ($R = 0.58$, $p = 0.014$), but not in insomnia ($R = 0.23$, $p = 0.276$), a positive correlation was observed between average plasma NE levels during the wake period and the amount of SO activity in the 1st cycle of sleep. In the insomnia group, lower 24-h plasma NE levels and SO activity in the 1st cycle of sleep were associated with poorer subjective sleep quality indicated by higher PSQI scores ($R = -0.62$, $p = 0.008$ and $R = -0.52$, $p = 0.001$, respectively).

Within the insomnia group, participants with lower 24-h plasma NE levels (median split) displayed shorter sleep duration, higher duration of wake after sleep onset and lower sleep efficiency as compared to participants with higher 24-h plasma NE levels ($p < 0.08$), and controls ($p \neq 0.01$).

In the insomnia group, lower 24-h plasma NE and SO activity in the 1st cycle of sleep were associated with lower working memory ($R = 0.50$, $p = 0.035$ and $R = 0.67$, $p = 0.001$, respectively).

Conclusions: Dysregulation of NA system activity may be an underlying mechanism that links objective and subjective measures of sleep quality in older adults with insomnia and potentially contribute to altered cognitive function. These results will help understand novel mechanisms of insomnia pathophysiology and risk for ADRD, and will help inform the development of novel therapeutic targets for older adults with insomnia who are at higher risk for cognitive decline and ADRD.

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Lay Language: Insomnia disorder is prevalent among older adults with detrimental consequences on health, including increased risk of cognitive decline and Alzheimer's disease-related dementias (ADRD). Yet, the mechanisms underlying these associations remain poorly understood. The noradrenergic (NA) system plays a fundamental role in the regulation of sleep and cognition, and its function significantly declines with aging. However, the potential mechanistic relevance of NA system's dysregulation in insomnia and insomnia-related cognitive impairment has never been investigated, particularly in older adults. In this study, we showed novel evidence of reduced 24-h NA activity in older adults with insomnia compared to good sleeper controls of similar age, which was associated with poorer sleep quality and cognitive function. These results will help understand novel mechanisms of insomnia pathophysiology and risk for ADRD, and help the development of novel therapeutic targets for older adults with insomnia who are at higher risk for cognitive decline and ADRD.

Structural brain network degeneration associated with agitation in dementia

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Background: Agitation is a behavioral syndrome involving increased motor activity, restlessness, aggressiveness and emotional distress. It has a 30% prevalence across multiple types of dementia and is associated with negative outcomes, including reduced quality of life, caregiver distress, and mortality. Pharmacological treatment risks serious side effects, including mortality. Understanding brain network topology could provide insights into novel treatment methods.

Method: Participants comprised 600 subjects from 3 existing databases: the Alzheimer's Disease Neuroimaging Initiative (ADNI), Frontotemporal Lobar Degeneration Neuroimaging Initiative (NIFD) and the Mesulam Center for Cognitive Neurology and Alzheimer's Disease at Northwestern University.

Participants were clinically diagnosed with either behavioral variant frontotemporal dementia (bvFTD), mild cognitive impairment (MCI), dementia of the Alzheimer type (DAT) or cognitively normal (CN). The Neuropsychiatric Inventory Questionnaire (NPI-Q) caregiver rating was used to determine whether individuals were agitated or not.

Morphometric similarity networks (MSNs) were generated from Freesurfer statistics calculated from T1-weighted MRIs. 7 surface-based cortical metrics (e.g. gray matter volume, surface area) were calculated for each of 360 parcels. Pairwise inter-parcel Pearson correlations of feature vectors were calculated to produce a morphometric similarity matrix for each individual. We calculated sub-matrices for salience (SN) cognitive control (CCN) and default mode networks (DMN). Brain Connectivity Toolbox calculated transitivity and global efficiency of each network. Metrics were calculated at different thresholds to ensure the results were not threshold-dependent.

We calculated 2 (Agitation present/absent) x 4 (Diagnosis) repeated measures ANCOVAs for transitivity and global efficiency for each network. Covariates were age, sex, race, database, education, ICV, CDR-SB and days MRI-NPI-Q.

Result: For the SN, people with Agitation had significantly lower global efficiency than people without Agitation. There were no significant effects of diagnosis or interaction.

For the CCN, people with agitation had significantly lower transitivity than people without Agitation.

There were no significant effect of diagnosis or interaction.

Conclusion: Across different forms of dementia, Agitation is associated with reduced integration (global efficiency) of the salience network, and reduced segregation (transitivity) of the cognitive control network. Interventions that alter these topological network features may be effective in reducing agitation in dementia, regardless of clinical diagnosis.

Lay Language: Agitation is a behavioral syndrome involving increased motor activity, restlessness, aggressiveness and emotional distress. It is associated with negative outcomes, including reduced quality of life, caregiver distress, and mortality. Using a new method to study structural brain imaging, we found that agitation was associated with reduced integration and specialization of different brain networks important for cognition. This information could provide insights into new treatment methods for agitation.

Poster 49

Amyloid beta oligomers, inflammatory astrogliosis, and the therapeutic action of NU-9 in the 5xFAD model

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The accumulation of neurotoxic amyloid beta (A β) protein is well established in Alzheimer's disease (AD). However, therapies targeting A β have shown minimal efficacy in clinical trials. While this has casted doubt on the amyloid cascade hypothesis, previous treatments have been selective for insoluble, aggregated, fibril forms of A β (i.e amyloid plaques), which are not the most toxic species. Soluble, non-fibrillar, amyloid beta oligomers (A β Os), rather, are now widely accepted as the most neurotoxic species of A β (Cline et. al, 2018). Substantial evidence implicates A β Os as early instigators of AD, but their spatiotemporal profile and primary mechanism of toxicity are not fully understood. Here, we show that among the first pathological changes in 5xFAD mice (Oakley et. al, 2006) at 2 months old (2 months prior to the onset of memory dysfunction) is A β O accumulation within degenerating neurons of the subiculum. Co-labeling A β Os and dendrites reveals a dramatic decrease in dendritic density precisely in regions of A β O+ degenerated neurons. Triple labeling A β Os, activated microglia, and reactive astrocytes shows the earliest innate immune cell activation events coinciding spatiotemporally with A β Os' first appearance. Using super-resolution microscopy, we observed nanoscale puncta of A β Os bound along reactive astrocyte processes. To better understand A β Os' potential role in inducing reactive astrogliosis, we treated young 5xFAD mice with NU-9, a small molecule that reduces protein aggregation and reverses neuronal damage in ALS mice (Genç et. al, 2021). NU9, which was recently discovered to inhibit the formation of A β Os in hippocampal cultured cells (E. Johnson, PhD Dissertation, Northwestern), was given orally to 3 month-old 5xFAD mice once a day for 60 days. 5xFAD mice given either 20 or 100 mg/kg NU9 had hippocampal reactive astrocyte levels remarkably decrease (more than 3-fold) from vehicle treated controls. Collectively, our data corroborate A β Os as primary instigators of AD that induce reactive astrogliosis and microglial activation well before symptom onset. Taken together, this study substantiates the value of early intervention in AD aimed at neutralizing A β Os and implicates NU9 as a small molecule inhibitor of A β Os with great therapeutic potential in AD.

Lay Language: We are working toward developing a treatment for Alzheimer's Disease (AD) that targets neurotoxic molecules that accumulate in the brains of AD patients (called amyloid beta oligomers; A β Os). The role of A β Os in AD was first proposed by our laboratory and has become well established as a key component in initiating the disease. Recently, A β Os have emerged as targets for experimental AD drugs in ongoing clinical trials. The current study of a drug recently developed at Northwestern provides great optimism for the drug's potential as a new type of Alzheimer's disease therapeutic.

Poster 50

Northwestern Alzheimer's Disease Research Center (NADRC) Clinical Core

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Introduction: The Northwestern Alzheimer's Disease Research Center (NADRC) is entering its 28th year of funding from the National Institute on Aging (NIA). The NADRC is one of 38 sites in the country, all of which have a Clinical Core component. The purpose of the Clinical Core is to establish a cohort of individuals across the cognitive aging spectrum to support clinical and basic research on memory and aging. The Clinical Core follows research participants annually and collects, stores, and disseminates clinical data, brain imaging scans, and biological samples. The data collected by each ADRC (the Uniform Data Set, UDS) are contributed to the National Alzheimer Coordinating Center to all large-scale, multicenter research collaborations. Over the past year, the Clinical Core has worked closely with the Education, Neuropathology, and Imaging Cores to recruit and enroll participants, facilitate brain donations, obtain Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) scans, and educate the public on effectively coping with cognitive aging and dementia.

Methods: The Clinical Core recruits individuals with different forms of cognitive impairment and dementia (e.g. memory dementia, primary progressive aphasia, behavioral variant frontotemporal dementia, due to Alzheimer's disease, Pick's disease, Lewy body disease and other neurodegenerative diseases). Participants and designated study partners complete annual assessments using the methods of the UDS (demographic information, health and family history, and neuropsychological tests. If eligible, participants also undergo MRI, amyloid (Florbetaben-PET), and tau (Flortaucipir-PET) scans so researchers can investigate brain structure, connectivity, and amyloid and tau proteins. Blood is collected to support studies of disease process and biomarkers. Participants are asked to consider brain donation which provides researchers with a valuable resource for understanding brain changes with aging.

Results: Since 1996, the Clinical Core has enrolled more than 2,300 participants; 447 are active with 9% followed for 10 or more years. Since the onset of the COVID-19 pandemic, the Clinical Core has completed over 804 remote research visits. Approximately 260 research participants and their care partners were surveyed about the impact of COVID-19, as well as their technology accessibility.

Additionally, we were able to accept brain donations from 30 research participants in 2022.

Conclusions: The Clinical Core is a valuable resource for researchers on Alzheimer's disease, frontotemporal dementia, primary progressive aphasia and age-related cognitive change. For many, participation is a lifelong, meaningful commitment and promotes national and international research efforts.

Lay Language: The Clinical Core is a longitudinal study that collects information on research participants yearly, following their neuropsychological testing scores throughout their participation. Our data includes participants across the cognitive aging spectrum to study memory and aging. Information collected from this study is shared across different collaborators associated with the National Alzheimer Coordinating Center. Participants are also able to donate their brain for research as the culminating aspect of their dedication to Clinical Core.

Poster 51

Neural Mechanisms Underlying Confrontation and Generative Naming in behavioral variant Frontotemporal Dementia

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Objective: Behavioral variant frontotemporal dementia (bvFTD) is a neurodegenerative condition that presents with deficits in behavior, executive functions, and language due to progressive brain atrophy. Individuals with bvFTD can have naming difficulties in conversational speech affecting fluency, or impairment of object naming. Comparative neural mechanisms of these two kinds of naming have not been well characterized. The purpose of this study was to investigate the patterns of grey matter GM atrophy underlying disrupted object and generative naming in bvFTD.

Methods: Participants of this study included 20 bvFTD and 22 healthy controls. All participants underwent 2D T1-weighted magnetic resonance imaging. Percent correct score on the Boston Naming Test, and Multilingual Naming Test were used as measures of language performance. Word fluency was evaluated using animal and vegetable fluency tests. Voxel-based morphometry (VBM) analysis was used to characterize detect regions of significant atrophy in bvFTD as compared to healthy controls. Regional grey matter volume loss associated with naming and fluency were assessed using regression analyses.

Results: Visualization of T-test results showed regions of significant atrophy in orbitofrontal, temporal, insular and, to lesser extent, in the parietal regions ($p < 0.001$ uncorrected) in bvFTD as compared to controls. Regression analysis showed significant correlations between picture naming scores and cortical volume within the left temporal lobe (70% of the variance), frontal pole (62% of variance), left thalamus (contributing to 55% of variance), and left fusiform (56% of variance). We found significant correlations between word fluency associated with atrophy within the left temporal pole (33% of variance), left superior parietal lobule (56% of total variance), left posterior medial temporal gyrus (32% of variance), and left middle frontal gyrus/frontal pole (contributing to 32% of the variance). We also found significant subcortical atrophy correlated to category fluency and naming.

Conclusion: Our findings confirm previous findings stating a correlation between left temporal and left frontal atrophy and picture (confrontation) and generative naming in bvFTD. In addition, we demonstrate that Picture naming, significantly relied on temporal regions while generative naming (fluency) relied both on frontal and temporal regions and more so on the frontal network (including parietal and frontal areas). Correlation between naming and subcortical regions is less discussed in the literature and could underscore collaboration between these structures and the frontal network. Our results shed light on the different mechanisms for object and generative naming in bvFTD and help us with better understanding of neurobiology of naming in general.

Lay Language: Behavioral frontotemporal dementia (bvFTD) is a neurological condition that presents with deficits in behavior, executive functions, and language. Individuals with bvFTD can have difficulties in naming such deficits in naming objects and fluency. The neural mechanisms for the correlation between generative naming and bvFTD are not well characterized. Our findings will help in the understanding of the connections between bvFTD and decline in grey matter volume correlated with deficits in naming.

Poster 52

Evaluating the Causal Association Between Genetically Proxied Psychiatric Disorders and SuperAging

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Introduction: SuperAgers are individuals aged 80+ who have episodic memory capacity that would be considered at least average for those 2-3 decades younger. The causal factors for SuperAging are not known. Observational studies have linked psychiatric disorders with the risk for late life cognitive decline. It is not known if psychiatric disorders or their genetic liability have a causal effect on SuperAging. We sought to assess the causal relationship between genetically proxied psychiatric disorders (major depression (MD), bipolar disorder (BD), and schizophrenia (SCZ)) and SuperAging using a 2-sample Mendelian randomization (MR). For comparison, we performed secondary analyses for the association of the same exposures with Alzheimer's dementia (AD), Lewy Body dementia (LBD), and Frontotemporal dementia (FTD).

Methods: Genome-wide significant single nucleotide polymorphisms (SNPs) associated with MD (102 SNPs, 246,363 cases, 561,190 controls), BD (64 SNPs, 41,917 cases, 371,549 controls) and SCZ (287 SNPs, 76,755 cases, 243,649 control), were used as genetic proxies for the exposures. Summary statistics of the genome wide association study (GWAS) for SuperAging was included as the primary outcome (69 SuperAgers, 3,479 controls). Summary statistics were obtained for the largest GWAS studies of neurodegenerative disorders: AD (111,326 cases, 677,663 controls), LBD (2,591 cases, 4,027 controls) and FTD (2,154 cases, 4,308 controls). Inverse variance weighted MR was performed as the main analysis for testing the relationship between the exposures and outcomes. Sensitivity analyses were completed to test the robustness of the results.

Results: MR analyses showed a significant association between higher genetic liability to SCZ and lower likelihood of SuperAging (OR=0.98, P= 0.02), but no significant association between MD or BD with SuperAging (P>0.05). Secondary analyses showed that genetic liability to BD was associated with an increased risk for AD (OR=1.1, P=0.003), while genetic liability to SCZ was associated with an increased risk for FTD (OR=1.16, P=0.04). The remainder of secondary analyses associations were not significant (P>0.05). Sensitivity analyses were supportive of the main results.

Discussion: This is the first study to investigate the potentially causal factors for SuperAging. We found that genetic liability to SCZ is causally associated with lower likelihood of SuperAging. We also found that the genetic liability to BP is associated with increased risk for AD, while the genetic liability to SCZ is associated with increased risk for FTD. Future studies should further evaluate whether the therapeutic intervention to the SCZ and BP can modulate their risk for neurodegeneration. Exploring other causal factors to SuperAging is warranted.

Lay Language: We found that genetically predicted schizophrenia and bipolar disorder are associated with increased risk for neurodegeneration and less chance of cognitive resilience.

Poster 53

Proteome fidelity during aging

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Unraveling the complex mechanisms underlying aging would have profound implications for both age-related diseases and, importantly, the quality of healthcare. A hallmark dysfunction of aging is the loss of proteostasis and one component of this delicate process is protein turnover. In this work, we created a continuous in vivo stable isotope labeling paradigm in mice to develop a robust quantification of fluctuations in protein turnover dynamics along the aging continuum. First, we found that cortical tissue uniquely experiences dynamic global fluctuations across aging compared to heart and liver tissue. Second, in cortical tissue, global turnover dynamics differed between males and females and specific trends during aging were tightly tied to subcellular location. Next,

To probe why there are distinct differences in turnover with subcellular compartments, we biochemically isolated the insoluble proteome and discovered that select subcellular compartments may experience dynamic turnover as a result of phase-separation. Finally, we discovered proteasome activity changes that were strikingly linked to the turnover of the 20S catalytic core subunits which we hypothesize underlie identified fluctuating turnover trends for select subcellular groups. Taken together, our study extends the current understanding of aging and shows that protein turnover is a dynamic process that undergoes differential fluctuations related to subcellular compartment and proteasome fidelity.

Lay Language: Unraveling the complex mechanisms underlying aging would have profound implications for both age-related diseases and, importantly, the quality of healthcare. We set out to investigate how protein turnover in the brain changes during aging. Taken together, our findings extend our current understanding of healthy aging and suggest that protein turnover is a dynamic process that undergoes differential fluctuations that may be caused by reduced proteasome fidelity.

Poster 54

The SuperAging Research Initiative: A multisite consortium focused on identifying factors promoting extraordinary cognitive aging

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Background: The designation of SuperAger is reserved for individuals age 80+ who have episodic memory capacity that would be considered at least average for those 2-3 decades younger. The presence of such outliers raises questions of fundamental importance to the neurobiology of brain aging. Have these superior memory performers resisted age-related changes, or have they simply started from a much higher baseline? Do they have identifiable peculiarities of genetic background? Is there something special about their brain structure or perhaps their resistance to age-related processes such as neurofibrillary degeneration and amyloid deposition? These are the questions that were initially addressed by the Northwestern SuperAging Project, which identified unique results encompassing cognitive, psychosocial, molecular, and neuropathologic markers that characterize SuperAgers. Obstacles to further progress have been the relative rarity of this phenotype and, consequently, the barriers to racial diversity in the cohort.

Methods: To address these challenges, we established the SuperAging Research Initiative, a multicenter study focused on increased minority representation, to identify behavioral, health, biologic, genetic, environmental, socioeconomic, psychosocial, neuroanatomic, and neuropathologic factors associated with SuperAging.

Results: Here we provide the organizational structure and progress to date of the SuperAging Research Initiative, which includes three Cores (Administrative/Biostatistics, Clinical/Imaging, and Biospecimen/Neuropathology) and two Research Projects. Enrollment (n=500) is planned across four US Sites located in Illinois, Wisconsin, Michigan, and Georgia, and a Canadian Site in Southwest Ontario, with a focus on enrollment of Black SuperAgers and Cognitively Average Elderly Controls with similar demographics. Project 1 uses state-of-the-art wearable technology to obtain quantitative everyday measurements of life sleep, physical activity, autonomic responsivity, and social engagement to determine whether SuperAgers have relatively preserved physiologic and behavioral 'complexity' compared to Controls. Project 2 focuses on transcriptomic, genetic, and protein profiling to examine central and peripheral immune and inflammatory system parameters of SuperAgers.

Conclusions: By identifying factors contributing to superior memory performance in old age, outcomes may help isolate modifiable factors that promote healthspan and perhaps also prevent age-related brain diseases such as Alzheimer's disease.

Lay Language: The Northwestern SuperAging Research Program was designed to approach aging and Alzheimer's disease differently. Instead of studying the negative consequences of aging and disease, the program is identifying and factors that allow for a unique aging trajectory where individuals maintain youthful memory function. In 2021 Northwestern received an award from the National Institute on Aging (NIA) and the McKnight Brain Research Foundation to expand and establish an international multi-center study, which aims to amplify efforts to isolate factors that promote highly preserved cognitive aging. The resulting SuperAging Research Initiative is now enrolling participants at five research sites across the United States and Canada.

Poster 55

Investigating the role of rare genetic variants in Angiotensin-1-Converting Enzyme in Alzheimer's Disease pathogenesis

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Background: Recent genome- and proteome-wide association studies have identified angiotensin-converting enzyme (*ACE*) as a risk locus for developing late-onset Alzheimer's disease (LOAD). However, the mechanism by which *ACE* causes AD is not known. Although ACE1 is most commonly known as a key blood pressure regulating enzyme in the renin-angiotensin system (RAS), it is also present in the brain and has other substrates, including amyloid- β . Whole genome sequencing (WGS) of LOAD families revealed rare *ACE* coding variants. Recent work from our lab investigated one such rare variant, ACE1 R1279Q, and found it to cause autosomal dominant hippocampal neurodegeneration and neuroinflammation in a mouse model. More recent WGS revealed additional AD-risk as well as novel AD-protective *ACE* variants in LOAD families. This work seeks to characterize these rare genetic variants in order to understand the mechanisms by which they could alter ACE1 expression, processing, function, and its effect on cell viability.

Methods: *ACE* variants were stably expressed in SH-SY5Y neuroblastoma cells. Cell lines were differentiated in retinoic acid and then subjected to experiments aimed at characterizing cellular ACE1 protein production, function, and localization.

Results: *ACE* variants altered ACE1 protein expression and enzymatic activity. A cell surface biotinylation assay showed that mutations also altered the localization of ACE1 on the cell membrane and its shedding into the cell media. Cell death assays did not show signs of apoptosis in the cell lines.

Conclusions: Our preliminary data suggest that ACE1 shedding from the membrane may be a characteristic of mutations associated with protection from developing AD. AD-risk mutants did not show signs of spontaneous cell death, which leads us to hypothesize that ACE1-associated cell death may operate via non-cell intrinsic pathways. ACE1 catalytic activity may link these mutations to AD pathogenic mechanisms, as ACE1 is able to cleave over 100 different substrates. Future directions involve further characterizing ACE1 functionality in cell lines and mouse primary neuron-glia co-cultures. Mechanistic studies will be pertinent in understanding how these mutations may inform on the role of ACE1 in AD pathologies.

Lay Language: Alzheimer's disease (AD) is the most prevalent form of dementia. AD causes neurons in the brain to die because of a buildup of sticky protein aggregates called amyloid plaques and tau tangles. Apart from these aggregates in the brain, some people with AD have shared comorbidities – or co-existing conditions – like high blood pressure. This research focuses on studying a protein, ACE1, that controls blood pressure and how it could be involved in the progression of AD. Importantly, our work may inform on how current blood pressure medications can be an effective treatment for AD.

Poster 56

Alterations in Basal Ganglia Connectivity in Individuals with Primary Progressive Aphasia due to Alzheimer's Disease and Frontotemporal Degeneration

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Background: Primary progressive aphasia (PPA) is a syndrome of progressive language decline due to neurodegenerative disease. The agrammatic subtype of PPA (PPA-G) has been more commonly linked to frontotemporal lobar degenerative pathologies including corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). CBD and PSP are two rare progressive neurological disorders characterized by cell loss and deterioration of specific areas of the brain causing changes in movement, language skills, or both. The logopenic subtype of PPA (PPA-L) has been more commonly linked to Alzheimer's disease (AD) pathology. Most studies investigating pathophysiology of PPA have focused on cortical alterations. Pathologic studies have shown basal ganglia to be affected in both CBD/PSP and AD pathologies. However, changes in basal ganglia connectivity and potential differences have not been studied in PPA with CBD/PSP and AD pathologies. The goal of this study was to observe any potential differences in basal ganglia connectivity in PPA individuals with CBD/PSP versus AD pathology. We hypothesized that PPA with CBD/PSP would have more decrease in basal ganglia connectivity compared to the AD group.

Methods: This study consisted of 26 individuals with PPA due to AD, 16 individuals with PPA due to CBD/PSP, and 31 controls. All participants were right-handed. Diagnosis of pathologies were made by either autopsy or *in vivo* biomarkers. Functional MRIs were conducted for each participant and each scan was preprocessed via DPARSF-A v4.3, 2014 in the Statistical Parametric Mapping (SPM) based platform. Three basal ganglia regions of interest (ROIs) for both the left and right hemispheres were selected from the WFU-Pick-Atlas toolbox in SPM: caudate, putamen, and globus pallidus. Connectivity between each basal ganglia ROI and the rest of the brain for CBD/PSP and AD groups was separately compared to the controls using two-sample t-tests thresholded at $FWEc = 0.05$ using CONN toolbox.

Results: The voxel-wise analysis of whole brain connectivity of left caudate, putamen, and globus pallidus ROIs for the left hemispheres showed significant decreased connectivity in the corresponding regions for both CBD/PSP and AD groups compared to controls (left > right). Comparisons between CBD/PSP and AD showed no difference in connectivity between the two groups.

Discussion: In this study, we showed a left dominant decrease in basal ganglia connectivity for PPA in both CBD/PSP and AD groups. However, contrary to our original hypothesis, voxel-wise analysis of the caudate, putamen, and globus pallidus connectivity did not show any difference between CBD/PSP and AD groups. Our findings suggest that CBD/PSP and AD may similarly affect functionality of the basal ganglia. Our next step is to evaluate how these changes affect symptoms in both groups of PPA.

Lay Language: Primary progressive aphasia (PPA) is a language disorder caused by neurodegenerative disease. There are several different underlying diseases that can cause PPA. In this study we compared the brain connectivity of patients based on which disease was causing their PPA, either corticobasal degeneration/progressive supranuclear palsy (CBD/PSP) or Alzheimer's disease (AD). We found that both groups of people with PPA had reduced brain connections in a specific area called the basal ganglia. This region is located deep in the center of the brain and plays an important role in many of the brain's functions including movement, thinking, and emotion. However, there was no difference between the two groups in this area, suggesting that CBD/PSP and AD may similarly affect the functionality of this important brain region.

Poster 57

Northwestern Alzheimer's Disease Research Center Neuroimaging Biomarker Core

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The Northwestern Alzheimer's Disease Research Center Imaging Biomarker Core at the Mesulam Center for Cognitive Neurology and Alzheimer's Disease aims to enhance research activities on aging and dementia within and outside of Northwestern University. Neuroimaging is focused on the spectrum of extraordinary cognitive aging to dementia, including the frontotemporal lobar degeneration-spectrum of disorders. The Imaging Core contains multimodal data from MR scans that provide optimal quantitative information on brain structure (MPRAGE), white matter properties (FLAIR), axonal pathways (diffusion MR), resting state hemodynamic fluctuations for establishing functional connectivity (rsfMRI), cerebral blood flow (PASL), amyloid (Florbetaben PET), tau (Flortaucipir PET) binding and glucose (18F-FDG – PET) uptake. Neuroimaging data are available to enhance diagnostic characterization of the participants and to enrich projects of our collaborators.

Lay Language: Imaging Biomarker Core at the Mesulam Center aims to enhance research activities on aging and dementia. Multimodal neuroimaging data are available to enhance diagnostic characterization of the participants and to enrich projects of our collaborators.

Poster 58

High Levels of the Dendritic Spine Protein Spinophilin in Cognitive SuperAgers

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Although memory decline is typically observed throughout the aging process, the Northwestern SuperAging Research Program has identified individuals who maintain superior memory performance in old age. "SuperAgers" (SA) are selected for having episodic memory at age 80 or older that is at least equivalent to those 20-30 years younger. Initial studies show SAs generally have larger cortical volumes, less ApoE4, more von Economo neurons, and less prevalence of Alzheimer's disease (AD) pathology compared to their cognitively average peers. Loss of synapses is a common feature of cognitive decline associated with aging and AD. Spinophilin is a protein found in dendritic spines, dynamic structures that form the postsynaptic element of a majority of synapses in the CNS. Spinophilin displays distinct localization to the heads of dendritic spines in all brain regions, making it an excellent marker for quantitative assessment of spine integrity, and thus integrity of synapses. We had previously observed overall higher cortical levels of the pre-synaptic protein synaptophysin, and the post-synaptic density 95 (PSD-95) protein in SuperAgers. In the current study, we examined cortical levels of spinophilin using fresh frozen post-mortem human tissue from the middle frontal gyrus (MFG), hippocampus (HPC), middle temporal gyrus (MTG), and visual cortex (VIS) in SuperAgers (n=10), normal cognitive elderly (n=5), and AD patients (n=5). Western blot analysis was carried out using specific antibodies and results were expressed as percentage of the housekeeping protein GAPDH. In all regions studied, spinophilin levels were higher in SuperAgers when compared with normal controls (12-41%, $p < 0.05$), while in most regions, levels were lower in AD when compared with controls (5-46%). These preliminary results indicate a potential relationship between the SuperAging phenotype and integrity of dendritic spines/synapses as indicated by spinophilin levels. The initial findings will be extended by determination of levels of spinophilin and other synaptic proteins in cortical tissue from additional participants to allow rigorous statistical analyses.

Lay Language: Synapses are points of contact between nerve cells that allow neural communication. The goal of this experiment was to determine whether there are differences in the levels of synaptic proteins in aged individuals with superior memory capacity, known as SuperAgers, when compared with cognitively normal elderly. It is known that synapses are lost in patients with Alzheimer's Disease. The initial results of this study suggest that SuperAgers may have higher levels of a protein found at sites of synapses than their cognitively average peers. These findings suggest that integrity of synapses is an important factor in preservation of cognitive abilities in old age.

Elevated Carotid Pulse Wave Velocity is associated with Cognitive Impairment and Cerebral Amyloid Deposition: A Phase-Contrast MRI Study

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Introduction: Previous studies have indicated that arterial stiffness could play an important role in the pathogenesis of Alzheimer's disease¹⁻². Arterial stiffness is typically measured by pulse wave velocity (PWV) from central and peripheral arteries. Recent work has introduced a two-minute robust MRI method to measure carotid PWV (cPWV) using a single-slice oblique-sagittal phase-contrast MRI (OS PC-MRI)^{3,4}. This study aims to evaluate cPWV measured by OS PC-MRI as a sensitive imaging marker of AD by studying the association of cPWV with cognitive performance and amyloid pathology.

Methods: Twenty-three elderly volunteers (13 female, 72.6 ± 7.1 years) participated in the study and underwent cognitive and functional assessments including Clinical Dementia Rating (CDR, n=23), Mini-Mental State Exam (MMSE, n=21), and Montreal Cognitive Assessment (MoCA, n=23) and F18-florbetaben amyloid-PET scans (n=14). A retrospectively gated single-slice 2D OS PC-MRI was performed on each participant at 3T to assess cPWV. The correlations between cPWV vs cognitive measures and cerebral amyloid status were calculated across subjects using Pearson or Spearman's correlation coefficients.

Results: Table 1 lists the demographic and clinical information of participants. cPWV showed significant negative correlations with both MoCA (Figure 1a) and MMSE (Figure 1b) (cPWV vs. MoCA: $r = -0.57$, $p = 0.0044$; cPWV vs. MMSE: $r = -0.74$, $p < 0.001$); and the correlations remained significant after controlling for age, gender, years of education (cPWV vs. MoCA: $r = -0.70$, $p < 0.001$; cPWV vs. MMSE: $r = -0.75$, $p < 0.001$). The participants were further separated into two groups (CRD=0: n=12; CDR \geq 0.5: n=11) based on their CDR scores. cPWV values were significantly higher in the group with CDR \geq 0.5 without and with correcting for age, sex, and educational level ($p=0.0019$, $p=0.015$) (Figure 1c). Individuals who presented with amyloid pathology had higher cPWV compared to the ones without amyloid pathology ($p=0.038$) (Figure 2), which indicates cPWV may be closely linked to amyloid pathology in AD.

Conclusion: This study demonstrates that elevated carotid PWV is associated with cognitive impairment and amyloid pathology in elderly adults. Longitudinal studies are necessary to determine whether cPWV contributes to accumulation of amyloid in brain parenchyma or results from deposition of amyloid in cerebral blood vessels.

Lay Language: Increasing evidence suggests that vascular compliance could offer valuable insights into the pathology of Alzheimer's disease. Recently, carotid pulse wave velocity (cPWV) between the internal carotid artery and common carotid artery has been successfully measured by a fast single-slice oblique-sagittal PC-MRI technique. In this study, we evaluated the role of cPWV in brain amyloid deposition and cognitive decline in an aged cohort. The results showed greater cPWV was associated with cognitive decline and amyloid pathology. Our findings suggest elevated cPWV may affect amyloid clearance in brain, leading to cognitive impairment. cPWV could be a potential sensitive imaging marker of AD.

Poster 60

Strain-Dependent Disease Progression in a Conditional Wild-Type Human TDP-43 Transgenic Mouse Model

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Frontotemporal lobar degeneration (FTLD) is among the most prevalent dementias of early onset. Pathologically, FTLD presents with tauopathy or TAR DNA-binding protein 43 (TDP-43) proteinopathy. A biallelic mouse model of FTLD was produced on a mix FVB/129SVE background overexpressing wild-type human TDP-43 (hTDP-43) employing tetracycline transactivator (tTA). tTA activates hTDP-43 which was placed downstream of the tetracycline response element (TRE). We have backcrossed the tTA and hTDP-43 transgenic mice to the C57BL/6 background and found significant strain-dependent differences in disease progression. TDP-43 expression was turned on at 21 days postmortem by taking animals off doxycycline in diet. Bigenic animals on the mixed FVB/129SVE background displayed rapid progression of pathology and neurodegeneration. Punctate, cortical intraneuronal TDP-43 inclusions were detected after 5 days of expression. Inclusions attained a peak in density between 14-20 days of expression. Thereafter, they decreased in density, such that few were observed after 8 weeks of expression, and at 24 weeks, none could be identified. Neuronal degeneration and cortical thickness displayed the opposite pattern, with decreased neuronal density and cortical atrophy peaking at 24 weeks of expression. A subpopulation of cortical neurons contained intense ubiquitin immunoreactivity, which showed the same pattern of appearance and disappearance as TDP-43 inclusions. In contrast, bigenic animals on the C57BL/6 background displayed a considerably slower progression of disease and milder pathology. Accumulation of human TDP-43 immunoreactivity in cortical neurons slowly increased and was at a peak at 20 months of expression (the oldest age tested). Few and very small TDP-43 immunoreactive inclusion-like structures were visible in cortical neurons at 10 months of expression and thereafter. Ubiquitin immunoreactivity in cortical neurons was considerably less pronounced when compared with that in the mixed FVB/129SVE bigenic animals. These observations point to significant strain-dependent differences in disease progression and pathology in a conditional TDP-43 transgenic model. Thus, attention to strain of animals is crucial in studies using transgenic mice overexpressing proteins involved in neurodegenerative disorders.

Lay Language: Frontotemporal dementia (FTD) is characterized by accumulation of abnormal proteins in the brain, including tar DNA binding protein (TDP-43). Here we describe a mouse model which has been genetically altered to produce human TDP-43 in the brain that mirrors many of the abnormalities seen in FTD, including accumulation of TDP-43, neuronal loss, loss of neuronal connections, and behavioral abnormalities. We also demonstrate that the strain of mice used has great influence on the speed of disease progression and severity. Our findings demonstrate that the mouse line described is appropriate for experimental studies of FTD with TDP-43 disease type and for testing potential therapeutic targets, and suggest that attention needs to be directed to the strain of mice used in models of neurodegenerative disease.

Poster 61

Quantitative Proteomics Based Identification of Novel AD Therapeutic Targets

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Purpose: Extracellular amyloid formation is an early event in pathogenesis of Alzheimer's disease (AD). The disease slowly progresses with subsequent pathological changes, including memory loss, and cognitive impairments. Amyloid plaques are primarily made up of a short A β 42 peptide. The importance of A β fibrils has long been recognized, yet our understanding of plaque development, structure, and composition is subtle. The most intriguing among all is the magnitude of their diversity.

Methodology: In past studies, a large number of amyloid-associated proteins were identified with plaques. However, the inefficacy in plaque/fibrils purification and lack of consistency in the proteomics dataset limit scope of many such studies. We have improvised the traditional biochemical isolation methods and achieved great purity with high reliability. We performed multiple MS based proteomic studies to identify protein components of purified amyloid fibril, other than A β 42.

Findings: We consistently recovered a consensus pool of proteins from A β -rich fibrils isolated from highly diverse and complex biological samples, including AD patients' postmortem brain samples and relevant mouse models. We hypothesized that some of these A β interaction partners could be active modifiers of amyloid formation and maturation. By assessing in vitro aggregation kinetics of recombinant A β 42 and assessing the neurotoxicity in A β 42 overexpressing flies, we confirmed multiple proteins, which influence A β aggregation and maturation.

Lay Language: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder affecting more than five million people in the United States. AD progresses at a slow rate and causes a gradual decline in cognitive abilities leading to dementia. An increased resurgence in the amyloid cascade hypothesis has been observed, following the approval of Aducanumab and the promising effects shown by Lecanemab, two antibodies targeting A β peptides and other higher-order structures, including fibrils. Now, the focus has again shifted to reinvestigate the A β modifiers and amyloid partners that may affect A β 42 aggregation and amyloid formation in AD patients' brains. Targeting these new proteins may provide novel candidates to develop future AD therapeutics.

Poster 62

Alterations in Auditory and Language Network Connectivity in Primary Progressive Aphasia

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Background: Most investigations into pathophysiology of primary progressive aphasia (PPA) have focused on the visual-verbal aspects of language with less studies addressing impairments in the auditory processing of language decline. Study of alterations in shared neuronal resources for speech and hearing may help us better understand neurological impairments in PPA. Primary auditory cortex (PAC), planum temporale (PT), and planum polare (PP) are major regions associated with processing of complex auditory signals. In this study we investigated alterations in brain connectivity between auditory and language regions in individuals with semantic PPA (PPA-S) and logopenic PPA (PPA-L). We hypothesized that in individuals with PPA-L (more commonly caused by Alzheimer's disease) there would be decrease in connectivity of planum temporale and the perisylvian language network, while in PPA-S (caused by frontotemporal lobar degeneration of the TDP43 type) there would be decrease in connectivity of planum polare and the perisylvian network.

Methodology: To address this issue, functional magnetic resonance imaging (fMRI) data were collected for 20 PPA-L and 17 PPA-S participants and preprocessed using Data Processing Assistance for Resting State fMRI. Seed-based resting state functional connectivity analysis was used to generate z-maps for each auditory seed (PAC, PP, and PT). Two sample t-tests compared connectivity of each seed with perisylvian region across PPA subtypes using the CONN toolbox. Cluster-level extent threshold was corrected for family wise error (FWE) at $p < 0.05$ while voxel-wise thresholding was set to p -uncorrected < 0.001 . Volume-correction was performed using an SPM12 script comparing binarized gray matter maps and thresholded cluster results. Gray matter volume for significant clusters was used as a covariate in reanalysis to reduce imprecisions due to atrophy.

Results: Atrophy corrected t-tests revealed regions of significantly decreased connectivity unique to each subtype. PPA-L had significantly decreased connectivity between PAC/PT and perisylvian region as compared to PPA-S. Decrease clusters were located in the posterior aspect of perisylvian region. In contrast, PPA-S had significantly decreased connectivity between PP and the anterior perisylvian region as compared to PPA-L.

Conclusion: In this study we find connectivity alterations within the auditory-language network which are specific to PPA-L versus PPA-S. PPA-L had uniquely decreased connectivity between PAC and PT and the perisylvian network which may explain characteristic impairment in phonological loop, causing repetition deficit and phonological paraphasia. On the other hand, PPA-S had uniquely decreased connectivity between PT and anterior perisylvian region which may support disconnection between downstream auditory processing and lexical knowledge specific to PPA-S. We plan to evaluate how these finding correlate with PPA-L and PPA-S symptoms to better understand abnormal neurobiology of language processing in PPA.

Lay Language: This study looked at how the brain connects the parts that process sound and the parts that process language in people with two different types of primary progressive aphasia (PPA), a neurological disorder that affects language. We used brain scans to compare the connections in people with semantic PPA (PPA-S) and logopenic PPA (PPA-L). We found that PPA-L had weaker connections between some parts of the brain responsible for storing language information, which could explain why people with this type have trouble repeating words and make word substitutions while speaking. PPA-S had weaker connections between parts of the brain responsible for language processing, which could explain why people with this type have trouble finding and understanding words. By understanding these differences, researchers can develop more targeted therapies to help individuals based on which type of PPA they have.

Proteomic Characterization of a Novel Antibody for FTLD-TDP Pathologic TDP-43

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Frontotemporal lobar dementia (FTLD) is the third most prevalent degenerative cause of dementia and can be characterized based on the contents of patients' pathological inclusions. One of the categories of FTLD, FTLD-TDP, is characterized by transactive response DNA binding protein with Mr 43 kD (TDP-43) abundant inclusions. A novel monoclonal antibody was produced that targets the c-terminal glycine-rich domain (GRD) of TDP-43 and seems to be strongly reactive to pathological TDP-43 inclusions with minimal reactivity to normal TDP-43. The aim of this study is to validate this novel antibody (MAb#9) using western blot, liquid chromatography with tandem mass spectrometry (LC-MS/MS), and immunoprecipitation using MAb#9 on the plasma, blood, and cerebrospinal fluid (CSF) of patients with a variety of neurodegenerative dementia diagnoses. Results point to a low abundance of pathological TDP-43 in the tested fluids with a possible explanation being the protein's aggregation in the brain. By examining the MAb#9-detected pathological TDP-43 levels in the plasma and CSF of patients with Alzheimer's Disease, FTLD-TDP, FTLD-Tau, Pick's Disease, and other dementias, we can validate MAb#9's ability to discern between dementias with pathological TDP-43 and without TDP-43. Potentially, MAb#9 can be used to create an assay to differentiate between FTLD-TDP and other dementias to diagnose patients faster and in a more cost-effective way.

Lay Language: Frontotemporal lobar dementia (FTLD) is the third most prevalent degenerative cause of dementia. One of its many subtypes, FTLD-TDP, is characterized by brain aggregates positive for transactive response DNA binding protein with Mr 43 kD (TDP-43). A novel antibody (MAb#9) was produced that targets TDP-43 and seems to be strongly reactive to pathological TDP-43 aggregates with minimal reactivity to normal TDP-43. The aim of this study is to validate MAb#9 using the blood, plasma, and cerebrospinal fluid (CSF) of patients with various forms of dementia including Alzheimer's Disease and FTLD-TDP. As it stands, it is very difficult, invasive, and time-consuming to diagnose different dementias. Potentially, MAb#9 can be used to create a test to differentiate between FTLD-TDP and other dementias to revolutionize the diagnosis and treatment process. Patients would be diagnosed faster and in a more cost-effective way.

Poster 64

The VIVA-MIND Study

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The VIVA-MIND Study is a Phase II multi-center, placebo-controlled study that will evaluate whether an oral investigational drug, varoglutamstat, can reduce amyloid deposits in older adults with early-stage Alzheimer's disease (Early AD). VIVA-MIND is specifically designed for Early AD, targeting individuals with Mild Cognitive Impairment (MCI) or mild Alzheimer's disease (AD) between the ages of 50 to 89. This study will enroll approximately 180 participants at 30 research sites. Participation lasts for at least 8 months and involves clinical and cognitive assessments, biomarker tests, MRI brain scans, EEGs, and cerebrospinal fluid (CSF) analysis. This trial is currently open at Northwestern University for screening and enrollment.

Lay Language: The VIVA-MIND Study is a Phase II multi-center, placebo-controlled study that will evaluate whether an oral investigational drug is safe and effective at slowing or halting Alzheimer's Disease (AD) progression. The investigational drug is aimed to reduce an abnormal form of a protein called "amyloid", which accumulates in the brains of people with AD.

Poster 65

The AHEAD Study

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The AHEAD Study is a Phase III multi-center, placebo-controlled, double-blind, parallel-treatment arm study that will evaluate the efficacy and safety of the investigational drug, BAN2401 (Lecanemab), in its ability to slow or stop brain changes in individuals with preclinical Alzheimer's Disease (AD). The investigational drug is an intravenous amyloid targeting monoclonal antibody therapy. In January 2023, BAN2401 was granted accelerated FDA approval for treatment of clinically diagnosed AD. This study will enroll approximately 1,400 participants with preclinical AD at 100 global research sites across two cohorts: (1) individuals with intermediate amyloid and (2) individuals with elevated amyloid. Participation in the study lasts for 4 years and involves biweekly or monthly infusions, clinical and cognitive assessments, biomarker and genetic tests, brain imaging scans (including PET and MRI), and optional cerebral spinal fluid analysis. Enrollment for this trial is open and currently screening and enrolling participants between the ages of 55 and 80.

Lay Language: An abnormal form of a protein called “amyloid” builds up in the brains of people with Alzheimer's disease (AD), but not every person with amyloid build up will develop memory problems or AD dementia. The AHEAD 3-45 Study is a Phase III multi-center, placebo-controlled study that will evaluate whether an investigational drug reduces the risk of developing AD dementia.

Poster 66

Study design and concepts for heart-brain MRI evaluation in aging and hypertension

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Background: Cardiovascular risk factors, such as hypertension and physical inactivity, are among potentially modifiable dementia risk factors that can be influenced in mid to later life. However, mechanisms underlying heart-brain hemodynamic coupling are not fully understood and integrating them may provide new mechanistic understanding of changes associated with brain aging, Alzheimer's disease and related dementias (ADRD).

Imaging methods and concepts: 4D flow MRI has emerged as a powerful technique for measuring blood flow in-vivo. This approach has been used to measure complex hemodynamics in the heart and large vessels of the brain. However, these regions are usually evaluated separately on scanners dedicated to either heart or brain imaging. Recent developments provide the ability to image faster and thus an opportunity for integrating cardiovascular 4D flow MRI with neuroimaging in a single ~1 hour session ("heart-brain MRI"). The goal of this study is to use novel imaging tools to systematically study relationships between hemodynamics and brain structure for hypertensive and healthy participants in mid to later life. This will help provide the foundation for future heart-brain studies in ADRD.

Study progress: We have developed a 1-hour heart-brain MRI protocol and acquired pilot data on 17 participants to demonstrate feasibility. The imaging protocol is currently being optimized for use in this Northwestern Pepper Center study. An integrated heart-brain analysis framework has been developed for the semi-automatic quantification of hemodynamic measures. We have identified regions of interest for gray matter volume (e.g., hippocampus, amygdala) and cortical thickness (e.g., entorhinal, inferior temporal, parahippocampal, fusiform, medial orbital frontal) for a fully integrated workflow. The Montreal Cognitive Assessment will be used for cognitive screening of all participants. We plan to enroll 40 participants with hypertension and 40 cognitively healthy adults >age 45 years to study potential heart-brain coupling relationships across mid and later life.

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Lay Language: Studies have linked cardiovascular risk factors, such as hypertension and physical inactivity, with dementia. However, the underlying details of how this can occur remain unclear. Imaging tools can be very helpful for studying these relationships. In this study we plan to use an advanced imaging technique called 4D flow MRI to measure blood flow in the chest and head. We have designed a 1-hour imaging session for capturing 4D flow MRI along with neuroimaging measures of brain structure. Our goal is to gain a better understanding of relationships between the heart and brain in individuals with hypertension and healthy cognitive aging.

Poster 67

Using Community Engaged Research Strategies to Promote Sense of Community in Diverse SuperAging Research Initiative Participants

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Studies demonstrate that community engaged research (CER) supports minority recruitment into Alzheimer's Disease research. In contrast, few studies have explored whether CER can engage diverse 'SuperAgers,' adults age 80+ with superior episodic memory. The SuperAging Research Initiative, a multi-site research program across the U.S. and Canada, seeks to recruit 40% Black adults over 80 years of age, using principles of recruitment and retention science and CER. The unique cultural historical background and socio-political conditions of Black Americans in this age cohort pose unique challenges and present an opportunity to implement novel approaches to recruitment and retention. Here we share the Northwestern SuperAging Research Initiative's CER efforts, which includes fostering community. Sense of community has been identified as an important factor in the lives black Americans (Coffman and Belue, 2009). Psychological Sense of Community is a feeling that members have belonging, matter to one another and to the group, and share faith that needs will be met through their commitment (McMillan, 1976). The four central tenets of psychological sense of community are: membership, influence, integration and fulfillment of needs and shared emotional connections.

The study is supporting feelings of *membership and community* by hiring diverse staff, creating culturally relevant study materials, and building trust through transparency. In the past year two new Community Engagement Coordinators joined the team and new study materials are in the process of being developed. *Influence* is being created by developing opportunities for participants to inform study materials and study design. In the spring of 2023 SuperAging participants provided guidance on new study material content and participated in a photoshoot to improve availability of representative images of healthy aging. The study is promoting *integration and fulfillment* among Black research participants by disseminating study information, increasing positive media representation of diverse older adults, and community partnerships. Over, study staff attended 65 community events, developed 19 community partnerships and engaged in local, national and international media opportunities including; CNN, Fortune, BBC News, WOSU Public Media, and the Today Show. Finally, a *shared emotional connection* is being fostered by connecting to participants and staff through events, communication materials and commemorative gifts. From our efforts, 18 participants who identify as Black enrolled in the study to date.

By following community engaged research principles the SuperAging Research Initiative strives to create a sense of community and belonging among Black SuperAgers while forging a path for new research principles, which will elevate aging science by filling an unmet need for understanding the drivers of health span in diverse populations.

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Psychosocial Pathway Seminar Series Training

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Background: The Mesulam Center developed the Psychosocial Pathway [PsP] for research participant facing staff [RPFS] to assist with identifying and responding to research participants' expressions and indications of stress that are beyond normal, specifically those that impact the persons' safety, wellbeing, and/or participation in research. RPFS underwent online training for the PsP at its inception in 2020. Feedback from RPFS noted interest in additional training to assist with navigating stressful encounters due to emotional distress around caregiving, changes in participant test scores, and other topics of concern like brain donation. While there is training focused on developing the dementia care workforce, there is no literature addressing dementia and communication skills training for research participant facing staff.

Method: Sixteen volunteer RPFS took part in an in-person, 1-hour exploratory workshop that introduced improvisation exercises as a method for providing communication training and emotional support around complex psychosocial issues that can occur during RP and SP encounters. RPFS completed a pre-survey about challenges they faced working with RP and SP and post-workshop survey requesting three take-aways from the workshop. Noting positive feedback, an in-person, 5-session Psychosocial Pathway Seminar Series Training [PPSST] curriculum was developed offering didactic presentations, applied improvisation training and panel discussions focusing on the Psychosocial Pathway referral process, enhancing communication, coping with emotional situations, working with diverse older adult populations and discussing brain donation. Twenty-six RPFS participated in the 5-week, 90-minute sessions and completed a pre-PPSST survey assessing their competency and comfort with the PsP referral process, communication around psychosocial stressors, working with diverse older adults and discussing brain donation. Weekly post-session surveys invited feedback on their weekly experiences. RPFS completed a post-PPSST survey to assess their comfort and competency around session topics with additional opportunities to share feedback about their experience.

Results: Survey results from the initial workshop noted value from improvisation tools and expressed interest in additional training and support. The weekly post-session PPSST surveys noted specific take-aways that could help RPFS address psychosocial stressors or concerns with RP and/or SP. Twenty-two RPFS completed the post-survey and while the results were being compiled at the time of abstract submission, there appears to be an increase of comfort and familiarity in the areas of the PsP referral protocol, enhancing communication around difficult emotions, working with diverse populations and discussing salient topics around brain donation. RPFS noted areas where the PPSST can improve and where it can consider virtual and/or hybrid learning.

Conclusion: This in-person 5-session Psychosocial Pathway Seminar Series pilot offers a feasible training model for RPFS to address psychosocial and retention concerns for research participants and their study partners.

Lay Language: The Psychosocial Pathway [PsP] identifies psychosocial concerns that may cause barriers to research participation for research participants and their study partners. To enhance training for research participant-facing staff [RPFS] in identifying these concerns, a Psychosocial Pathway Seminar Series Training [PPSST] was designed to offer didactic presentations, applied improvisation skill building and panel discussions to develop competency with the PsP referral process, communication strategies for navigating challenging conversations and situations, developing cultural humility with diverse populations and discussing brain donation. PPSST appears to be a feasible training model for RPFS to address research participant safety, well-being and retention concerns.

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Reducing Fear and avoidance of memory loss (REFRAME) study: A pilot randomized control trial to reduce fear and avoidance and improve well-being in older adults

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Introduction: Alzheimer's disease and related dementias (ADRD) are among the most feared age-related conditions. This study aimed to determine the impact of a brief psychological intervention on ADRD-specific anxiety, well-being and psychosocial functioning in community-based older adults experiencing heightened fears around memory loss and patterns of social and cognitive avoidance.

Methods: Eighty-one older adults self-reporting high levels of fear around memory loss were recruited and randomized into REFRAME or an active comparison condition. Both treatment arms involved psycho-education and mindful monitoring of difficult feelings and thoughts related to memory loss. The REFRAME condition included an additional behavioral activation component intended to disrupt maladaptive avoidant coping strategies.

Results: Treatment adherence was strong in both conditions. A significant reduction in anxiety specific to memory loss was observed in both conditions. Significant reductions were also observed for the fear of Alzheimer's disease, the intensity of self-reported memory failures, and depression. The decrease in depression was larger in the REFRAME condition relative to the comparator. Both interventions were associated with an increase in social function and well-being.

Discussion: Findings suggest that psychological interventions can alleviate ADRD-specific anxiety in vulnerable older adults and that therapeutic benefits might extend to broader health-related outcomes including depression, social functioning, and psychological well-being. Addressing fear and avoidance has implications for healthy aging and lifestyle risk reduction, as individuals may be more likely to engage in activities that are protective against ADRD but were previously avoided because of fear.

Lay Language: For a large portion of the population (~40%), Alzheimer's disease and other types of dementia are the most feared diagnosis, surpassing even cancer. Growing evidence suggests that experiencing high levels of fear around dementia is linked to poorer health and well-being and can cause people to avoid seeking help when they need it. Here, we investigated if a short psychological intervention targeted at older adults who were highly fearful could reduce fear of dementia and associated avoidance behaviors. We found that our intervention led to a significant reduction in dementia-related fear. We also found reductions in the intensity of self-reported memory failures, and depression, and increases in social function and well-being at the end of the intervention. Overall, our findings suggest that psychological interventions can alleviate fear of dementia, and that the therapeutic benefits may extend to broader health-related outcomes. Addressing dementia-related fears has important implications for healthy aging, as individuals may be more likely to engage in activities that are protective against dementia but were previously avoided because of fear.

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A randomized controlled trial of a positive affect skills intervention to reduce stress in family caregivers of individuals with Alzheimer's disease: Protocol and design for the LEAF 2.0 study

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Caring for a loved one with Alzheimer's Disease can be stressful. Family caregivers of individuals with dementia face detriments to both emotional and mental health due to the daily stressors they face. Studies are increasingly demonstrating the unique importance of positive emotions in coping with stress and depression. However, few have examined the benefits of interventions that target positive emotions for caregivers of individuals with a chronic and debilitating disease such as Alzheimer's. This poster presents the design and methods of LEAF 2.0 (Life Enhancing Activities for Family caregivers), a randomized controlled trial (RCT) of a positive affect skills intervention for family caregivers of individuals with Alzheimer's disease. LEAF 2.0 builds on previous randomized trial findings from LEAF 1.0 that demonstrated that facilitated web delivery of the LEAF positive affect skills decreased depression in dementia caregivers. However, facilitated delivery of interventions is resource intensive and may limit dissemination and scalability. Thus, in the present study, we will compare the effects of two different delivery methods of the skills-based intervention on AD caregiver well-being: (1) by trained facilitators via six one-on-one Zoom video sessions, similar to LEAF 1.0, or (2) via an online, self-guided version on the study website, which aims to make the program more widely accessible in the future if its effects are comparable to the facilitated version. The control group is an emotion reporting/waitlist that receives the intervention after 7 months in one of the two ways listed above. Follow-up assessments are conducted post-intervention and at about every two months during the fourteen-month study involvement. Outcomes include caregiving burden, positive emotion, perceived stress, depression, and anxiety), caregiving self-efficacy, positive aspects of caregiving, quality of care, and AD patient quality of life. We hypothesize that LEAF will positively influence these caregiving outcomes and that the effects will be mediated through increased caregiver positive emotion.

Lay Language: LEAF 2.0 (Life Enhancing Activities for Family Caregivers) is a research study to examine the effects of a positive emotion regulation intervention for family caregivers. LEAF 2.0 is testing whether delivery of the intervention by (1) by trained facilitators via Zoom or (2) via an online, self-guided version can improve psychological well being in caregivers.

Construct Validity Indicators for the Tablet Computer-Based NIH Toolbox Cognition Battery (NIHTB-CB) from the ARMADA STUDY

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Background: The Advancing Reliable Measurement in Alzheimer's Disease and Cognitive Aging (ARMADA) study's primary goal was to broaden the normative development of the tablet-based NIH Toolbox Assessment of Neurological and Behavioral Function for an older, racially diverse population. This ARMADA cohort study reports validity data for the Toolbox Cognition Battery (NIHTB-CB) based on: (a) correlational results with tests from the National Alzheimer's Disease Coordinating Center (NACC) Unified Data Set (UDS3) neuropsychological battery demonstrating convergent (high correlations to related constructs) and discriminant (low correlations with dissimilar constructs) validity and (b) factor structure of the NIHTB-CB across age and race groups.

Methods: Participants (age range 65-99 years, 142 aged 85+) were classified based on UDS-based consensus conference with normal cognition (N=367) or amnesic mild cognitive impairment (N=136). NIHTB-CB assesses domains of Fluid Executive, including Set Shifting (Dimensional Card Sort/DCCS), Inhibitory Control and Attention, (Flanker) and Working Memory (List Sort Working Memory/LSWM); Fluid Processing Speed (Pattern Comparison/PCPS), Fluid Episodic Memory (Picture Sequence Memory/PSM) and Crystallized Language (Oral Reading/ORR, Vocabulary/TPVT). Participants were also given the NACC UDS3 cognitive measures: Memory (Benson Figure, Craft Stories Delayed Recall); Processing Speed (Trail Making Test, Part A), Executive (Trail Making, Part B), Attention (Number Span Forward), Figure Copy (Benson), and Language (Multi-lingual Naming Test/MLNT). Unadjusted, (uncorrected) standard scores were created based on the full Toolbox and UDS populations.

Result: Based on the large sample size, most all correlations between NIHTB-CB and UDS3 were significant, though patterns were evident. NIHTB-CB/Fluid Executive tests had highest correlations with the related UDS3 Executive measures ($r=0.50-0.59$), approaching threshold for a "good" designation (>0.6), and "low" designation (<0.3) correlations ($r<0.28-0.43$) for Digits Forward. PSM correlated highest with UDS memory measures ($r=0.48-0.53$), and lowest with the Digits Forward ($r=0.25$). PCPS was highest with the Trail Making/A ($r=0.52$) and lowest with MLNT ($r=0.26$). Crystallized NIHTB-CB correlated highest with MLNT ($r=0.41-0.49$) versus ORR Craft Delayed ($r=0.22$) and TPVT with Figure Copy ($r=0.26$). Next, the basic two-factor structure of the NIHTB-CB was evaluated, suggesting that, in general, the two-factor model was upheld, with the exception of the Black/African American group in which PCPS loaded in the Crystallized Language.

Conclusion: Results demonstrated that the highest correlations between NIHTB-CB and UDS3 measures were between related constructs and lowest correlations were between dissimilar constructs. Thus, convergent/discriminant expectations were supported across NIHTB-CB measures, reinforcing NIHTB-CB construct validity. Consistent two-factor models were evident across three of the four factor modes, except for a three-factor model for Black/African Americans for Crystallized measures, suggesting memory should be considered as part of this factor and perhaps supporting past research noting racial differences on Crystallized measures. Further research in factor invariance may be warranted across race.

Lay Language: The purpose of this investigation is to determine the extent to which different sets of measures can potentially be harmonized, or meaningfully compared, so that previously unconnected datasets can be used to further accelerate scientific discovery. The Advancing Reliable Measurement in Alzheimer's Disease and Cognitive Aging (ARMADA) study's primary goal is to describe the extent of many health outcomes in a cognitively impaired population, compared to those that do not present such symptoms. This study examines how well one set of standardized measures, the NIH Toolbox Assessment of Neurological and Behavioral Function Cognition Battery, compares with tests from a national neuropsychological battery administered across many research centers focusing on Alzheimer's Disease participants. We find that measures of cognitive flexibility and episodic memory exhibited the highest correlations, followed by measures of general knowledge. This helps support construct validity, or the ability of similar measures to assess similar underlying relevant themes.

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Differences in Intra-individual Variability on the NIH Toolbox in Older Adults with Normal Cognition, Mild Cognitive Impairment, and Dementia of the Alzheimer Type

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Introduction: Variability in cognitive performance within an individual, termed intra-individual variability (IIV), is a sensitive and dynamic measure for detecting cognitive decline. Specifically, prior studies have found greater variability in reaction time on tests of attention and executive functioning in individuals with mild cognitive impairment (MCI) or dementia compared to those with normal cognition (NC). To our knowledge, IIV has not been investigated on the NIH Toolbox (NIHTB), a computerized suite of tests measuring cognitive and neurological functions. The purpose of this study was to evaluate IIV in older adults in individuals with NC, amnesic MCI, and dementia of the Alzheimer type (DAT) within the ARMADA (Advancing Reliable Measurement in Alzheimer's Disease) study, a multi-site, longitudinal study that validated that NIHTB across the cognitive aging spectrum.

Methods: Participants ages 65 and older with normal cognition (NC; $n = 275$), aMCI ($n = 107$), and DAT ($n = 73$) were included. Participants completed the NIHTB as part of the larger ARMADA study. Reaction time on two different measures of executive functioning, the Flanker Inhibitory Control and Attention Test and Dimensional Change Card Sort (DCCS) Test, were assessed. ANOVAs were conducted to examine if there were differences in reaction time variability of all completed trials, correct trials, and trial type between the groups. Analysis included three types of variance estimates: standard deviation, interquartile range, and median absolute deviation.

Results: Regardless of measure of executive function, trial type, or variance estimate, individuals with DAT showed significantly higher levels of IIV than MCI and NC groups, with large effect sizes (range of Cohen's d : [0.84, 1.63] when compared to NC; range of Cohen's d : [0.49, 0.96] compared to those with aMCI). Although the differences between NC and aMCI were not significant after correction for multiple comparisons ($p > 0.0027$), effect sizes were small (Range of Cohen's d : [0.33, 0.47]). The largest effect sizes of DAT versus other groups were for intraindividual standard deviation of congruent Flanker trials. For MCI versus NC, the largest effect size was for intraindividual standard deviation of overall DCCS trials.

Discussion: Findings from this study demonstrate differences in IIV on the Flanker and DCCS tests in NC, aMCI, and DAT with a range in effect sizes, but yielding meaningful information. These findings indicate that IIV on measures of the NIHTB can be used to detect differences in clinical groups. Future work will determine which measures of IIV will maximally differentiate between clinical groups, as well as examine differences in IIV over time.

Lay Language: Variability in how quickly an individual responds to different cognitive tasks can differentiate older adults with normal cognition, mild cognitive impairment (MCI), or dementia of the Alzheimer type (DAT). The purpose of this study was to look in intra-individual variability (IIV), or how variable someone responds across trials on the same test, on the NIH Toolbox. The NIH Toolbox is a computerized suite of tests measuring cognition, and has been recently validated in older adults across the cognitive aging spectrum. Our study showed large differences in IIV when comparing individuals with DAT to individuals with NC or MCI. There were smaller, but meaningful, differences between the NC and MCI groups. These results indicate that IIV is an important cognitive measure, and future plans include investigating which measure of IIV is the most useful, and how it may change over time.

Health-related quality of life in patients with Primary Progressive Aphasia

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Background: Primary progressive aphasia (PPA), first described by M.-Marsel Mesulam, is a rare neurodegenerative dementia syndrome characterized by a gradual loss of language function. Individuals with PPA often experience a decline in their quality of life (QoL) due to their progressive symptoms. Yet, current literature evaluating QoL in a large sample of PPA patients is lacking. The Health Utilities Index (HUI) is a comprehensive, reliable, and valid rating scale used to assess health status and health-related quality of life (HRQoL). This study aims to provide a summary of HRQoL in a large sample of PPA patients and compare the HUI overall utility scores by disease severity using the aphasia quotient of Western Battery Aphasia (WAB-AQ).

Methods: Data were obtained from 167 participants enrolled in either Language in PPA observational study (in-person visits) and/or Communication Bridge (telemedicine visits through video chat) randomized controlled clinical trial study. For 39 participants who are co-enrolled in both studies, data from earlier visit were used. All participants have a diagnosis of PPA based on the current research criteria, and 2 participants were excluded due to the diagnosis of primary apraxia of speech or semantic dementia. Additionally, 8 participants were excluded due to the incompleteness of required neuropsychological testing or questionnaires, providing the final sample of 118 participants for analysis. The WAB-Revised was administered to PPA patients in person or over video chat. Communication partners completed the HUI2/3 15-item questionnaires as proxy respondents for the PPA patients. The HUI questionnaires provide single-attribute utility scores for each domain of health status such as vision, hearing, speech, etc. as well as multi-attribute utility scores, which is the overall HRQoL derived from all domains. The multi-attribute scores of HRQoL are defined such that the score of 0.00 indicates dead and the score of 1.00 indicates perfect health. Both HUI2 and HUI3 allow for negative scores to represent health status worse than dead, with the lowest possible score of -0.03 for HUI2 and -0.36 for HUI3. HUI2 and HUI3 multi-attribute (overall) utility scores were compared by disease severity determined by WAB-AQ. Multivariate linear regression analysis was performed to examine whether HUI2 and HUI3 multi-attribute utility scores were associated with demographic variables and/or disease severity.

Results: Participants were primarily white (97.5%) and college-educated (years of education $M = 16.5$, $SD = 2.37$). Participants ranged in age from 52 years to 81.9 years ($M = 67.5$ years, $SD = 7.46$ years), and WAB-AQ score ranged from 43.6 to 97.6 ($M = 80.6$, $SD = 11.5$). HUI2 multi-attribute scores ranged from 0.360 to 1.00 ($M = 0.787$, $SD = 0.0987$), and HUI3 multi-attribute scores ranged from -0.147 to 1.00 ($M = 0.685$, $SD = 0.179$). There was a statistically significant positive association between the HUI2 multi-attribute utility score and WAB-AQ ($p = 0.012$), but not between HUI3 multi-attribute utility score and WAB-AQ ($p = 0.442$). There seems to be a trend towards negative association between HUI3 multi-attribute utility score and disease duration ($p = 0.097$), but it did not reach statistical significance. Sex, age, and years of education were not correlated with either HUI2 or HUI3 multi-attribute utility scores.

Discussion: Health-related quality of life as assessed by communication partners in PPA may be associated with severity of aphasia but was not significantly correlated to other demographic or disease variables in this sample. The presence of a significant association between disease severity and HUI2 multi-attribute score, but not HUI3 multi-attribute score underlines the different aspects of quality of life captured in these complementary measures and the importance of including both HUI2 and 3 in assessments in this population. Additionally, average HUI3 multi-attribute utility score was lower than average HUI2 multi-attribute utility score, indicating that HUI3 attributes may be capturing specific factors that are associated with a decline in HRQoL in this population which are not captured in HUI2 attributes, or that there is a floor effect in HUI2 which is relevant to this study population. Future analyses will examine how HUI2 and HUI3 single attribute scores differ within this population, and differences between HRQoL in PPA subtypes. Limitations include a homogeneous sample population in regard to race, years of education, and mild disease severity. Future research analyzing this population longitudinally will be helpful to better understand the relationship between disease severity and HRQoL.

Lay Language: PPA is a type of neurodegenerative dementia characterized by a gradual loss of language function. The worsening of language impairment over time often negatively impacts the quality of life in individuals with PPA. The Health Utilities Index (HUI) is a reliable and valid rating scale used to measure health-related quality of life (HRQoL) by providing the overall utility scores as well as single utility scores in each health domain such as vision, hearing, speech, etc. In this sample, health-related quality of life as assessed by communication partners in PPA may be associated with disease severity but was not significantly correlated to sex, age, disease duration, and years of education.

Longitudinal Performance on the NIH Toolbox Cognition Module in a Cognitive Aging Sample

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Objective: As the older adult population increases in the coming decades, the number of persons that develop dementia of the Alzheimer's type (DAT) will increase accordingly. Though curative treatment for Alzheimer's disease remains elusive, early detection of cognitive decline allows for initiation of pharmacological treatment to slow disease progression and non-pharmacological approaches to support quality of life and well-being of affected individuals and their care partners. Streamlined approaches that bridge the gap between brief screenings and comprehensive neuropsychological evaluation are needed. The NIH Toolbox Cognition Battery (NIHTB-CB) is a brief, easily administered, computerized cognitive battery that assesses various aspects of both fluid and crystallized cognitive abilities. ARMADA (Advancing Reliable Measurement in Alzheimer's Disease and Cognitive Aging) is a multi-site study that aims to validate the NIHTB across the spectrum from normal aging to DAT. The current study utilized longitudinal data from ARMADA to determine whether performance on the NIHTB-CB detects cognitive decline in persons with normal cognition (NC), mild cognitive impairment (MCI), and mild DAT over the span of two years. We predicted that scores would decline for the MCI and DAT groups, but not for the NC group.

Participants and Methods: Participants were 191 participants drawn from the larger ARMADA cohort aged 65-84 ($n_{NC} = 118$, $n_{MCI} = 47$, $n_{DAT} = 26$) that completed the NIHTB-CB at baseline and 12 months. The clinical groups were significantly older than the NC group at baseline ($M_{NC} = 72.72$, $M_{MCI} = 76.63$, $M_{DAT} = 75.42$; $p < .001$) and the NC and MCI groups had significantly more years of education than the DAT group ($M_{NC} = 17.03$, $M_{MCI} = 16.83$, $M_{DAT} = 15.54$; $p = .008$).

Results: Mixed model ANOVAs determined differences in uncorrected NIHTB-CB scores between clinical groups at baseline and 12 months, controlling for age and education. There were significant interactions between time and clinical group for Flanker ($p < .001$), Pattern Comparison ($p < .001$), and Picture Vocabulary ($p = .001$), such that the DAT group demonstrated a more negative slope of change than the NC and MCI groups. For Oral Reading, the MCI group demonstrated a more negative slope of change than the NC and DAT groups ($p = .01$).

Conclusion: Differential score trajectories were found for the Flanker task, with a more negative pattern of change in scores in the DAT group compared to the NC and MCI groups. Contrary to expectation, scores decreased for the two crystallized subtests across groups, which may reflect regression to the mean given high baseline scores, especially for Picture Vocabulary; however, these results were also moderated by group with less decline in scores in the NC group, which may indicate involvement of non-crystallized abilities in executing a single word comprehension task. Group differences were subtle, which may in part reflect the relatively short period of follow up. The Flanker task appears to be most sensitive to decline in mild DAT compared to MCI and NC. Results provide preliminary support for the utility of NIHTB-CB in detecting cognitive decline along the cognitive aging to DAT spectrum.

Lay Language: Early detection of cognitive changes that occur due to Alzheimer's disease (AD) is crucial, as this allows for timely implementation of behavioral interventions and disease-modifying treatments. Historically, diagnosis of early AD dementia has required many hours of cognitive testing, which is time- and resource-intensive and not readily accessible for many people. Efficient tests of memory and other thinking abilities are needed to be able to catch AD dementia at the earliest stages across diverse populations. One example is the NIH Toolbox Cognition, which includes a number of different tests of thinking abilities and is easily administered on an iPad. The current study focuses on how scores on the NIH Toolbox Cognition change over time in persons without cognitive difficulties and those with early AD dementia. Ultimately, this may allow for a better understanding of how NIH Toolbox Cognition can pick up on subtle signs of cognitive decline in older adults.

Boosting Positive Emotion in Caregivers: Moderators of a Positive Psychological Intervention

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Purpose: There are a number of negative mental health effects associated with dementia caregiving, including increased stress and depression. Resilience and hopefulness are two positive emotional resources linked to increased caregiver wellbeing and reduction of burden. As such, the development and implementation of interventions aiming to increase positive emotion could be an effective way to improve health and psychological outcomes for dementia caregivers.

Methodology: The current study was a secondary analysis of data collected from 170 participants enrolled in the Life Enhancing Activities for Family Caregivers (LEAF) intervention, an online-facilitated, 6-week, evidence-based program designed to increase the frequency of dementia caregivers' experiences of positive emotion and subsequently improve their physical and psychological functioning (R01NR014435). The intervention consists of 8 positive emotion regulation skills (e.g., gratitude, mindful awareness) and was delivered to individual caregivers by a trained facilitator via video conference. The control participants reported their emotions daily during a 6-week waitlist period, then received the intervention. Using multiple linear regression, we aimed to identify which specific characteristics of dementia caregivers (e.g., age, gender, caregivers' relationship to the person with dementia, length of time caregiving, level of functional impairment in the person with dementia [PWD]) had moderating effects on LEAF caregiver outcomes from baseline to post-intervention.

Findings: Length of time as a caregiver significantly moderated the effect of positive emotion from baseline to post-intervention, such that longer-term caregivers in the LEAF intervention group experienced less of an increase in positive emotion compared to longer-term caregivers in the emotion-reporting waitlist control group ($b = 0.119$, $t = 2.1$, $p < .05$). Moreover, gender moderated the effect of the intervention on positive emotion, such that males in the LEAF intervention group and females in the emotion reporting waitlist control group experienced greater increases in positive emotion over time than males in the emotion reporting waitlist control group and females in the LEAF intervention group, respectively ($R^2 = 0.06$, $F[3, 139] = [2.75]$, $p = <.05$). No other significant moderating effects were found. Our results suggest that gender and length of time providing care play an important role in the extent to which a dementia caregiver benefits from a positive emotion skills intervention. This study will assist in better identifying the types of caregivers for whom positive skills interventions (like LEAF) work best, suggest ways that the intervention needs to be tailored to match different caregiver characteristics, and target outcomes most positively impacted according to caregivers' individual differences. These findings have key implications for which caregiver programs might be most beneficial for individual caregivers.

Lay Language: There are numerous negative health effects associated with dementia caregiving, including increased stress and depression. Interventions aiming to increase positive emotion could improve health and psychological outcomes for dementia caregivers. The Life Enhancing Activities for Family Caregivers (LEAF) intervention is an online-facilitated, 6-week, evidence-based intervention designed to increase positive emotion in caregivers. We examined data collected from the LEAF trial to identify which caregiver characteristics (e.g., age, gender, caregivers' relationship to the person with dementia, and length of time caregiving) affected LEAF outcomes over time. Our results suggest that gender and length of time providing care play an important role in the extent to which a caregiver benefits from a positive emotion skills intervention. This study will assist in identifying caregivers for whom positive skills interventions work best, suggest ways that the intervention should be tailored to match caregiver characteristics, and target outcomes most impacted according to caregivers' individual differences.

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PPA Tele-Savvy: Results of an Online Pilot Intervention with Caregivers of Persons with Primary Progressive Aphasia

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Primary Progressive Aphasia (PPA) results from a neurodegenerative disease such as frontotemporal lobar degeneration or Alzheimer's disease and is characterized by a progressive loss of specific language functions eventually progressing to widespread cognitive decline consistent with generalized dementia. Most interventions available to dementia caregivers do not match PPA caregiving families' needs for tailored psychosocial support. This pilot study is an adaptation of Tele-Savvy, an evidence-based online psychoeducation caregiver program. Goals: (1) address communication and other cognitive and behavioral challenges facing informal caregivers of those living with PPA throughout disease progression, and (2) help caregivers achieve competence in their role. Nine spousal caregivers were recruited to a pilot mixed methods study, which included seven 90-minute weekly videoconference sessions, mindfulness exercises and homework assignments. Participants provided feedback throughout the intervention. Pre-post effects were assessed on PPA knowledge, mood, caregiver burden, perceived stress, competence, quality of life and dyadic relationship. A focus group was held 4 weeks post-intervention. Pre-post results revealed a post-intervention trend toward decreased depression and reported relationship strain. Thematic analysis of recorded videos and transcribed weekly sessions, in addition to an evaluation focus group revealed four themes: a) Increasing knowledge of PPA; b) Learning communication and connection strategies; c) Initiating care planning; d) Integrating intellectual and emotional aspects of PPA caregiving. Participants were provided findings for their feedback. This study demonstrated the feasibility of offering an adaptation of the Tele-Savvy intervention for caregivers of persons with PPA. An informed second pilot study will be held in Spring 2023.

Managing Medications across the Alzheimer's disease spectrum from a Patient-Caregiver Perspective

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Background: Older adults with Alzheimer's disease and related dementias (ADRD) have higher rates of multimorbidity and polypharmacy. Medication adherence is critical to maintain health but is difficult with complex regimens. Little is known about how older adults with varying levels of cognitive impairment self-manage medications, and how responsibilities transition to caregivers. We examined medication-taking strategies across the ADRD cognitive spectrum.

Methods: We conducted separate qualitative interviews among patient-caregiver dyads that explored how patients managed multidrug regimens. Patients were eligible if they had 1) MCI, mild or moderate ADRD, 2) ≥3 chronic conditions, 3) ≥5 medicines and 4) a caregiver. A team of 3 coders applied a priori codes to transcripts and reviewed using the framework method.

Results: We interviewed 56 participants (Patients: mean age 77 years, 60% female, 46% white, 35% Black; Caregivers: mean age 65 years, 73% female, 60% spouse, 28% child). Patients had an average of 5 comorbidities and 10 medicines; cognitively, 36% had MCI, 39% mild ADRD and 25% moderate ADRD. Patients with MCI and mild ADRD managed their medications independently using multiple strategies (establishing a daily routine, using pillboxes, visual cues). While their caregivers were willing to assist, they were not proactively familiarizing themselves with prescribed medication regimens. When caregivers observed errors, they sought to take a greater role, but patients often rejected assistance and preferred autonomy. Among patients with moderate ADRD, caregivers assumed all medication responsibilities except when living separately. In those scenarios, caregivers set up organizers and made reminder calls, but did not observe medication intake.

Conclusions: In MCI and mild ADRD, patients self-manage their multidrug regimens until an error is observed and transition is mutually agreed upon. With moderate ADRD, caregivers assume the medication management role but many cannot directly monitor intake. This is concerning when patients take medicines multiple times a day and may forget doses. Clinicians should work to simplify regimens, reduce polypharmacy, and initiate conversations with caregivers and patients about medication assistance.

Lay Language: Many individuals with Alzheimer's disease and related dementias (ADRD) are managing other health conditions and multiple medications. Taking medications is a critical component of health management but can be difficult with multi-drug regimens. We talked with people living with ADRD and their care partners to better understand how individuals were managing their medications. We found that individuals with early stage ADRD prefer to maintain independence in managing their medications, while those with later stage ADRD delegate responsibilities to care partners. Care partners became more involved with medications after observing individuals were having greater difficulty with medicines.

Poster 78

The Alzheimer's Drug, Lecanemab: Patient and Family's Understanding, Perceptions and Experience with Drug Consultation

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Background: On January 6th, 2023, the FDA (Food & Drug Administration) granted accelerated approval for the Alzheimer Disease's treatment, Lecanemab (MacMillan, 2023). This followed two phase 3 clinical trials, published in the New England Journal of Medicine. The results indicated a 27% slowing of decline of Alzheimer's Disease compared to the placebo, based on the change in the Clinical Dementia Rating Scale Sum of Boxes score compared to baseline over an 18-month period (van Dyck et al., 2023). At the time this study is being initiated, the drug company, Eisai has filed for traditional FDA approval and the drug is not currently covered by Medicare. The treatment involves an intravenous infusion every other week. There are significant side effects associated with this medication, including Amyloid Related Imaging Abnormalities (ARIA) with edema and/or hemorrhage, which typically are not symptomatic but occur in about 1/6 persons on the medication, and require frequent monitoring with MRI scans. Certain scenarios increase the risk of these aforementioned side effects, including ApoE4 carrier status, and concurrent use of anticoagulant medications may also increase the risk of symptomatic brain hemorrhage.

Lecanemab drug consultations are currently taking place at the Northwestern Neurobehavior and Memory Clinic with potentially eligible patients and their families. Study aims are to: 1) measure patient and family perception and understanding of the drug treatment following consultation with a neurologist, and 2) gather data on the patient and family experience with the drug consultation as a method for making an informed decision.

While there have been studies to measure patient perceptions of treatments, none have been specific to Lecanemab. One study aimed to measure patient understanding and attitudes after starting a treatment for rheumatoid arthritis using focus groups (Arkell, P et al., 2013). Notably, this data was gathered after patients had already been started on the treatment, as opposed to those who were contemplating treatment.

While decisions loom over whether the Center for Medicare & Medicaid Services (CMS) will provide coverage for Lecanemab, it is important to hear directly from those who are impacted by this disease today.

Method: Participants will be recruited from the NM Neurobehavior and Memory Clinic. Those who are coming to the clinic for a Lecanemab drug consultation will be provided a handout with a link to a survey at the end of their consultation. The survey will ask questions to measure interest in starting this treatment, understanding of the risks and benefits, concerns and barriers surrounding the treatment, as well as overall experience with the drug consultation. Patients and family members may elect to complete the survey and do so at their convenience. Those who complete the survey will be included in the study, however, their identities will remain anonymous. Data for this study will be collected through a Qualtrics survey. Qualitative and quantitative analysis will follow.

Result: While this study is currently in the planning phase, we expect to measure interest in, concerns with, as well as understanding of the potential risks and benefits in starting Lecanemab by persons living with AD and their family members. We will provide a feedback loop to our clinicians to ensure the drug consultations are effective and speak to the needs and concerns of our patient population.

Conclusion: We expect that drug consultations with patients and families on the new Alzheimer treatment will help to identify concerns, understanding of the risks and benefits and overall impact of taking the newly approved drug Lecanemab.

Lay Language: Lecanemab is a treatment for Alzheimer's Disease that was recently granted accelerated approval from the FDA. Through clinical trials, this treatment was reported to show a 27% reduction in decline from Alzheimer's Disease while also being associated with some serious side effects. The primary aim of this study is to hear directly from patients and families how interested they are in this treatment, what their concerns are and measure their understanding of the risks and benefits.

Longitudinal Performance on Three Words Three Shapes in Primary Progressive Aphasia

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Objective: Primary progressive aphasia (PPA) is a dementia syndrome characterized by initial development of progressive language deficits in the absence of impairment in other cognitive domains. It has historically been difficult to assess the presence or nature of true memory deficits in this population due to interference from language disturbance on task performance. Three Words Three Shapes (3W3S) is a relatively easy memory test that evaluates both verbal and nonverbal learning and memory within the same modality and assesses different aspects of memory, including incidental encoding, effortful encoding, delayed recall, and recognition. Persons with PPA show a material-specific dissociation in performance on 3W3S; specifically, deficits in incidental encoding and recall are limited to verbal, not nonverbal material, in PPA. However, it is not known whether this pattern persists over time as the disease progresses. The current study determined longitudinal patterns of performance on 3W3S over time in persons with PPA.

Participants and Methods: Participants were 73 patients enrolled in an observational PPA research study at the Northwestern Mesulam Center for Cognitive Neurology and Alzheimer's Disease (M age = 66.75, SD = 6.77; M years of education = 16.11, SD = 2.38; 51% female). Participants were characterized as semantic (PPA-S, n = 15), logopenic (PPA-L, n = 27), or agrammatic subtype PPA (PPA-G, n = 31) based on Gorno-Tempini et al., 2011. 3W3S and other neuropsychological measures were administered longitudinally during annual study visits. All participants in the current study had 3W3S scores from at least two research visits collected between September 2012 and September 2022.

Results: One way ANOVAs analyzed group differences in 3W3S performance at baseline visit. There were no significant baseline group differences in copy, effortful encoding, or recognition of shapes or words; PPA-L had better incidental encoding than PPA-S for shapes ($p = .040$) and words ($p = .043$). There was a trend for worse delayed recall of words ($p = .072$), but not shapes ($p = .768$), in PPA-S compared to the other two groups. We then conducted a series of mixed measures ANOVAs (material X group) to compare between person baseline conditions. Across groups, performance on incidental encoding, effortful encoding, and recognition was worse for words than shapes ($ps < .01$). There was an interaction between material and group for delayed recall ($p < .001$) such that there was a significantly larger discrepancy between word and shape recall in PPA-S ($M_{diff} = -9.14$) compared to PPA-L ($M_{diff} = -3.07$) and PPA-G groups ($M_{diff} = -2.13$). Repeated measures ANOVAs analyzed changes in scores over 1 and 2 year periods collapsed across PPA subtypes. Incidental encoding ($ps < .01$), effortful encoding ($ps < .05$), and delayed recall ($ps < .01$) declined for both words and shapes over time. Copy and recognition of words ($ps < .05$), but not shapes declined over time.

Conclusion: The current results are consistent with prior findings of relative preservation of memory for nonverbal compared to verbal material in PPA as measured by 3W3S, especially in the semantic subtype. Learning and recall of words and shapes declined over time in all groups, whereas there was selective decline in copy and recognition of words compared to shapes. Since language worsens in PPA over time, it clearly contributes to decreased memory especially for words over the same period of time.

Lay Language: Primary progressive aphasia (PPA) is a dementia syndrome caused by neurodegenerative brain disease. In PPA, difficulties in language abilities (speaking, understanding, reading, writing) are the earliest signs of illness because the disease starts in the language parts of the brain. Memory, or the ability to recall recent events and other information, is spared early in early PPA; however, as the disease worsens, it is hard to test memory not only because memory declines as the brain disease spreads to memory centers but also because, as language worsens, it is hard to communicate what one remembers. 3W3S is a test that allows us to show the true state of memory ability in individuals with PPA and to measure that state over time.

Poster 80

Teleconference Group Singing Programs for Well-being of Healthy Older Adults and Persons with Neurocognitive Disorders During the COVID-19 Pandemic

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Background: During the COVID-19 pandemic, older adults experienced a marked decline in well-being, attributed largely to social isolation (Tilburg et al, 2021; Krendl et al, 2021). Previous literature shows that participatory musical interventions, like group singing, improve well-being and provide social and emotional support (Pentikäinen et al, 2021; Johnson et al, 2020). However, the pandemic highlighted the need for research on how such programs may be administered in an online setting. The enforced shutdown of in-person choirs in 2021 provided an opportunity for such assessment.

Method: Two types of group choir programs were conducted via teleconferencing. One program engaged participants in sing-along to familiar music only, offered weekly (52 in 2021). The other involved structured rehearsals (14 sessions) where participants learned choir music, culminating in a recorded "virtual concert". Program participants were 55 and older, divided into persons with neurocognitive disorders (NcD) and cognitively healthy individuals (CH). Self-report assessments of the programs were solicited. Four Likert scale questions covered anxiety, social connections, physical well-being, and "other" areas of well-being. Two free response questions requested elaboration on other well-being improvement.

Result: Results of Likert scales indicated at least moderate improvements in all measured aspects of well-being. Feedback was overwhelmingly positive (>95%). Free response analysis revealed 7 themes, the most prominent being emotional, social, and intellectual well-being. 87% of respondents mentioned positive effects on well-being. Intellectual well-being was mentioned with significant frequency by choir participants versus sing-along ($p=0.02$). While the NcD choir group was small, hampering statistical power, clear trends were present; 40% of participants in the NcD choir highlighted social well-being (25-29% in other groups), and 20% discussed improvements to physical well-being (0-6% in other groups).

Conclusion: Online group music programs administered during the COVID-19 pandemic showed improvements in overall measures of well-being, with different programs and participants highlighting specific aspects. These results establish feasibility for such programs as a method for providing meaningful improvement to well-being in older adults, providing stability and connection amidst a time of disruption and isolation.

Lay Language: This research looks at different types of online singing programs during the COVID-19 pandemic, and how programs like these may improve the well-being of older adults. One type of program was a virtual choir, where they learned and performed new songs, and the other was a sing-along to familiar songs. Groups were split into cognitively healthy and cognitively impaired older adults. People who participated in the choir reported via online survey that it helped to improve their well-being. The survey asked specifically about anxiety, social connections, and physical well-being, and also gave space to discuss "other" areas of well-being (emotional, social, and intellectual well-being were mentioned the most). This research is important because it shows that these programs can improve well-being, and can be administered effectively online, providing stability and connection amidst a time of disruption and isolation.

Poster 81

Let's talk: Preliminary results of a conversation-based hearing aid trial for adults with cognitive impairment

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A significant number of older adults experience subjective declines in memory and other cognitive abilities as they age. For some of these adults, vascular or neurodegenerative pathologies can lead to mild cognitive impairment or dementia. Many of these individuals also have age-related hearing loss and the combined demands of hearing and cognition have disproportionate impacts on communication. In this ongoing double-blind clinical trial, we measure benefit of hearing aids for adults with combined hearing loss and cognitive impairment. To determine the best hearing aid processing for this population, two different hearing aid programs are created by manipulating the level of signal modification: the speed with which the aid adjusts to changes in speech level (WDRC); and how the aid makes high-frequency information audible (frequency lowering). Study participants are provided with behind-the-ear hearing aids customized for their hearing loss and wear the hearing aids in their everyday environments for six weeks. The study emphasizes communication between the participant and their primary communication partner (spouse or caregiver) using outcome measures with strong relevance to everyday communication. The primary outcome is analysis of spoken communication between the participant and partner, including the efficiency with which the pair can exchange information and the accuracy of that information. The secondary outcome is a subjective communication rating by the listener's partner or caregiver. Results to date demonstrate that hearing aids improve accuracy and efficiency of dyadic communication. Our data also suggest that the amount of improvement depends on the listener's abilities and the type of hearing aid processing. This work emphasizes the utility of novel and relevant assessments for understanding the functional impact of hearing loss and hearing therapies in older adults with cognitive impairment. The project was supported by NIH supplement R01 DC012289-S1.

Lay Language: When adults with mild cognitive impairment or dementia also have age-related hearing loss, the combined demands of hearing and cognition may make communication very difficult. Hearing aids can be helpful but are often not used, due in part to questions about how much benefit they provide when memory or thinking skills are affected. In this clinical trial, we measure the benefit of hearing aids for adults with combined hearing loss and cognitive impairment. The study includes tests of how well participants and those they communicate with often (such as spouse or caregiver) can converse without hearing aids versus with hearing aids, and with different types of hearing aid sound processing. Our data suggests that hearing aid benefit depends on the listener's hearing and cognitive abilities and on the way the hearing aid processes sound.

Poster 82

Combined Music Enrichment and Verbal Stimulation for Individuals with Neurocognitive Disorders: Preliminary Feasibility Results

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Objective: In this feasibility study, we investigated whether individuals with neurocognitive disorders and their care partners would benefit from clinically-informed music interventions combined with patient-adjusted verbal stimulation.

Background: Isolation and lack of cognitive stimulation are known risks for accelerated decline in dementia. Research has demonstrated that music interventions for individuals with dementia enhanced feelings of well-being, reduced anxiety, increased agency, and fostered social interaction. Lifelong learning delays the progression of dementia and increases cognitive reserve. Here we investigated the feasibility and effectiveness of music interventions combined with verbal stimulation.

Methods: Forty to eighty individuals with mild to moderate dementia and their care partners attended each 45-minute intervention. Genres were selected based on patient demographics at Northwestern. Short, prepared verbal introductions preceded each musical selection designed for the cognitive capacities of dementia. Post-intervention surveys collected quantitative and qualitative data using a 1-5 Likert scale. Surveys tracked overall satisfaction, degrees of pleasure and relaxation, verbal introductions, and additional comments.

Results: Six interventions were completed. Based on post-intervention surveys, persons with dementia and care partners' overall ratings of the interventions averaged 4.3. Ratings included points for pleasure (4.4) and relaxation (4.3). Verbal introductions received a rating of 3.9. Shared written feedback from the interventions included comments such as, "uplifted," "happy," "lovely," "enjoyable," and "relaxed."

Discussion: Our results show that music enrichment programs for individuals with dementia and their care partners are feasible and that the majority of the participants positively experienced the interventions. Participants and care partners found the music pleasurable and the verbal sections challenging but intellectually enriching. We plan to collect more data on music enrichment programs including neural biomarkers such as Frequency-following Response (FFR) while adjusting each session according to the participants' feedback.

Lay Language: The social world of persons with neurocognitive disorder (dementia) and their care partners contracts as their condition progresses. However, the need for social and intellectual stimulation and interaction persists. Creating safe environments and social interventions which respect the cognitive capacities of the person with neurocognitive disorder are a means by which to support the social, emotional, and intellectual lives of the person with neurocognitive disorder and their care partners. In this study, we show the feasibility of clinically-informed social-musical programs for persons with neurocognitive disorders and their care partners.

Developing a Method for Memory Improvement Overnight in the Home

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Purpose: Sleep is a critical time for memory consolidation, a gradual process that can prevent memories from being forgotten. Memories are reactivated during sleep such that memory storage can potentially be strengthened. Targeted Memory Reactivation (TMR) is an experimental technique whereby sounds played softly during sleep induce replay of specific memories, thus enhancing subsequent remembering. Our research aims to adapt the TMR method for use in improving the memories that are becoming difficult for an individual to remember. This method could be particularly helpful for individuals with mild memory impairments, including people in early stages of Alzheimer's Disease. In the present study, we are testing whether memories in young healthy adults can be improved with an easy-to-use version of this method applied in the home.

Methodology: On Day 1, participants learn biographical information about 20 simulated family members (e.g., "Your oldest son is Henry; Henry is an engineer"). They are then tested about the relationships and facts (e.g., "Your oldest son is ___? Henry's occupation is ___?"). On Day 2, participants learn some interfering biographical information about 10 simulated neighbors, followed by memory testing. While participants sleep over the next three nights, they receive auditory stimulation using wearable sleep technology we developed for this purpose. Participants either receive sounds corresponding to learned family relationships or control sounds. On Day 5, memory is tested again to determine whether the TMR method produced a memory benefit.

Findings: In our on-going study, we predict that memory for simulated family members will improve in an experimental group using TMR compared to a control group. Additionally, we predict that memory for relationships will improve more than memory for facts. We also have results from a recently published study focused on spatial memory. We will present data from multiple studies showing the feasibility of this methodology for memory improvement when applied in an individual's own home.

Lay Language: The goal of this new line of research is to improve quality-of-life in individuals in the early stages of a neurological disorder of memory. We are developing an innovative and easy-to-use methodology for this purpose. Based on our prior research, we are hypothesizing that this method, when used overnight repeatedly, can boost recall abilities for a small set of important memories. This memory facilitation will be achieved using scalable technology by softly presenting sounds during sleep in a way that avoids any sleep disruption. The sounds we use are designed to focus on specific information that is difficult to consistently recollect in each person's daily life.

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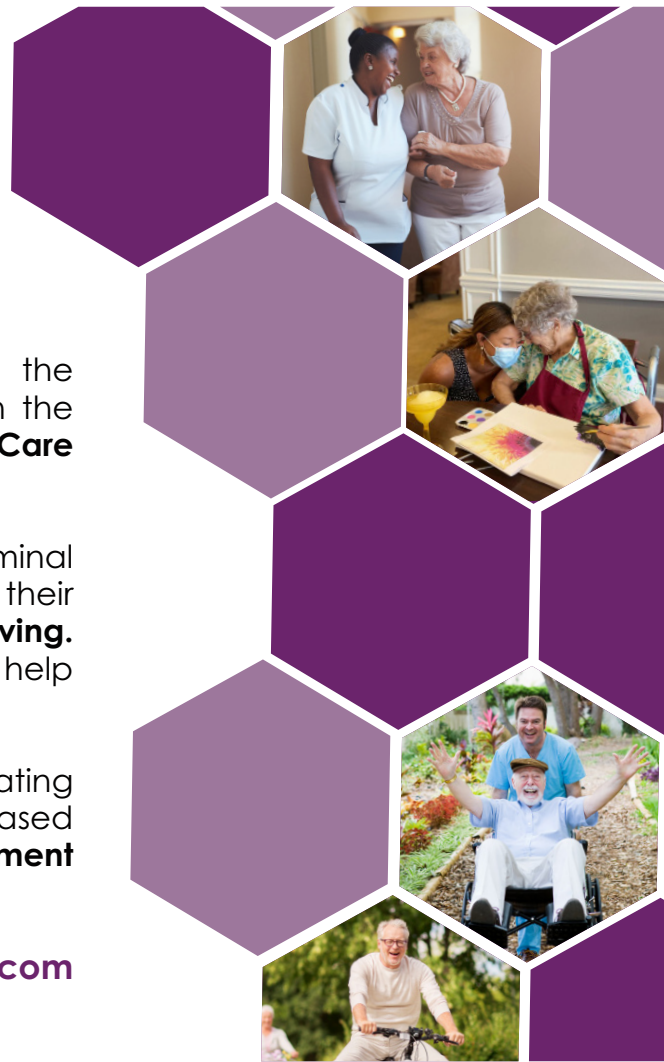


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