

**MCKNIGHT BRAIN RESEARCH FOUNDATION (MBRF)
Meeting of the Research Committee of the Board of Trustees**

**Monday, October 5, 2020
4:00 pm – 5:00 pm ET**

Conference Call Number 877-934-2901 Passcode 8630398 (No ZOOM)

Members: Dr. Madhav Thambisetty, Committee Chair; Dr. Robert Krikorian; Dr. Richard Isaacson; Dr. Sue Pekarske; and Dr. Mike Dockery, MBRF Chair

Also Attending: Ms. Amy Porter, Ms. Melanie Cianciotto

AGENDA

4:00 pm EDT	1.	Call to Order/Roll Call	Dr. Thambisetty
ACTION	2.	Current Grants/Programs	Dr. Thambisetty
	a.	MBRF Pilot Grant Submissions	
	b.	McKnight Clinical Translational Research Scholarship Program Report (American Brain Foundation) • 2021 Scholarship Applications and Review • Consideration of Program Renewal	
	c.	Foundation for the NIH (FNIH) Report on the Research Partnership	
	3.	MBRF Mid-Career Research Award in Cognitive Aging and Memory Loss	Dr. Thambisetty
5:00 pm ET	4.	Adjourn	Dr. Thambisetty
ACTION			All

**MINUTES
MCKNIGHT BRAIN RESEARCH FOUNDATION (MBRF)
RESEARCH COMMITTEE
CONFERENCE CALL
June 15, 2020**

The Research Committee of the MBRF was called to order at 5:05 pm EST on June 15, 2020, by Dr. Madhav Thambisetty.

The following members were present:

Dr. Madhav Thambisetty, Chair of the Research Committee, Trustee
Dr. Richard Isaacson, Trustee
Dr. Robert Krikorian, Advisory Member
Dr. Sue Pekarske, Trustee
Dr. Mike Dockery, Chairman, MBRF

Others attending:

Ms. Melanie Cianciotto, Corporate Trustee
Ms. Amy Porter, Executive Director

1. Call to Order/Roll Call

Dr. Thambisetty welcomed the members of the committee and Ms. Porter called roll.

2. Minutes of the March 12, 2020, Meeting

The minutes of the March 12, 2020, Research Committee were reviewed and approved as presented (Attachment 1).

Action Item 1: The minutes of the March 12, 2020, Research Committee (Attachment 1) were approved as presented.

3. Updates on Current Grants/Programs

a. Precision Aging Network

Dr. Thambisetty provided the committee with an update on the changes to the Precision Aging Network Demonstration Project (Attachment 2). The committee would like to know the anticipated timeline by which the group hopes to have completed the virtual cohort for recruitment.

Action Item 2: Ms. Porter and Ms. Cianciotto will reach out to Susan Fox-Rosellini to inquire about the timeline.

b. LOI MBRF Pilot Grants

Ms. Porter informed the committee that only two LOIs had been received prior to the deadline being extended. Ms. Porter reached out to Dr. Bonnie Levin and Dr. Ron Lazar for an update prior to this call but has not yet received a response.

c. 2020 SfN Poster Session

The committee discussed the MBRF 2020 SfN Poster Session. As of now, the SfN is still planning to host their conference in October. If the trustees decide to cancel the event by July 3, 2020, there is a cancellation charge of \$6,100. This charge increases to \$7,000 if the event is cancelled between July 4, 2020, and September 1, 2020. The committee decided to wait until September to make a decision about moving forward with or cancelling the poster session.

Action Item 3: The committee decided to wait until September to make a decision about moving forward or cancelling the poster session.

d. 2021 McKnight Scholarship RFA

The committee received a copy of the McKnight Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss RFA (Attachment 3). Ms. Porter has asked the ABF to enlarge the MBRF logo to make the tagline legible. In item 2 under Eligibility, the word training needs to be added after residency. Ms. Porter will share the changes with her contact at the American Brain Foundation.

Action Item 4: Ms. Porter will share the changes that need to be made to the RFA with her contact at the American Brain Foundation.

e. MBRF Website Primary Care Physicians (PCPs)

The committee received a draft of the Content Outline for Primary Care Physicians Area of the McKnight Brain Website dated June 4, 2020 (Attachment 4).

f. Diagnostic Tests to be included on the MBRF website

The committee discussed the diagnostic tests that could be included on the MBRF website. The MOCA and computer based tests were discussed. Dr. Robert Krikorian suggested including a brief 5-minute test for memory. It was mentioned that including links to tests instead of the actual tests will help to avoid copyright issues.

4. Annual Report Template

The committee received the current Annual Report Templates (Attachment 5) for information. During the review of the Annual Reports in the February meeting, some trustees expressed frustrations with the reports that had been received and it was thought changes could be made to the template. The committee was asked to review the templates and provide recommendations for changes, if any. Ms. Porter mentioned that the Education Committee and Finance Committee will also be reviewing the template and suggested changes. It was suggested that the following paragraph be added to the top of the Annual Report Template.

"Please provide an easy to read and easy to evaluate summary of your MBI's activities, focusing on those that are new since last year's report. Please be as succinct as possible and include only accomplishments and activities that are relevant to age-related cognitive decline and memory loss."

5. Reserve & Resilience Workshop Pilot Grants

The committee received the request for support of year two of the Reserve & Resilience Workshop (Attachment 6). The in-person Reserve & Resilience workshop scheduled for September 14-15, 2020, has been canceled. The request is for \$30,000 to support pilot proposals as a major focus of the work of the Reserve & Resilience Workshop. The committee recommends approval of the \$30,000 request. Dr. Mike Dockery suggested that a vote could be taken before the July 22 Trustees Meeting to approve the request. Ms. Porter suggested she will poll the trustees not on the Research Committee call (Dr. Ryerson, Dr. Lee Dockery and Dr. Robert Wah) for their votes.

Action Item 5: The committee recommended approval of the \$30,000 request to support pilot proposals as a major focus of the work of the Reserve & Resilience Workshop. Ms. Porter will ask Drs. Ryerson, Wah and Lee Dockery for their votes and notify Dr. Stern before June 30 if approval is secured.

6. Summary of New Grant Program

Dr. Thambisetty provided the committee with a summary of the new grant program focused on mid-career scientists who are carrying out clinical translational research in cognitive aging. The committee discussed potential funding partners. Dr. Isaacson will put together a list of potential partners and Dr. Thambisetty will develop the draft summary to share with the committee and then the full board on July 22.

Action Item 6: Dr. Isaacson will put together a list of potential partners and Dr. Thambisetty will develop the draft summary to share with the committee and then the full board July 22.

7. Adjourn

Dr. Thambisetty asked if there was any further discussion. Hearing none, he called for adjournment of the meeting at 6:10 p.m.

Summary of Action Items:

Respectfully Submitted,

Melanie A. Cianciotto
Corporate Trustee



MCKNIGHT CLINICAL TRANSLATIONAL RESEARCH SCHOLARSHIPS IN COGNITIVE AGING AND AGE-RELATED MEMORY LOSS

FUNDED BY THE MCKNIGHT BRAIN RESEARCH FOUNDATION

REQUEST FOR RENEWAL | OCTOBER 1ST, 2020

AMERICAN
BRAIN
FOUNDATION

CONTENTS

Executive Summary	4
Program History	5
Program Summary	7
Program Improvements	8
Current and Previous Recipients	9
Bryan Baxter, MD, PhD (2020)	12
Sarah Getz, PhD (2020)	13
Christian Camargo, MD (2019)	15
Sanaz Sedaghat, PhD (2019)	16
Kimberly Albert, PhD (2018)	18
Brice McConnell, MD, PhD (2018)	19
Request for Renewal	20
Budget	21
American Brain Foundation Board of Directors	22
American Brain Foundation Research Advisory Committee	23



“Societies world-wide are aging, and age is the biggest risk factor for neurodegenerative diseases. Yet it is not certain how age interacts with neurodegeneration. Memory loss, sleep disturbances and compromised motor function are but a few of the neurological changes with aging. Research on cognitive aging and neurodegenerative diseases is of paramount importance to the American Brain Foundation and forms the cornerstone of the Next Generation Research Grants designed to train the next generation of investigators.”

**RONALD C. PETERSON, PHD, MD, FAAN
MAYO CLINIC, DEPARTMENT OF NEUROLOGY
BOARD OF DIRECTORS, AMERICAN BRAIN FOUNDATION**

EXECUTIVE SUMMARY

Since 2018, the McKnight Brain Research Foundation has funded annually two McKnight Clinical Translational Research Scholarships (CTRS) in Cognitive Aging and Age-Related Memory Loss through the American Brain Foundation, and the American Academy of Neurology. These scholarships support early career clinician scientists with the purpose of developing the next generation of researchers working to better understand and alleviate the effects of age-related cognitive decline and memory loss.

Thanks to the generosity of the McKnight Foundation, ten early career researchers will receive scholarships between 2018-2022. To date, six clinician scientists have received McKnight scholarships, and two additional scholarships will be awarded each year in 2021 and 2022. The current McKnight scholars are engaged in interdisciplinary research projects that range from exploring the role of sleep in memory formation, to the impact of kidney disease on cognitive impairment and memory loss, to the correlation between hearing loss and scam susceptibility in older adults. Their achievements and progress to date are described in the subsequent pages.

The American Brain Foundation is deeply grateful for the McKnight Brain Research Foundation's support, and we seek the McKnight Foundation's renewed commitment to this productive collaboration with a 5-year, \$1.65M grant to support 10 additional McKnight scholars.

Thank you for your support!

PROGRAM HISTORY AND NEED

The American Brain Foundation's Next Generation Research Grants, of which the McKnight scholarships are a part, have provided crucial support to early career researchers since 1993. The program fosters a pipeline of early-career physicians and post-docs who want to devote some portion of their careers to research, helping position them to leverage funding from NIH and other entities, encouraging their passion for research and laying the groundwork for their future success.

Grants like the McKnight scholarships give clinician scientists the time and funding that they need to start their independent research career. For many, these grants are their first large-scale funding for an independent research project and provide an imprimatur on their research aims, as well as an opportunity to demonstrate effective management of a research grant, which they can then leverage for future funding. Since the start of the American Brain Foundation's Next Generation Research Grants program, over 85% of recipients have gone on to receive funding from the NIH and other sources.

Since 2018, the McKnight Brain Research Foundation has funded annually two McKnight Clinical Translational Research Scholarships (CTRS) in Cognitive Aging and Age-Related Memory Loss through the American Brain Foundation. Six researchers have already received awards, and four more scholarships will be awarded in 2021 and 2022.



“This program gave me the time and funding I needed to start my research career. I was able to demonstrate that my research is valid, and that I am able to manage a large research grant.”

2017 NEXT GENERATION RESEARCH GRANT RECIPIENT

PROGRAM SUMMARY

The McKnight scholars are truly the among the best and brightest early career physician scientists, and their projects have been vetted and selected by the American Academy of Neurology's Science Committee and three Donor Trustees of the McKnight Brain Research Foundation. Each McKnight scholarship consists of a commitment of \$65,000 per year for two years, plus \$10,000 per year to support formal education in clinical research methodology.

To date, six clinician scientists have received McKnight scholarships, and two new researchers will be awarded each year in 2021 and 2022. The current McKnight scholars are engaged in interdisciplinary research projects that range from studies exploring the role of sleep in memory formation, to the impact of kidney disease on cognitive impairment and memory loss, to the correlation between hearing loss and scam susceptibility in older adults. Their achievements and progress to date are described in the subsequent pages.

PROGRAM IMPROVEMENTS

Applications for the McKnight scholarships have increased 71% from 2018 to 2020, however, there is still room to grow. In 2018, there were seven applications for the McKnight scholarships, four in 2019, and twelve in 2020. As of the day before the 2021 application deadline, eight applications have been received for the 2021 McKnight scholarships. Applications for all of the 2021 Next Generation Research Grants will likely be lower than average due to COVID-19, but are anticipated to increase in 2022 and beyond as researchers are able to return to in-person clinical settings.

Targeted outreach and advertising of the McKnight scholarships will continue to be crucial. The American Brain Foundation engages its Board and Research Advisory Committee in outreach, and works closely with the American Academy of Neurology to coordinate marketing efforts to its 36,000 members. For this year's application cycle, the ABF also sent personalized letters advertising the Next Generation Research Grants to over 140 neurology department chairs across the US as well as all of our neurologist donors, and created a promotional video that was shared across social media. For the past two years, the McKnight Foundation has advertised the McKnight scholarships in *Neurology*, and has shared the scholarship opportunities across its networks.

The ABF is also embarking on a nationwide public awareness campaign that we anticipate will bring additional momentum to the Next Generation Research Grants program by raising the program's profile among the public. Over the next three years, the ABF seeks to grow public awareness of brain disease and the value of neurology by 40%, and triple its grantmaking for brain disease research to \$25M by 2024.

CTRS RECIPIENTS

AT A GLANCE

The current McKnight scholars represent the best and brightest early career clinician scientists investigating cognitive aging and age-related memory loss. Hailing from five institutions across the country, their interdisciplinary research projects are advancing our understanding of age-related cognitive decline and memory loss.



\$900,000

Awarded to six recipients in three years.



23

Applications for six McKnight scholarships.



19

Papers published by McKnight scholars.

2020 CTRS RECIPIENTS

BRYAN BAXTER, PHD



Massachusetts General Hospital, Postdoctoral Research Fellow

- **Project Title: “Characterizing and enhancing sleep oscillations to improve memory: developing a scalable treatment for healthy aging and age-related memory loss”**
- **Interim report due June 30, 2021.**
- **Grant period ends June 30, 2022.**

Humans spend a third of their lives sleeping, yet the functions of sleep are still not clear. Over the past 20 years, research has shown that to understand memory, one must also understand sleep. It has also revealed the breadth of sleep-dependent memory consolidation, and the importance of this consolidation to cognition at all stages of life.

Dr. Baxter’s research will study sleep-dependent memory consolidation to understand where this process occurs in the brain, identify a biomarker for this process that can be detected through non-invasive EEG, and develop an auditory stimulation that can improve memory consolidation during sleep.

The selection committee writes that findings from Dr. Baxter’s research “could ultimately lead to better understanding of the biological basis of sleep-memory interactions, and as a result, the study has realistic implications for possible clinical interventions.”

SARAH GETZ, PHD



University of Miami Department of Neurology, Instructor of Neuropsychology

- **Project Title: “Neurocognitive correlates of scam susceptibility in age-related hearing loss”**
- **Interim report due June 30, 2021.**
- **Grant period ends June 30, 2022.**

Scammers target people of all ages, but individuals 50 years and older are the most vulnerable to scams. Individuals with age-related diminished sensory abilities and cognitive decline are especially vulnerable targets. Hearing loss has been associated with cognitive decline and dementia and has negative impacts on depression, socialization, and isolation. Older adults with impaired hearing may be at a particularly high risk for scamming due to difficulty with fully processing complex demands under some circumstances.

Dr. Getz’s project will study the association between hearing loss and deception, and identify what leads older adults to be more susceptible to scams in order to develop an intervention to reduce the risk of scamming among those most vulnerable.

The selection committee noted that “characterizing neuro-cognitive correlates associated with and without hearing loss will be an important step forward in the field. Dr. Getz’s novel and clinically relevant project makes her a superb candidate for this award.”

2019 CTRS RECIPIENTS

CHRISTIAN CAMARGO, MD



University of Miami Dept. of Neurology, Assistant Professor of Clinical Neurology

- **Project Title: “Reducing the Effects of Aging on Cognition with Therapeutic Intervention of an Oral Nutrient: The REACTION Study”**
- **Interim report due January 29, 2021; final report due September 1, 2022.**
- **No-cost extension approved May 19, 2020 due to COVID-19; grant period ends June 30, 2022.**

Dr. Camargo’s research focuses on improving the memory and cognition in individuals with age-related cognitive decline (ARCD). Participants in his study receive a specifically-formulated nutrient drink. This drink contains specific nutrients that form the backbone neurons and their connections. The hypothesis is that by restoring and promoting the connections between brain cells, memory and cognition may improve.

Dr. Camargo’s project has encountered some unexpected challenges from COVID-19 and access to the nutrient drink mixture due to restructuring at the industry partner’s R&D division. To address these challenges, Dr. Camargo has been working closely with his research mentor and department chair to implement changes to the study design to increase the likelihood of successful execution while COVID-19 remains a concern. The recruitment goal will be reduced from 120 participants to 60 (30 experimental arm, 30 placebo), and some neuropsychological tests will be substituted for equivalent tests validated in a virtual context.

SANAZ SEDAGHAT, PHD



Northwestern University, Assistant Professor of Clinical Neurology

- **Project Title: “Cognitive aging in kidney impairment: role of uremic toxins”**
- **Final report due September 1, 2021.**
- **Grant period ends June 30, 2021.**

Dr. Sedaghat’s research aims to identify toxic molecules that target the brain and can cause an excessive risk of cognitive impairment and memory loss. In her first year of funding from the McKnight Foundation, Dr. Sedaghat has successfully tested and validated her statistical model. Her pilot data show that higher 4-hydroxyphenylacetate metabolite is associated with worse cognitive performance. This same uremic metabolite has been previously associated with more severe stages of kidney disease. Her findings extend this prior work to show that even within the normal range of kidney function, lower levels of glomerular filtration is also associated with the presence of higher uremic metabolites and related to lower cognitive performance.

Dr. Sedaghat has also developed a number of successful collaborations through Northwestern’s Aging Brain Circulation (ABC) lab, the NIH, and the Chronic Kidney Disease Genetics (CKDGen) Consortium, and has co-authored nine publications since the start of her McKnight scholarship. Her mentor notes that “this is an impressive level of scholarly productivity. I am delighted with Dr. Sedaghat’s progress on her proposal and her development towards research independence.”

2018 CTRS RECIPIENTS

KIMBERLY ALBERT, PHD



Vanderbilt University, Research Instructor, Psychiatry and Behavioral Sciences

- **Project Title: “Changes in attention network dynamics related to performance in aging”**
- **Final report due September 1, 2021.**
- **No-cost extension approved June 25, 2020 due to COVID-19; grant period ends June 30, 2021.**

The goal of Dr. Albert’s research is to examine whether differences in attentional control networks are related to subjective and objective real-life cognitive performance. This study will provide important information about whether altered attention control network function is related to subjective and objective memory performance.

Dr. Albert’s mentor writes that “Dr. Albert's progress has been substantial....She has successfully initiated a complex and multifaceted project that includes phenotypic assessment, novel cognitive testing methodologies, and neuroimaging. She has successfully garnered approval from multiple regulatory bodies within Vanderbilt for study initiation and has made substantial progress on initiating study enrollment and validating data collection. In addition, Dr. Albert has continued writing and publishing research results....I believe that she will be very competitive for a career development award.”

BRICE MCCONNELL, MD, PHD



University of Colorado Anschutz Medical Center, Assistant Professor of Neurology

- **Project Title: “Development of Transcranial Electrical Stimulation for Modulation of Sleep and Cognitive Performance in Aging Adults**
- **Final report due September 1, 2021.**
- **No-cost extension approved April 14, 2020 due to COVID-19; grant period ends June 30, 2021.**

Dr. McConnell’s research explores transcranial electrical stimulation as a therapy to enhance slow wave sleep activity, and to modulate sleep quality and cognitive performance. Despite promising preliminary results with transcranial electrical stimulation, there are significant gaps in our understanding of how to reliably deliver this type of treatment during sleep to produce clinically meaningful results. Dr. McConnell is working to develop and refine this technology as a treatment for aging-associated sleep and cognitive impairment. He is exploring the potential for this technology to act as a disease modifying therapy to prevent the progression of age-associated cognitive decline and the development of Alzheimer’s disease.

Dr. McConnell has leveraged the support of his McKnight scholarship to secure additional grant funding for his ongoing research that focuses on identifying and enhancing the restorative and neuroprotective aspects of sleep that are lost with aging.

REQUEST FOR RENEWAL

The American Brain Foundation seeks the McKnight Brain Research Foundation's renewed investment in the McKnight Clinical Translational Research Scholarships in Cognitive Aging and Age-Related Memory Loss. The current partnership between the McKnight Brain Research Foundation and the American Brain Foundation extends through 2022. We now seek your renewed commitment to this productive collaboration with a 5-year, \$1.65M grant to support 10 additional McKnight scholars. Two scholarships per year will be awarded from 2023 to 2028.

With a renewed investment from the McKnight Foundation, we will continue the momentum around the important research on cognitive aging and age-related memory loss that has already been generated through the first three years of the McKnight scholarships. Eighty-eight percent of Next Generation Research Grant recipients have gone on to receive funding from the NIH and other national entities. With your support, we will continue to cultivate a pipeline of early career clinician scientists dedicated to finding improved diagnoses, new treatments, and ultimately cures, for brain diseases and disorders.

BUDGET

- Ten two-year McKnight Clinical Translational Research Scholarships (CTRS): **\$1.5M**
 - Cost per CTRS: **\$150,000**
 - Salary: \$65,000/year for two years
 - Education expenses stipend: \$10,000/year for two years
- 10% ABF Program Management Cost: **\$150,000**
- **Total: \$1.65M**

AMERICAN BRAIN FOUNDATION BOARD OF DIRECTORS

CHAIR:

David W. Dodick, MD, FAAN
Mayo Clinic Arizona

VICE CHAIR:

Susan Schneider Williams, BFA
Artist and Advocate

TREASURER:

James Essey
TemPositions Group

SECRETARY:

Shafali Jeste, MD, FAAN
UCLA Semel Institute

IMMEDIATE PAST CHAIR:

Kevin Goodno
Fredrikson & Byron, P.A.

HONORARY CHAIRMAN:

Walter F. Mondale

EX OFFICIO VOTING DIRECTOR:

James C. Stevens, MD, FAAN
Allied Physicians, Inc.

EX OFFICIO, NON-VOTING DIRECTORS:

Jane Ransom
Executive Director
American Brain Foundation

Mary E. Post, MBA, CAE
Chief Executive Officer
American Academy of Neurology

HONORARY DIRECTORS:

Rich Clifford
Richard Essey
Leeza Gibbons
Billy McLaughlin

DIRECTORS:

David Eagleman, PhD
Neuroscientist & Entrepreneur

James Erwin
Chicago Title Company

Jacqueline French, MD
New York University and Epilepsy
Foundation

Dan Gasby
Author, Alzheimer's & Brain Health
Advocate

Robert C. Griggs, MD, FAAN
University of Rochester Dept. of Neurology

James C. Grotta, MD, FAAN
Memorial Hermann –Texas Medical Center

Frances Jensen, MD, FACP, FAAN
University of Pennsylvania, Dept. of
Neurology

Sharon L. Klein
Wilmington Trust, N.A.

Ben Lenail
Rare Disease Activist and Biotech Investor

Cindy McCain
Businesswoman and Philanthropist

Suzanne Miller
Empire State Properties

Ronald C. Petersen, PhD, MD, FAAN
Mayo Clinic, Department of Neurology

Sean Sansiveri
NFL Players Association

Martin Shenkman, CPA, MBA, PFS, AEP, JD
Shenkman Law

Joseph I. Sirven, MD, FAAN
Mayo Clinic

AMERICAN BRAIN FOUNDATION RESEARCH ADVISORY COMMITTEE

CHAIR:

Robert C. Griggs, MD, FAAN
*University of Rochester Dept. of
Neurology*

VICE CHAIR:

Raymond Roos, MD, FAAN
University of Chicago

MEMBERS:

Carsten Bonnemann, MD
Porter Neuroscience Research Center

Jose E. Cavazos, MD, PhD, FAAN
University of Texas Health – San Antonio

Merit Cudkowicz, MD, MSC
Massachusetts General Hospital

James C. Grotta, MD, FAAN
Memorial Hermann – Texas Medical

Mark F. Mehler, MD, FAAN
Albert Einstein College of Medicine

John Morris, MD, FAAN
Washington University

Ralph Sacco, MD, MS, FAAN, FAHA
University of Miami

Eugene Scharf, MD
Mayo Clinic

Ira Shoulson, MD, FAAN
Georgetown University

Phyllis C. Zee, MD, PhD
Northwestern University Medical School



Research Partnership in Cognitive Aging

A report to the McKnight Brain Research Foundation

October 2, 2020

Foundation for the National Institutes of Health

Plasticity and Mechanisms of Cognitive Remediation in Older Adults is the centerpiece of a Research Partnership in Cognitive Aging between the McKnight Brain Research Foundation (MBRF) and the National Institute on Aging (NIA), coordinated by the Foundation for the National Institutes of Health (FNIH). The partnership—now more than a decade long—currently supports an NIA grant for a multicenter clinical research trial on remediating age-related cognitive decline through mindfulness-based stress reduction and exercise, the MEDEX trial.

The FNIH is pleased to present this 2020 report to the MBRF. It provides updates from the NIA on the MEDEX trial, as well as information on three other trials investigating plasticity and mechanisms of cognitive remediation in older adults that the NIA supports with grant awards stimulated by the MBRF/NIA partnership. An updated report of outcomes from the Cognitive Aging Summit III, held in 2017, is also provided.

“Plasticity and Mechanisms of Cognitive Remediation in Older Adults”

RFA-AG-14-016 (R01)

Remediating Age-related Cognitive Decline: Mindfulness-based Stress Reduction and Exercise (MEDEX)

The MEDEX clinical trial (R01 AG049369), awarded to Eric Lenze, M.D. at Washington University, has completed data collection. Due to the COVID-19 pandemic, a small proportion of the participants were unable to complete the final follow-up. Publication of results is expected in 2021.

The abstract for the grant:

DESCRIPTION (provided by applicant): The vast majority of older adults will suffer declines in cognitive functions such as memory and cognitive control (or executive function), interfering with their ability to participate and engage in meaningful activities. Importantly, the recent observation that the brain retains plasticity late into life suggests that timely and personalized interventions might remediate age-related cognitive decline. Two promising interventions are Mindfulness-Based Stress Reduction and Exercise, each of which appears to act in multi-modal ways to make plastic changes in CNS function to improve memory and cognitive control in older adults. Our research team has conducted several studies of these interventions, supporting their benefits and pathways to improved cognitive functioning. We propose a 2x2 factorial design RCT to definitively test MBSR and exercise for remediation of age-related cognitive decline. We will randomize 580 healthy community-living adults aged 65+ to one of four conditions: MBSR alone, exercise alone, MBSR + exercise, or health education (a control condition).

Participants will receive protocolized interventions for a six-month acute period, followed by a 12-month maintenance period. We will examine (1) cognitive improvements using a well-validated and sensitive neuropsychological battery focusing on memory and cognitive control; (2) mechanistic changes such as reduced cortisol and improved insulin sensitivity (3) neuroimaging markers of plasticity: structural and functional connectivity changes indicating plastic CNS changes underlying the cognitive improvements (4) individual variability that predicts response to the interventions. Our main goal is to carry out a high-quality clinical trial, such that data and biosamples will become a resource for the scientific community. Then, we can not only improve the lives of older adults in the

near-term by matching individuals to readily available interventions that most benefit them, we can also understand the mechanisms of neuroplastic changes with interventions to rescue cognitive decline with aging, leading to a more active and vital senior community.

PUBLIC HEALTH RELEVANCE: The world is graying, and the vast majority of older adults will have declines in cognitive function, interfering with function, quality of life, and engagement in valued activities. We will test two promising interventions - Mindfulness Based Stress Reduction (MBSR) and Exercise - for their ability to remediate age-related cognitive decline. MBSR and exercise are both inexpensive, well-tolerated, safe, and highly scalable interventions; therefore i our project can demonstrate how effective they are, for whom, and by what mechanisms, in the near term older adults could receive lifestyle strategies that would benefit their brain and cognitive functioning, staving off disability and dependence on others and maintaining engagement in life's most valued activities.

Other grants supported by the NIA, originally in response to RFA-AG-14-016

Augmenting Cognitive Training in Older Adults – The ACT Grant (R01 AG054077) Adam Woods, Ronald Cohen, Michael Marsiske (MPIs) – University of Florida

The trial is currently active. Due to the COVID-19 pandemic, there was a hiatus in data collection. Data collection has since resumed. Trial completion is now anticipated in April/May 2022 with publication of findings in July/August 2022.

The abstract for the grant:

DESCRIPTION (provided by applicant): This randomized clinical trial will test whether transcranial direct current stimulation (tDCS) of frontal cortices enhances neurocognitive and functional outcomes achieved from cognitive training in older adults experiencing age-related cognitive decline. Change in well-validated measures of neurocognitive function and everyday abilities will serve as outcome measures. Functional and structural neuroimaging biomarkers of neural plasticity and learning (fMRI, GABA MRS, etc.) will measure intervention-associated alterations in specific brain regions impacted by cognitive aging. tDCS is a noninvasive brain stimulation method that facilitates neural plasticity and learning. Accordingly, when used as an adjunctive intervention, tDCS may augment cognitive training effects. This study will leverage existing multisite clinical trial infrastructure at McKnight Brain Institutes located in two of the states with the largest representation of older adults in the United States: University of Florida, University of Miami, and University of Arizona. Adults over the age of 65 represent the fastest growing group in the US population. As such, age-related cognitive decline represents a major concern for public health. Recent research suggests that cognitive training in older adults can improve cognitive performance, with effects lasting up to 10 years. However, effects are typically limited to the tasks trained, with little transfer to other cognitive abilities or everyday skills. Effects may also be reduced in people with Alzheimer's disease risk factors. A two-phase multisite randomized clinical trial will examine the individual and combined impact of pairing cognitive training with transcranial direct current stimulation (tDCS) in older adults experiencing age-related cognitive decline (n = 360; 120 per site). Participants will consist of elderly men and women 65-90 years of age with evidence of age-related cognitive decline, but not MCI or Alzheimer's disease (MoCA $\geq$ 25). We

will compare changes in cognitive and brain function resulting from CT and CT combined with tDCS using a comprehensive neurocognitive, clinical, and multimodal neuroimaging assessment of brain structure, function, and metabolic state.

Functional magnetic resonance imaging (fMRI) will be used to assess brain response during working memory, attention, and memory encoding; the active cognitive abilities trained by CT. Proton magnetic resonance spectroscopy (MRS) will assess markers of neural plasticity, GABA concentrations, and cerebral metabolism. We hypothesize that: 1) tDCS will enhance neurocognitive function, brain function, and functional outcomes from CT; 2) Effects of tDCS on CT will be maintained up to 12 months following training, and 3) Neuroimaging biomarkers of cerebral metabolism, neural plasticity (GABA concentrations) and functional brain response (fMRI) during resting vs. active cognitive tasks will predict individual response to tDCS, with certain Alzheimer's risk factors (e.g., APOE4 genotype, family history of Alzheimer's disease) predicting poorer cognitive and functional outcome. To date, no studies have comprehensively examined combined CT and tDCS intervention in the elderly. This study will provide definitive insight into the value of combating cognitive decline in a rapidly aging US population using tDCS with cognitive training.

PUBLIC HEALTH RELEVANCE: This randomized clinical trial examines the effect of augmenting cognitive training with transcranial direct current stimulation to maximize cognitive and functional outcomes older adults experiencing age-related cognitive decline. Change in well-validated measures of everyday abilities and neurocognitive function will serve as outcome measures. Functional and structural neuroimaging biomarkers of neural plasticity and learning (fMRI, GABA MRS, etc.) will measure intervention-associated alterations in specific brain regions impacted by cognitive aging.

***Enhancing Cognitive Control Older Adults with Complementary Interventions* (R01**

AG054077) Adam Gazzaley, Patricia Arean (MPIs) – UC San Francisco

Data collection is complete and publication of primary results is expected in 2021.

The abstract for the grant:

DESCRIPTION (provided by applicant): Deficits in cognitive control are at the core of many functional declines in healthy older adults. A fundamental contributor to these deficits is compromised regulation of both external and internal attention processes, which leads to a decreased ability to effectively engage in complex, goal-directed behavior. As a result, there is a critical need to develop targeted interventions to reverse or prevent declines in regulation of attention processes in healthy older adults. Targeted cognitive training and focused-attention meditation are two interventions that hold great promise for boosting attention and cognitive control abilities in healthy older adults, but we lack a firm understanding of the neural and physiological mechanisms that underlie this positive neuroplasticity.

We also know little about whether such interventions might have multiplicative effects on cognition when administered in a combinatorial manner. The goals of the proposed research are threefold. First, we will determine the unique and synergistic effects of an externally oriented attention training paradigm and an internally oriented meditation paradigm on enhancing regulation of external and internal attention in healthy older adults, leading to improvements in functional outcomes. Second, we will examine the impact of potential genetic, physiological, and social moderators of the treatment effects in individuals and subgroups who show variability in their response to the

interventions. Third, we will document the neural and physiological mechanisms underlying the unique and synergistic plasticity associated with each individual or combined intervention. To accomplish these aims, we will conduct a randomized clinical trial in healthy older adults of two novel cognitive training paradigms that are deployed on wireless mobile devices. We will collect data from two samples: a large (N = 1650) sample that will be recruited nationally who will complete the study entirely on mobile devices and a smaller (N = 225) local sample who will also complete more in-depth lab-based cognitive assessments, EEG, structural MRI, and functional MRI. The national sample will provide the numbers needed to examine individual and subgroup differences in treatment response in an extremely diverse sampling of the general population. The local sample will allow us to dive deeper into the underlying neural and physiological mechanisms that give rise to training effects. Both groups will complete baseline, immediate follow-up, and one-year follow-up assessments of cognitive and functional outcomes, while the local group will undergo neuroimaging at all three time points. We anticipate that the unique methodological approach and experimental design will significantly advance the development of rehabilitation programs directed at the broad range of cognitive abilities and functional outcomes in both healthy and clinical populations that suffer from problematic regulation of attention and cognitive control.

PUBLIC HEALTH RELEVANCE: Cognitive deficits that occur with aging are a pervasive concern to older individuals and a growing public health issue. The goal of this project is to determine the neural and physiological mechanisms by which older adults reap cognitive and functional benefits from individual and combined cognitive and meditation training. This knowledge gained from this high-impact study will transform the field of cognitive interventions, leading to new methods that improve quality of life for older adults and individuals with cognitive impairment from neurological and psychiatric disease.

Investigating Gains in Neurocognition in an Intervention Trial of Exercise (IGNITE) (R01 AG0532952) Kirk Erickson, Jeffrey Burns, Arthur Kramer, Edward McAuley (MPIs) – University of Pittsburgh (parent site)

The trial is active. Due to the COVID-19 pandemic, data collection was first halted and now slowed. Most sites are up and running again as of this date. The exercise intervention was continued during the pandemic with videos for at-home use distributed to the study participants. Trial completion now is anticipated in 2022 with publication of primary findings anticipated for December 2022.

The abstract for the grant:

DESCRIPTION (provided by applicant): Despite the ubiquity of normal age-related cognitive decline there is an absence of effective approaches for improving neurocognitive health. Fortunately, moderate intensity physical activity (PA) is a promising method for improving brain and cognitive health in late life, but its effectiveness remains a matter of continued skepticism and debate because of the absence of a Phase III clinical trial. Here we propose a Phase III multi-site randomized clinical trial called IGNITE (Investigating Gains in Neurocognition in an Intervention Trial of Exercise) to more definitively address whether exercise influences cognitive and brain health in cognitively normal older adults. We are proposing a 12-month, multi-site, randomized dose-response exercise trial (i.e., brisk walking) in 639 cognitively normal adults between 65-80 years of age. Participants will be randomized to a (a) moderate intensity aerobic exercise condition at the public health recommended dose of 150 minutes/week (N=213), (b) a moderate intensity exercise condition at 225 minutes/week (N=213), or

(c) to a stretching-and-toning control condition for 150 minutes per week (N=213). Participants will meet 3 days/week for site-based exercise and do home-based activity on two more days of the week for 12 months. A comprehensive state-of-the-science battery of cognitive, MRI, amyloid imaging, physiological biomarkers, cardiorespiratory fitness, physical function, and quality of life measures will be assessed at baseline and after completion of the intervention. We have assembled a highly creative, productive, and interdisciplinary team with a long history of collaboration and experience conducting exercise interventions in older adults to test the following aims: Aim 1: Using a comprehensive neuropsychological battery and the NIH Toolbox, we will test whether a 12-month moderate intensity exercise intervention improves cognitive performance in older adults and (b) test whether the improvements occur in a dose-dependent manner. Aim 2: We will test whether a 12-month PA intervention augments MRI markers of brain health and whether these changes happen in a dose-dependent manner. Aim 3: We will test the hypothesis that cardiometabolic, inflammatory, and neurotrophic changes mediate improvements in brain and cognition. Aim 4: We will examine subgroups (i.e., individual differences) that attenuate or magnify the effect of the intervention on cognitive, brain, and physiological systems to better understand the factors that predict 'responders' versus 'non-responders' to the intervention. We will explore three categories of variables: (1) demographic (e.g., age) (2) genetic (e.g., APOE), and (3) baseline A β burden. Exploratory Aims: We will explore (a) whether baseline brain health metrics predict adherence and compliance to 12-months of PA, and (b) the utility of multi-modal brain imaging analytical approaches to more comprehensively understand the effects of PA on the aging brain. The results from this trial could transform scientific-based policy and health care recommendations for approaches to improve cognitive function in cognitively normal older adults.

PUBLIC HEALTH RELEVANCE: In this Phase III randomized clinical trial, we will examine the effects of aerobic exercise on cognitive and brain function in late adulthood. We will be collecting a battery of cognitive, neuroimaging, amyloid, psychosocial, physical function measures, and blood-based biomarkers to examine the outcomes and mechanisms of the intervention.

Updates on Outcomes from the Cognitive Aging Summit III

A special issue of the journal *Neurobiology of Aging* was published in November 2019 (Vol. 83, pp. 122-154 <https://www.sciencedirect.com/journal/neurobiology-of-aging/vol/83/suppl/C>) that included an introduction to the issue and six articles co-authored by the presenters and chairs of each of the six Summit sessions. (For a description of the Summit and an Executive Summary see <https://www.nia.nih.gov/research/dn/cognitive-aging-summit-iii>)

The NIA also has launched two research initiatives based on the set of recommendations from the Cognitive Aging Summit III:

- One recommendation from the 2017 Summit was to support a longitudinal study of rats that would closely track the animals throughout their lives. That recommendation is now an action.

NIA's Intramural Research Program (IRP) is developing a longitudinal study with the name **STARRS—Successful Trajectories of Aging: Reserve and Resilience in RatS**. The study will generate state-of-the-art neuroimaging, along with phenotypic results, non-invasive biological samples plus other indicators that could give insight into the mechanisms of healthy neurocognitive aging. STARRS will create open-source data and a sample hub to be shared with the entire aging science community. The goal is to bring us closer to an understanding of the factors that contribute to successful versus unsuccessful neurocognitive aging. The study was described in a recent presentation for the Research Centers Collaborative Network supported through NIA funding (see <https://vimeo.com/438607388>). Due to the COVID-19 pandemic, the initiation of the study had to be postponed. A state-of-the-art neuroimaging scanner is expected for delivery and set up in Spring 2021 with the first cohort of animals expected to enter the study around September 2021.

- A second recommendation from the 2017 Summit was to develop uniform definitions of terms such as resilience, reserve, compensation, maintenance, etc. so that the research community, nationally and internationally, could advance the field and our knowledge base more rapidly and lead to a better understanding of how individuals can promote and sustain brain and cognitive health. In response to that recommendation, the NIA issued an RFA (RFA-AG-18-024), "Collaboratory on Research Definitions for Cognitive Reserve and Resilience to Alzheimer's Disease (R24-Clinical Trial Not Allowed)."

One award was made to Yaakov Stern and Columbia University Health Sciences for a network grant titled "**Collaboratory on Research Definitions for Cognitive Reserve and Resilience**" (R24 AG061421).

The abstract for the grant:

Research indicates that specific life exposures and genetic factors contribute to some people being more resilient than others, with lower rates of cognitive decline with aging, and reduced risk of developing Alzheimer's disease and related dementias (ADRD). There are likely several complex and highly interactive mechanisms that lead to these individual differences in vulnerability to decline, probably reliant on both structural and functional brain mechanisms. Key

concepts often used in research in this area are cognitive reserve, brain reserve and brain maintenance. However, the definitions of these concepts differ across researchers, and the translation from human to animal research is not well developed. Also, their relationship to other invoked concepts such as efficiency, capacity, and compensation are not well explicated. The goal of this project is to work towards achieving state-of-the-art definitions for these concepts to allow researchers to use common nomenclature. In addition, the goal is to validate approaches to help advance research on these approaches that will lead to better maintenance of brain and cognitive health and treatment and/or prevention of AD/AD. To that end we will hold three cross-discipline workshops that will bring together investigators to discuss and come to consensus on these concepts, create focused workgroups that will examine each of these issues, fund pilot grants designed to further the understanding and research applicability of these concepts, and to develop data sharing and information exchange platforms to help guide promote research in this area.

PUBLIC HEALTH RELEVANCE: In order to achieve state-of-the-art definitions and research guidelines for key concepts associated with resilience against cognitive aging and Alzheimer's disease related dementia, this project will hold three multidisciplinary workshops, establish focused work groups, create a data sharing and information platform, and support pilot grants designed to further the understanding of these concepts.

Now moving into its third year, the PI, Dr. Stern, and his Executive Committee (Marilyn Albert, Carol Barnes, Roberto Cabeza, Alvaro Pascual-Leone, Peter Rapp), continue to advance the goals of the RFA. The website for the effort <https://reserveandresilience.com/> contains information for the two workshops that have been held to date, the latest being in early September 2020.

- A third recommendation from the 2017 Summit was to develop a registry of cognitive super agers for intensive study of factors for support of brain maintenance, cognitive reserve and resilience to neurodegenerative disease. A Request for Applications (RFA-AG-21-015; <https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-21-015.html>) was released in early 2020, ***"Network for Identification, Evaluation and Tracking of Older Persons with Superior Cognitive Performance for Their Chronological Age (U19 Clinical Trial Not Allowed)."*** Applications were due October 1, 2020. NIA anticipates making an award in Summer 2021. This activity is another example of an initiative that will be supported through the Research Partnership in Cognitive Aging between the MBRF and the NIA, coordinated by the FNIH.

McKnight Brain Research Foundation Mid-Career Research Award in Cognitive Aging and Memory Loss

Founded in 1999 by Evelyn F. McKnight, the specific goal of the McKnight Brain Research Foundation (MBRF) is to better understand and alleviate age-related cognitive decline and memory loss.

While it has been stated that one in eight people 65 and older has Alzheimer's Disease, cognitive changes due to the normal aging process will affect many of the remaining 87%, impacting abilities like processing speed and decision-making and contributing to some types of memory loss. The McKnight Brain Research Foundation champions research to better understand age-related cognitive decline and memory loss and educate the public on how to maintain cognition and brain health while aging successfully.

As the only private foundation focused exclusively on differentiating cognitive aging, age-related cognitive decline and memory loss from pathological disease states, (such as Alzheimer's disease and related dementias), the MBRF has established a national platform for outreach to the scientific community and the public. To accelerate the mission of the MBRF, the Foundation has previously partnered with other institutions to establish McKnight Brain Institutes at the University of Alabama at Birmingham, the University of Arizona, the University of Miami, and the University of Florida.

The McKnight Brain Research Foundation and the McKnight Brain Institutes are leaders in cognitive aging research. Together, they are committed to sharing innovations in research and practical suggestions for maintaining brain health with the public, while supporting research leading to better understanding and alleviating age-related cognitive decline and memory loss.

OUR COMMITMENT TO RESEARCH

With direct contributions from the MBRF and strategic initiatives led by the MBRF through partnerships with the National Institute on Aging through the Foundation for the National Institutes of Health, and the four McKnight Brain Institutes, more than \$180 million dollars have been provided in funding research specifically targeted towards cognitive aging, age-related cognitive decline and memory loss. By supporting three Cognitive Aging Summits and commissioning the National Academy of Medicine's study and report on Cognitive Aging (<https://www.nap.edu/catalog/21693/cognitive-aging-progress-in-understanding-and-opportunities-for-action>), the Foundation has made great progress leading to the understanding and alleviation of the effects of age-related cognitive decline and memory loss over the last two decades.

In fulfilling its mission of *"nurturing scientists dedicated to exploring and pursuing innovative research to advance the understanding and alleviation of age-related memory loss"*, the MBRF has partnered with the American Academy of Neurology through the American Brain Foundation to fund two cognitive aging clinical translational research scholarships per year for five years. The program is designed to support physicians or PhDs who are committed to a research program in cognitive aging and memory loss and have completed their training within five years of application. Each scholarship is a two-year award for a total of \$150,000. In addition to the Scholarship program, the MBRF has previously funded individual block grant research support for inter-institutional collaborators between the four McKnight Brain Institutes.

The MBRF now proposes to extend its mission of supporting the next generation of world-class research scientists in the field of cognitive aging and memory loss by targeting outstanding mid-career scientists who have already demonstrated a firm commitment to cognitive aging research. This group of scientists is at a key milestone in their career trajectory having already proven themselves to be committed to research in cognitive aging and clearly demonstrated their potential to become leaders in their field. By providing research funding to these promising investigators as they continue to embark upon independent careers, the MBRF proposes to build a core group of outstanding research scientists across the United States with the potential to lead transformative research in the field of cognitive aging.



PROPOSAL

The MBRF proposes to establish the ***McKnight Brain Research Foundation Mid-Career Research Award in Cognitive Aging and Memory Loss***

- Length of Award: three years, renewal annually after satisfactory review
- Amount of Award: \$250,000 per year with match from the host institution
- The Foundation commits to funding the program for a five-year initial trial period which would have supported 12 scientists at the conclusion of the five-year cycle

BUDGET

Year 1	Two Awards	\$500,000
Year 2	Four Awards	\$1,000,000
Year 3	Six Awards	\$1,500,000
Year 4	Four Awards	\$1,000,000
Year 5	Two Awards	\$500,000
Total 12	Mid-career awards	\$4,500,000 (MBRF commitment)

ELIGIBILITY

All applicants for the award program must have:

- completed research/clinical training i.e. formal post-doctoral research training post-PhD and/or physicians who have completed post-residency fellowship training.
- a proven track record of research accomplishments in cognitive aging as indicated by their publications in high-impact journals, awards, and other metrics of peer recognition.
- tenure-track faculty in an academic institution in the United States with evidence of long-term institutional support as indicated by commitment of resources including laboratory space, start-up research funds and personnel. Candidates not in a tenure-track position are also eligible and should also demonstrate similar evidence of long-term institutional support and not be in a time-limited appointment.

The proposed MBRF initiative would add substantial start-up support for a period of three years to help these investigators develop and/or expand an outstanding research program in cognitive aging and memory loss. Each year, one award will be made to support studies focusing on clinical translational research and another toward understanding basic biological mechanisms underlying cognitive aging and age-related memory loss. For example, this support could be deployed towards conducting a pilot clinical trial, developing proof-of concept interventions to ameliorate age associated cognitive impairment, gather preclinical data to accelerate testing of potential interventions, and further study the mechanistic basis of age-associated cognitive impairment with a view to identifying novel treatment targets. Scientists proposing to pursue basic research should clearly articulate the potential of their findings to be translated.