MCKNIGHT BRAIN RESEARCH FOUNDATION (MBRF)

Meeting of the Research Committee

Tuesday, September 24, 2024

5 pm EDT – 6 pm EDT Zoom (invitation in calendars)

Members:	Madhav Thambisetty, MD, PhD, Chair Patricia Boyle, PhD Michael L. Dockery, MD Roy H. Hamilton, MD, MS, FAAN, FANA, FCPP Susan L. Pekarske, MD
Other Attendees:	Amy Porter, Melanie Cianciotto, Valerie Patmintra

AGENDA

5:00 pm	1.	Call to Order/Welcome	Dr. Madhav Thambisetty
5:05	2.	Approval of the April 25, 2024 Minutes	
5:10	3.	Activity Timeline Updated September 15, 2024	
	4.	Cognitive Aging and Memory Intervention (CAMI) Core Pilot Grant Program	
	5.	Cognitive Aging Summit IV Summary	
	6.	McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss	
	7.	McKnight Clinical Translational Research Scholarship in Cognitive Aging and Age-related Memory Loss	
	8.	Society for Neuroscience Poster Session Chicago, October 6	
	9.	Other Business	
6:00	10.	Adjournment	Dr. Thambisetty/All

MINUTES
MCKNIGHT BRAIN RESEARCH FOUNDATION (MBRF)
RESEARCH COMMITTEE
CONFERENCE CALL
April 25, 2024

The Research Committee of the MBRF was called to order at 5:05 pm ET on April 25, 2024, by Dr. Madhav Thambisetty.

The following members were present:

Dr. Madhav Thambisetty, Chair of the Research Committee, Trustee
Dr. Mike Dockery, MBRF Chair
Dr. Patricia Boyle, Trustee
Dr. Sue Pekarske, Trustee

The following members were absent:
Dr. Roy Hamilton, Trustee

Others attending:
Dr. Lee Dockery, Chair Emeritus
Ms. Melanie Cianciotto, Corporate Trustee
Dr. Angelika Schlanger, Executive Director

1. Call to Order

Dr. Thambisetty welcomed the members of the committee to the call.

2. Minutes of the March 4, 2024 Meeting

The minutes of the March 4, 2024, Research Committee Meeting (Attachment 1) were approved as amended.

The changes were:

Item 5: The first three sentences were amended to read:

The proposal is to renew the current Innovator Awards grant for another three years to fund two three-year awards per year in the amount of $750,000 each (total 6) with maximum of 15% indirect expenses or institutional overhead. The proposed budget represents an increase of $11,500 in administrative costs by AFAR.

Item 6: insert "annual" before research award/prize throughout the section

Item 6: delete the following:

The committee proposed the research award/prize be named in honor of Dr. Lee Dockery. Dr. Dockery appreciated the gesture but feels the MBRF needs to be kept in the forefront.

Action Item 1: The minutes of the March 4, 2024, Research Committee Meeting were approved as presented (Attachment 1).

3. Updated Activity Timeline

The committee reviewed the updated Activity Timeline (Attachment 2) for information.

4. MBI Leadership Council's Proposal – McKnight Brain Aging Registry (MBAR)

The committee reviewed the MBI Leadership Council's McKnight Brain Aging Registry proposal (Attachment) and proposed the following changes:

Add the following items to the Deliverables in year 1: "Year-end report outlining all accomplishments to date; projects/publications using MBAR data; use of funds; and criteria used to approve requests for access to biospecimens."

Add the following items to the Deliverables in year 2: "Year-end report outlining all accomplishments to date; projects/publications using MBAR data; and use of funds."

The MBI Leadership Council's McKnight Brain Aging Registry proposal was approved as amended.

Action Item 2: The MBI Leadership Council's McKnight Brain Aging Registry proposal was approved as amended.

5. Cognitive Aging and Memory Core (CAMI) – RFA

The committee reviewed the Cognitive Aging and Memory Core (CAMI) RFA and proposed the following changes:

Under Eligibility Requirements:

The 2nd bullet point has been changed to read " Applications must propose preliminary or pilot interventions with promise for ameliorating cognitive decline associated with normative aging (that is, non-pathological aging), including memory decline."

The 5th bullet point has been changed to read "Awardees may be asked to serve as a reviewer for 1-2 cycles (2025 & 2026) after completion of their award cycle."

Under Application Review Criteria:

The second paragraph has been changed to read "The rankings and final recommendations provided by the Cognitive Aging and Memory Intervention Core will be reviewed by the MBRF. Awardees will be contacted by email."

The Cognitive Aging and Memory Core RFA was approved as amended.

Action Item 3: The Cognitive Aging and Memory Core RFA was approved as amended

6. Current Grants/Programs

a. MBRF Innovator Awards in Cognitive Aging and Memory Loss (AFAR) – RFA and Institutional Commitment Form

The committee reviewed the MBRF Innovator Awards in Cognitive Aging and Memory Loss RFA and Institutional Commitment Form (Attachment). The committee proposed the following changes to the Institutional Commitment Form:

Change the first paragraph to read; "Candidates for the McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss must be independent investigators with independent research space. As part of the evaluation, the committee will evaluate the institutional commitment for each applicant in order to ensure that adequate research space and resources are available to the candidate. To complete the application, this form must be completed by the Dean or the CEO of the institution. The form is NOT to be included in the application, but must be submitted directly to AFAR by the person completing the form (NOT the applicant), to afarapplication@afar.org as a Word or PDF file.

Item 7: Restate to read: "Indicate percentage of the applicant's profession time (FTE) allocated to: a. Research b. Teaching c. Clinical

Item 8: fix the verb tenses in the series of unnumbered boxes

Add "A letter documenting the institution's commitment to the candidate is an essential component of the application. This letter should be prepared by the Chair of the department in which the candidate holds their primary appointment and co-signed by the Dean or CEO of the institution. The letter should include the following:

- A statement of commitment to the candidate's development into a productive, independent investigator and to meeting the requirements of this award. It should be clear that the institutional commitment to the candidate is not contingent upon receipt of this award.
- Assurances that the candidate will be able to devote the required effort and time to complete the proposed project.

- Assurance that the candidate will have access to appropriate office and laboratory space, equipment, and other resources and facilities (including access to clinical and/or other research populations) to carry out the proposed project.
- Assurance that appropriate time and support will be available for any proposed mentor(s) and/or other staff needed to complete the proposed project.
- In the case of candidates who will be using the resources managed by another investigator or project leader, a letter of agreement from the PD/PI of the project documenting their support is required."

Dr. Schlanger will email the committee the updated Institutional Commitment Form for their review and approval prior to sending to AFAR. The approved document will be included in the May 15, 2024, Board of Trustees' meeting package.

Action Item 4: Dr. Schlanger will email the committee the updated Institutional Commitment Form for their review and approval prior to sending to AFAR. The approved document will be included in the May 15, 2024, Board of Trustees' meeting package.

b. MBRF Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss (ABF) RFA

The committee reviewed the MBRF Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss RFA (Attachment) and proposed the following changes:

Update all dates for the current cycle.

Under Eligibility, item #1 the end of the last sentence was changed to read "or tools to mitigate age-related cognitive decline and memory loss."

Under Evaluation and Selection, the last bullet point was changed to read "Project Significance: the ability to advance the field of cognitive aging."

The MBRF Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss RFA was approved as amended.

Action Item 5: The MBRF Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss RFA was approved as amended.

7. MBI Annual Report Reviewer Template Updates

Due to time constraints, the MBI Annual Report Reviewer Template updates (Attachment) will be circulated to the committee by email for review and approval.

Action Item 6: Dr. Schlanger will circulate the MBI Annual Report Reviewer Template updates to the committee by email for review and approval.

8. Adjourn

Dr. Thambisetty asked if there was any further discussion. Hearing none, he called for adjournment of the meeting at 6:20 p.m. ET.

Summary of Action Items:

Respectfully Submitted,

Melanie A. Cianciotto
Corporate Trustee

Research Committee Activity Timeline

2022 - 2024

Updated September 15, 2024

Duty (from Committee Charter)	Activity/Action	Outcome	Date	Comments
"Encourage and assess research at the McKnight Brain Institutes (MBIs)"	Review of the Annual Reports of the MBIs	Information for scientific review includes: scientific achievements, publications, presentations, collaborations	Annual Reports were reviewed by the Trustees on Feb. 20, 2024	Reviewers presented at Feb. 2024 Trustees Meeting. Follow up letters were written and sent to each of the MBIs. All Requests of MBIs are being addressed by MBIs.
	Review of all New Funding Requests from MBIs. Most Funding Requests should be reviewed by the Interventional Core Committee of the MBIs first.	The Leadership Council, by way of the CAMI-Core Chair, Dr. Sara Burke, submitted a proposal to relaunch the Pilot Grant Program. UM submitted a request for $250,000 to co-fund a fellowship over 5 years –	The board approved the proposal to re-launch the CAMI Core Pilot Grant Program at $75,000 per year for each award at its February 20, 2024 meeting. A memorandum notifying UM of the approval for	The revitalized CAMI-Core Pilot Grant program was officially launched at the 2024 IIM. Dr. Burke shared that 10 LOIs were submitted this year involving 28 faculty from the 4 institutes. Distribution by MBI is as follows: 10 from UAB, 8 from UF, 5 from U Miami, and 5 from UA. From the 10 LOIs, 8 teams have been invited to submit full proposals that are due Nov. 1, 2024. (The other 2 LOIs were not appropriate for CAMI-Core pilot funding.) The distribution by Faculty Rank is 9 New Investigators and 19 Established PIs. There is a balance of $150,000 on this grant commitment.

Duty (from Committee Charter)	Activity/Action	Outcome	Date	Comments
		The Evelyn F. McKnight Neurocognitive Clinical Scholar in Brain Health and Aging"	funding the Evelyn F. McKnight Neurocognitive Clinical Scholar in Brain Health and Aging for a total of $250,000 ($50,000 over 5 years) to be matched by UM was signed on Nov 10, 2021.	
	Review of Travel Award Fund: Originally established to fund research scholars and faculty to visit other McKnight institutions.	Few applications for travel. The funds allocated for travel have been used to fund the activities of focus groups: Epigenetics, MRI standardization and cognitive test battery working group	Reviewed as needed	Travel funds have been approved to fund travel and lodging for Innovator Award winner(s) to attend the 2024 IIM meeting at UF – Dr. Denise Cai attended.
	Inter-Institutional Block Grants	Cognitive Assessment and McKnight Brain Aging Registry (MBAR) Core	The Leadership Council, by way of Dr. Kristina Visscher, submitted a proposal to support MBAR with remaining dollars. The proposal was approved with minor amendments by the research committee on April 25, 2024 and by the Full Board at its May 15, 2024 Meeting. The Board also approved an additional $88,000 to cover the proposed	

Duty (from Committee Charter)	Activity/Action	Outcome	Date	Comments
			budget for the MBAR over the next two years, based on a recommendation from the Finance Committee.	
	Inter-institutional Block Grants	Cognitive Aging Core Working Groups	No Updates	5 Areas: Brain and Cognitive Health Cognitive Aging & Memory Cognitive Testing Battery Epigenetics MRI standardization
	Inter-institutional Block Grants	Bio-Informatics Core (Epigenetics)	No Updates	
	Inter-institutional Block Grants	Neuroimaging Core	No Updates	
"Identify opportunities…to foster greater interest in cognitive aging and age-related memory loss (in the scientific community)"	Research Partnership with the Foundation for NIH and the NIA.	1st cycle-2009, 2nd cycle-2014, 3rd cycle-2019	2023 annual progress report was submitted in January and reviewed by the board on March 19, 2024	History: Established 2009 $5 M over 5 years from MBRF; match from NIA and partners was $23 M for total of $28 M (17 five-year grants funded). The 2014 Partnership renewal funded one 5-year project for $15 million with $5 M from MBRF and $10 M from NIA Current Cycle: NIA committed to provide $15M to be pooled with MBRF's $5M. Two grants

Duty (from Committee Charter)	Activity/Action	Outcome	Date	Comments
		Cognitive Aging Summit (CAS) IV	CAS IV, with a theme of "Precision Aging and Brain Health" took place on March 20-21, 2024. There were 170 in-person attendees and up to 449 virtual attendees. Session Chairs, NIA leaders, FNIH and the MBRF met for an Executive Session following the summit.	were provided from the Research Partnership, led by to Dr. Thomas Perls and Dr. Emily Rogalski. The FNIH/NIA developed the meeting summaries and the recordings have been posted online (here). Follow-up reflections and takeaways from the Summit and the Executive Session will be shared by NIA, by way of Dr. Molly Wagster and Dr. Jonathan King, later this year. In August, FNIH provided a report on the Cognitive Aging Summit IV. It is included in the material for the September 24, 2024, Research Committee meeting.
	MBRF Innovators Awards in Cognitive Aging and Memory Loss The McKnight Brain Research Foundation committed $4.5 million over the next five	AFARI award cycles under the current grant were implemented (2021, 2022, 2023)	The research committee reviewed the draft RFA and Institutional Commitment Form at its	AFAR Review Committee: Chair: Dr. Anna Maria Cuervo Members:

Duty (from Committee Charter)	Activity/Action	Outcome	Date	Comments
	years to support outstanding mid-career scientists committed to researching the basic biological mechanisms underlying cognitive aging and memory loss. AFAR was invited to submit a renewal proposal for three additional years with updated program guidelines to broaden the applicant pool and able greater access to applicants from institutions with fewer resources	AFAR presented a renewal proposal to provide two 3-year awards each year for the next three years. It was approved by the MBRF board on March 19, 2024. The MBRF committed to $4,626,500 over the next 5 years.	meeting on April 25, 2024. The committee suggested several edits to the documents. The RFA and application were finalized and posted by AFAR at the end of May, following input from the Board at its meeting on May 15, 2024. Upcoming 2024 grant cycle deadlines include: *July 1: application period opens *August 12: application submission deadline *September 30: review committee meets *Oct 1: Award start date	Dr. Rafa de Cabo Dr. Thambisetty Dr. Boyle and Dr. Roz Anderson Dr. Hamilton (joined in 2023) Ms. Odette van der Willik reported that AFAR received 11 applications for the 2024 program, compared to 5 applications last year. Nine applications will be presented to the Selection Committee when they meet on September 30. Her report is included in the material for the Research Committee meeting on September 24.
"Encourage young investigators in this area of research"	McKnight Brain Research Foundation Clinical Translational Research Scholarship with American Academy of Neurology (AAN) and American Brain Foundation (ABF)	Seven award cycles have been completed. Two awardees have received the CTRS every year since 2018, with the exception of 2023, when one award was made. Members of the 2022-23 Review Committee include Dr. Madhav Thambisetty and Dr. Patricia Boyle. Dr Hamilton joined in 2023-24.	The Research Committee approved the draft RFA for 2024 with minor amendments at the April 25, 2024 meeting. Upcoming 2024 grant cycle deadlines include: *May: application period opens	<u>2023-24: Seventh Scholarships</u> Two applications were submitted to the MBRF Award mechanism, and one was awarded to Haopei Yang, PhD. The Trustees determined that the other project did not align with the scope or spirit of the award guidelines.

Duty (from Committee Charter)	Activity/Action	Outcome	Date	Comments
			*September 10: application submission deadline *November 7: review committee meets *January: notification of awardees *July: Award start date	10 applications were received by the deadline of September 10 and they appear to all be focused on cognitive aging. Last year only 2 applications were received; in 2023, 8 were received; and in 2022 there were 5 received. Question – Would the Trustees be interested in making 3 awards this year since only 1 was awarded last year? This would keep the program on track towards 10 researchers over 5 years.
	Poster Reception at Society for Neuroscience annual meeting	Poster sessions were held in 2008, 2019 and 2023.		Vicky Hixon submitted a proposal to organize the poster session to take place on October 6, 2024 in Chicago. The trustees approved the proposal at their March 19, 2024 meeting. On June 23rd, Vicki sent a Save-the-Date to MBI leadership and communications teams to announce the event will take place on October 6, 2024 at the Chicago Hilton. Dr. Patricia Boyle will attend as a representative of the MBRF.

Duty (from Committee Charter)	Activity/Action	Outcome	Date	Comments
				Ms. Vicki Hixon reported that 48 abstracts have been received with a few more expected before the event. Included in the Sept 24 meeting material are a list of those abstracts, a report and information about the event.

Cognitive Aging Summit IV

March 20-21, 2024

Revised July 22, 2024

Executive Summary

The fourth Cognitive Aging Summit was held on March 20-21, 2024, in Bethesda, MD. This Summit was devoted to discussion of biological, behavioral, and social factors that affect age-related brain and cognitive changes. An international cohort of investigators presented research into the causes of aging-related neurodegeneration and discussed how this research could inform strategies and future interventions for sustaining brain health and cognitive function during aging and the importance of individualized approaches to risk reduction. The meeting was convened by the National Institute on Aging of the National Institutes of Health (NIH) and made possible by the McKnight Brain Research Foundation through a generous grant to the Foundation for the NIH. Key themes from each of the six sessions are highlighted below.

Session One, *Blood, Metabolism, and Systemic Environment*, explored plasma proteins and hormones that affect brain morphology and function and cognitive ability. Levels of several inflammatory proteins increase in the brain with age, which may exacerbate cognitive decline. Declining estrogen levels due to aging or menopause can also lead to cognitive decline, while higher estrogen levels during pregnancy can lead to increased brain functional connectivity. Research into the specific mechanisms by which plasma protein and hormone levels affect brain function may help inform individualized therapeutic interventions that sustain or rejuvenate brain health during aging. Speakers emphasized that because brain health and body health are intricately linked, improvements in lifestyle factors also may benefit cognition as individuals age. Understanding individual responses to such lifestyle changes can provide another individualized pathway to improving cognitive and brain health.

Session Two, *Structural and Social Environment*, addressed the cognitive effects of sociodemographic factors, the built environment, and interpersonal social determinants of health, all of which may contribute to individual differences across the life course. Researchers have leveraged historical and survey data by adding cognitive measures to examine how early life language development and education bolster cognitive abilities throughout life. By contrast, stressors like perceived discrimination, racial violence, and lack of equitable access to education correlate with increased inflammation in the brain as well as increased depressive symptoms and contribute to diminished cognitive ability later in life. However, resilience pathways appear to be protective of memory function in the context of such stressors. The session highlighted the need for further research to disentangle the impacts of frequently intersecting social and experiential factors on individual cognitive health outcomes. Improving our understanding of the influence of these factors on the brain and cognitive aging may illuminate promising avenues for policy and neighborhood-level interventions to ameliorate entrenched health disparities.

Session Three, *Genetic Environment*, focused on the role of specific chromosomes, genes, and proteins in shaping cognitive aging and disease. During hormonal changes like perimenopause, when lowered levels of circulating estrogens disrupt normal glucose metabolism, female APOE4 carriers display worse metabolic and cognitive outcomes than noncarriers. Cognitive decline also correlates with reduced gene expression throughout neuronal cells and on the X

chromosome. Further research on these sex and gene interactions, including systematic comparisons of gene expression across populations, may contribute to the development of targeted and personalized interventions to prevent cognitive decline and improve individual cognitive health. Such findings could aid efforts to determine appropriate levels of hormone therapy for individuals based on gene expression, boost expression of silenced genes that may improve cognitive ability, or address barriers to preventive care.

Session Four, *Circuit Environment*, examined how gene expression, cellular activities, and brain morphology can affect learning, memory, and navigation. In human and animal experiments, upregulation of the Per1 gene, higher levels of estrogens, and consistency in neuronal firing patterns correspond with better ability to learn and remember spatial environments in young individuals. By contrast, aging results in loss of synaptic density and inconsistency in spatial firing patterns, leading to increased difficulty in spatial learning and memory. Further studies may help identify other genes involved in these changes in cognition, their mechanisms of action, and possible interventions to protect against age-related cognitive decline. These studies may also facilitate a greater understanding of individual differences in genes and behavior that lead to aging-related neural and brain changes.

Session Five, *Co-morbidities and Sleep Environment*, explored the importance of sleep, cardiovascular disease, and depression in risk for cognitive decline and dementia. Sleep plays a central role in learning and memory and helps clear the brain of misfolded proteins and other debris that could lead to neurodegeneration. Yet as individuals age, the percentage of time spent in REM sleep and slow wave sleep decreases. Sleep apnea, nocturia, and noisy environments (such as areas near airports) can exacerbate such sleep disruptions, while prevention and treatment of risk factors and co-morbidities—such as high blood pressure, depression, smoking and physical inactivity in midlife—may improve sleep quality and reduce the risk of cognitive decline. Because Alzheimer's disease and related dementias are primarily diagnosed late in life, studies of how co-morbidities and sleep in early life and midlife affect risk for cognitive decline and dementia may rely on surrogate biomarkers of risk. These studies need to account for the fact that some co-morbidities, such as kidney disease and obesity, independently affect biomarkers of Alzheimer's disease (e.g., phosphorylated tau 181 and amyloid beta 40) and thus require careful interpretation of the interaction among various conditions. Finally, both comorbidities and sleep are often related to lifestyle factors that interact with biological sex and genetic risk factors to determine individuals' risk for cognitive decline. To probe such interactions in animal models, researchers must utilize genetically heterogeneous strains.

The final session, *Study Design and Intervention Environment,* delved into novel methods for delaying cognitive decline and reviewed the results from several recent intervention trials. These study results underscore the complexity and heterogeneity of treatment responses within interventions. For example, provision of hearing aids reduced the risk for dementia among older individuals in a community cohort with relatively elevated risk factors but not in a normal risk cohort. Speakers also explored novel approaches to intervention design. For example, use of "digital twins"—the virtual representation of real-world individuals with

varying risk and protective factors for cognitive decline—may help researchers design multifactor interventions that target individuals based on genetic and lifestyle risk factors for cognitive decline and determine the appropriate size and duration for testing these interventions. In addition, machine learning and other AI-based methods can enable researchers to dynamically incorporate electrophysiological data in ongoing animal studies, dramatically reducing the amount of time required to understand neuronal responses to stimuli. Presenters discussed the importance of rate of decline, genetic variation, and exposures to social determinants of health in determining individual responses to interventions, as well as whether interventions have the largest impacts when initiated in midlife or earlier.

Several themes emerged from discussions across the sessions. Understanding the impacts and interactions of diverse biological, social, and environmental factors—ranging from genes to proteins to social structures—may help researchers and clinicians develop personalized therapeutic interventions. Additional research is required to understand the mechanisms through which these factors influence age-related brain and cognitive health. Speakers also emphasized the importance of early and midlife risk factors such as education, physical activity, cardiovascular disease, and sleep for predicting cognitive decline in later life. Finally, speakers discussed the need to conduct interventions for extended periods of time, among populations experiencing health disparities, and in midlife or earlier.

afar american federation for aging research

PROGRESS REPORT

Grantee:	American Federation for Aging Research
Project Title:	McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss
Reporting Period:	July 1, 2023 – September 15, 2024
Submitted:	September 15, 2024

Program Summary

The major goal of the program is to identify emerging scientific leaders by building a cadre of outstanding research scientists across the United States to lead transformative research in the field of cognitive aging. The program provides up to two 3-year awards of $750,000 (USD) each to advanced Assistant Professors and recently appointed Associate Professors (MDs and PhDs.) One award is to be made to support studies focusing on clinical translational research and another award toward understanding basic biological mechanisms underlying cognitive aging and age-related memory loss. The program targets full-time independent investigators at the rank of Assistant Professor or Associate Professor (or equivalent) with established independent research programs who have already demonstrated a firm commitment to cognitive aging research. The program provides 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.

AFAR submitted a proposal to MBRF in early 2024, requesting continued support for the program. The proposal was approved by the foundation in support of an additional three cohorts (2024, 2025 and 2026.)

Accomplishments in achieving the objectives

During the past three years, we identified two areas that needed further examination: 1: Number of applications received and 2: Balance between basic and clinical/translational research applications.

We conducted a survey among academic leadership and other funding agencies to identify alternative non-monetary markers of institutional commitment. With input from the MBRF Trustees, we updated the guidelines accordingly, specifically an updated Institutional Commitment form to be completed by the CEO or Dean of the institution and a letter from the Department Chair, addressing specific commitments re. time and resources.

Also based on feedback from the MBRF Trustees, we added language to the eligibility

criteria, considering exceptions to the 7- and 12-year eligibility limits, acknowledging that life events (e.g. familial, personal commitments or other exceptional circumstances) may effect these eligibility criteria.

We also increased our outreach, specifically targeting clinical and translational research investigators. We also worked closely with the MBRF Executive Director for a targeted announcement to the attendees of the 2024 Cognitive Aging Summit and we also reached out to the American Brain Foundation to cross-promote our MBRF-supported initiatives.

2024 Program:

AFAR received 11 applications for the 2024 program, compared to 5 applications for the 2023 program. There were 6 basic research applications, 1 basic/translational application, 1 basic/translational/clinical application and 3 clinical/translational applications. Nine applications will be presented to the Selection Committee for evaluation and discussion.

The Selection Committee will meet September 30, 2024, to review the applications. The committee is comprised of the following members:

Ana Maria Cuervo, MD, PhD, *Chair*
Albert Einstein College of Medicine

Rozalyn Anderson, PhD
University of Wisconsin, Madison

Patricia Boyle, PhD
Rush University and The McKnight Brain Research Foundation

Rafael de Cabo, PhD
National Institute on Aging

Roy H. Hamilton, MD, MS
University of Pennsylvania Perelman School of Medicine/The McKnight Brain Research Foundation

Madhav Thambisetty, MD, PhD
The McKnight Brain Research Foundation

- **Outreach/Communications**

As mentioned above, AFAR disseminates the program announcement widely. The program was promoted through a variety of mailings and e-mail announcements, including outreach through three of our NIA-managed networks, which includes websites, social media and direct communications to more than 100 NIA Center Programs. AFAR's scientific distribution list includes more than 8,000 individuals in the aging research community, and beyond.

Once grantees are selected, we create grantee profiles that are posted on the AFAR website, are included in our newsletter and shared through social media.

AFAR's Communications Department prepared a report which is attached to this report.

- **Awardee Progress reports**

The grantees are asked to present their recent findings at the Annual Grantee Conference. The two 2021 grantees, Lindsay De Biase and Saul Villeda, reported on their MBRF-supported work at the 2024 annual meeting, May 29 – 31 in Santa Barbara, California. See photos below.

For the 2021 and 2022 grantees, the most recent progress reports are attached.

The 2023 grantee reports are due at the time of writing this report.

- Financial Report

To be submitted under separate cover.

MCKNIGHT BRAIN RESEARCH FOUNDATION INNOVATOR AWARDS IN COGNITIVE AGING AND MEMORY LOSS

Communications and
Dissemination Report
2021-2023

Research Profiles

Every year, AFAR posts Research Profiles on all recipients of our grant programs. The profiles detail the research that their grants will support and advance. Please find below a hyperlinked list of the Research profiles for the McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipients from 2021-2023, followed by screen captures of each awardee's profile.

2023

- **Denise Cai, PhD**, Associate Professor, Icahn School of Medicine at Mount Sinai: *Memory stability and flexibility across a lifetime*
- **Christoph Thaiss, PhD**, Assistant Professor, University of Pennsylvania: *Counteracting age-associated cognitive decline via gut-brain signaling*

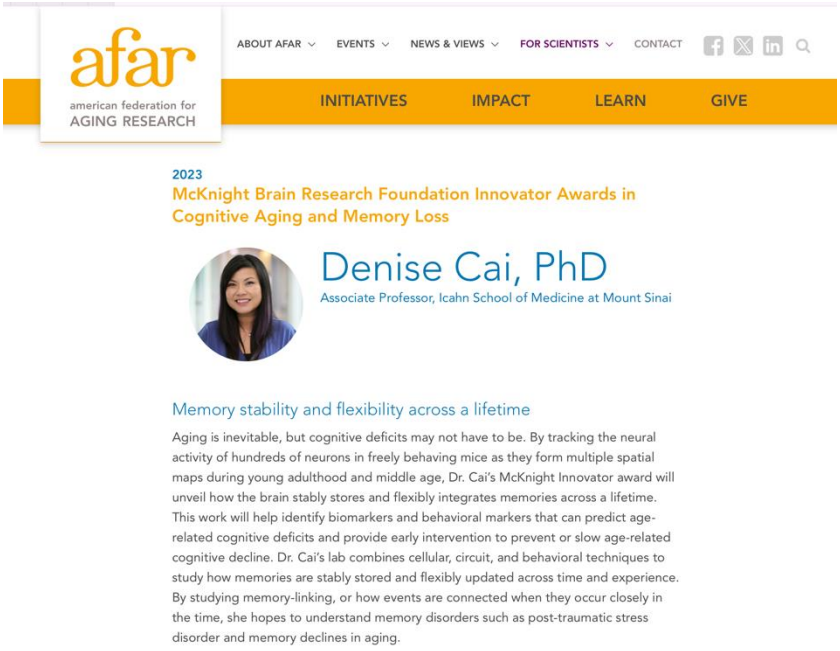
2022

- **Emilie Reas, PhD**, University of California, San Diego: *The mediating role of bloodbrain barrier dysfunction in effects of systemic inflammation on brain microstructure and memory*
- **Tara Tracy, PhD**, Buck Institute for Research on Aging: *Role of KIBRA in Age-Related Memory Loss*

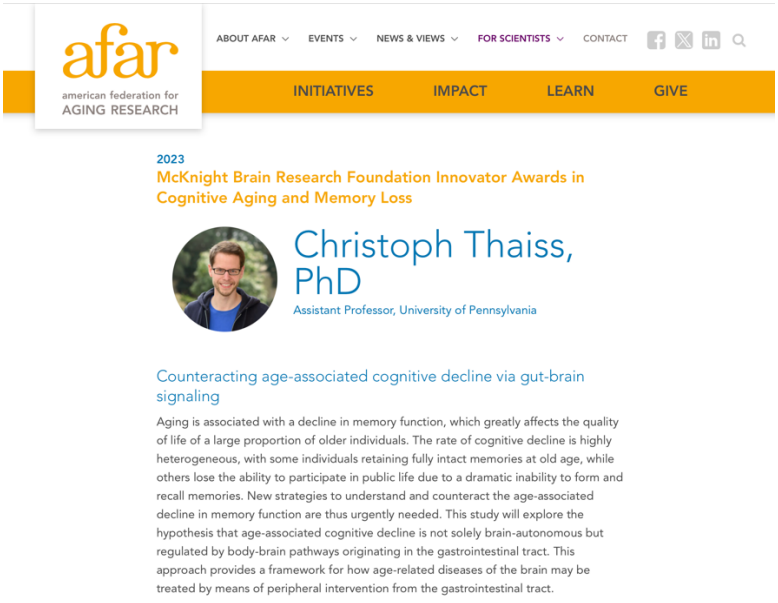
2021

- **Lindsay De Biase, PhD**, University of California, Los Angeles: *Synapse health in cognitive aging: central roles for microglial regulation of extracellular matrix (ECM)*
- **Saul Villeda, PhD**, University of California, San Francisco: *Caloric-restriction Induced Mechanisms of Cognitive Rejuvenation*

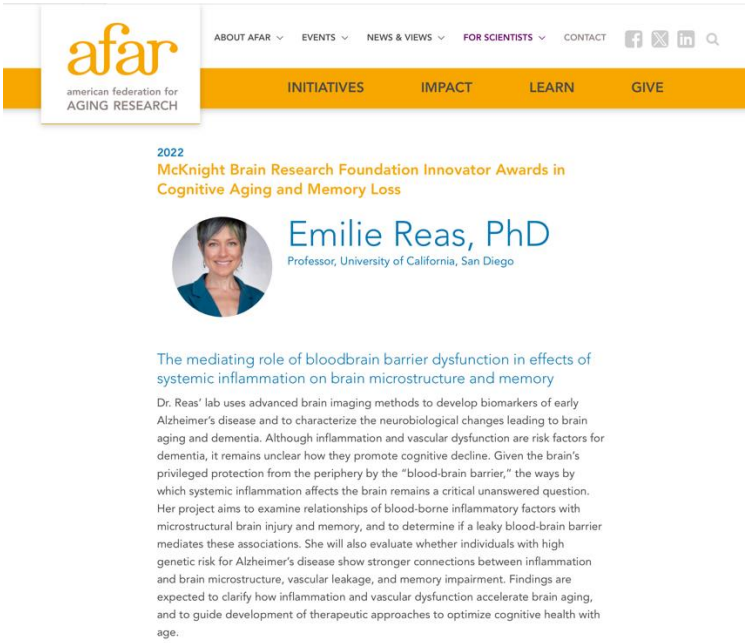
https://www.afar.org/grantee-profiles/denise-cai



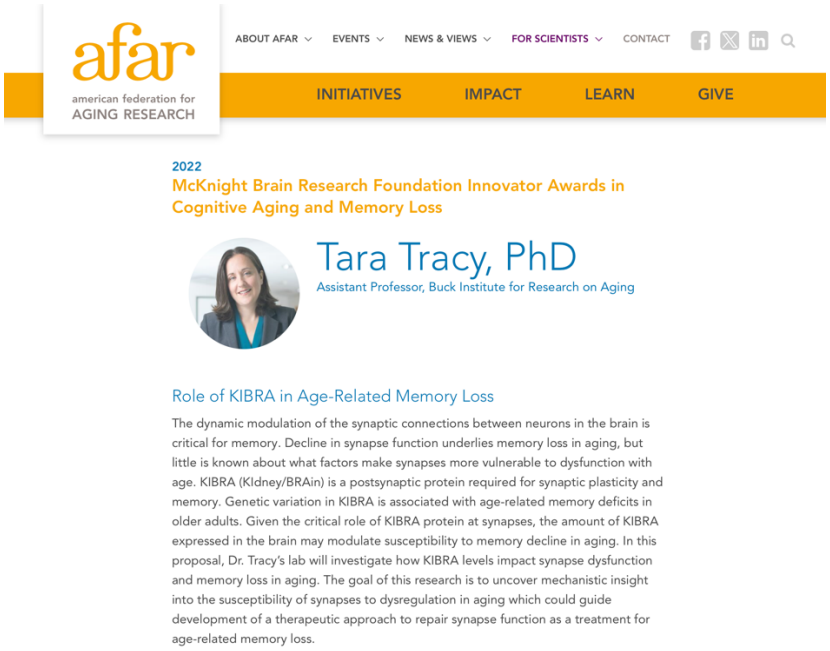
https://www.afar.org/grantee-profiles/christoph-thaiss



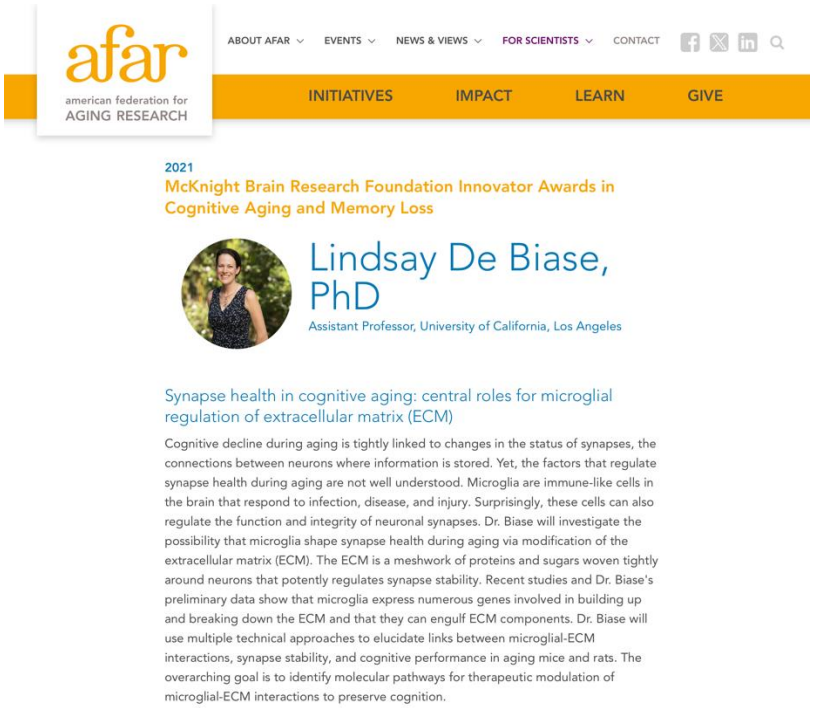
https://www.afar.org/grantee-profiles/emilie-reas-1



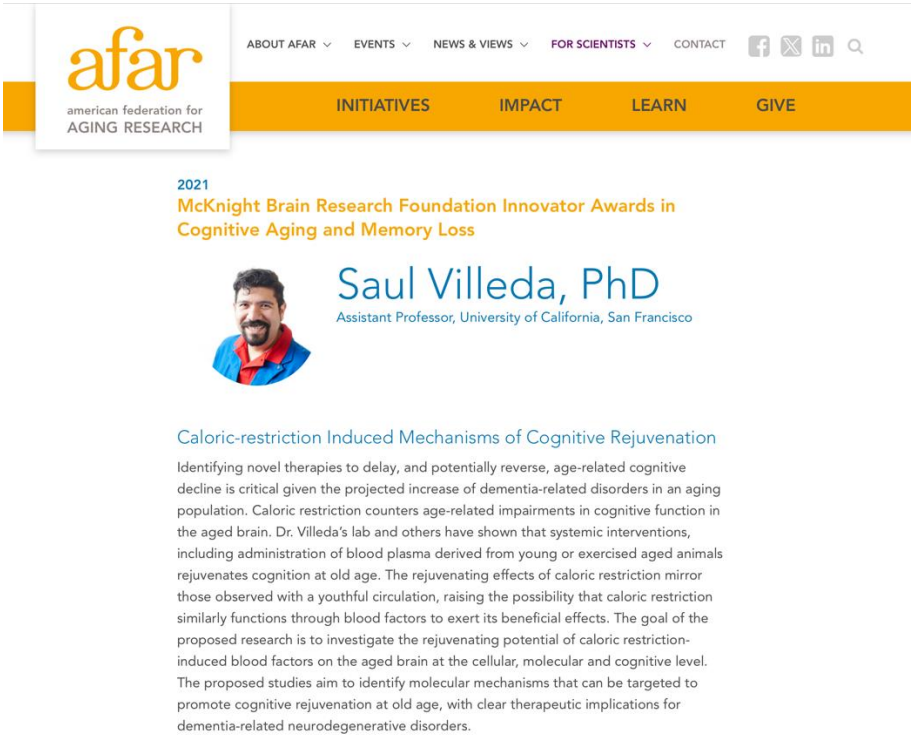
https://www.afar.org/grantee-profiles/tara-tracy



https://www.afar.org/grantee-profiles/lindsay-de-biase-1



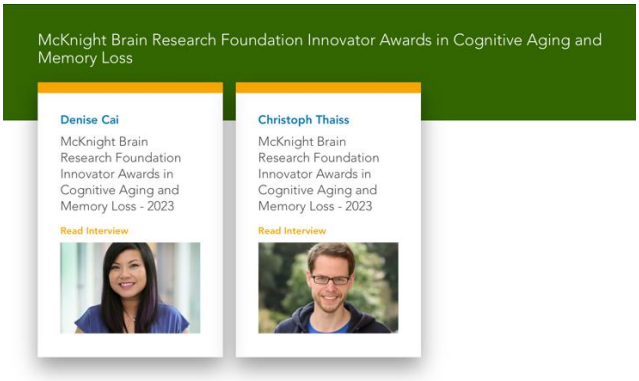
https://www.afar.org/grantee-profiles/saul-villeda

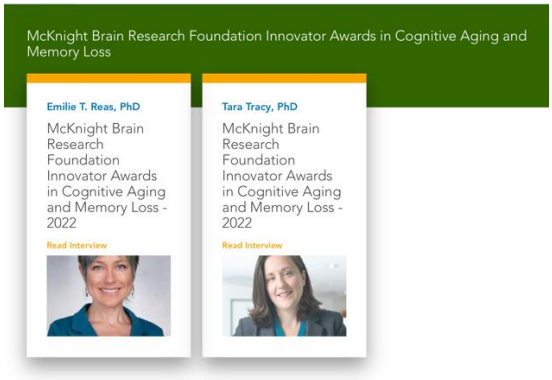


Grantee Spotlight Interviews

Annually, AFAR asks grantees to share a Grantee Spotlight Interview. In their own voices, the grantees share both their inspirations to join the aging research community and their aspirations for their research path and hopes for its potential to help extend healthspan, as well as the impact of receiving support like this early in their careers.

McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipients from 2021-2023. Each interview is hyperlinked above a screenshot of the interview.





https://www.afar.org/grantee-spotlight-interviews/denise-cai-spotlight

Grantee Spotlight Interview

Denise Cai, PhD

Associate Professor, Icahn School of Medicine at Mount Sinai
McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss - 2023

What inspired you to pursue aging research?

I was inspired to pursue aging research because there are many questions that still need to be answered. Aging affects us all; understanding the brain mechanisms behind it will have numerous applications to human lives and human diseases. I approach aging from my own area of expertise in memory, seeking to answer a few questions out of the endless questions we still have about what aging is, how it happens, and the myriad ways it affects us.

In your view, what does AFAR mean to the field, and what does it mean, for you, to receive an AFAR grant now?

AFAR provides necessary funding for researchers like me, who are seeking to understand aging from a variety of perspectives. This grant provides me the means to apply my expertise in neuroscience and the neuronal mechanisms of memory to answer questions about aging that may provide invaluable insights into new research directions and, ultimately, into understanding and treating memory declines in humans.

What is exciting about your research's potential impact?

The most exciting aspect of my research's potential impact is that it may provide new avenues to treat the cognitive and memory declines that accompany aging.

How would you describe your research to a non-scientist?

Memory is a complex process that is always updating and changing and is based on groups of neurons in the brain. By imaging these groups of neurons as new memories are made and old memories are updated, we can understand *how* memories work, and more importantly, what goes wrong with our memory ability, on a neuronal level, as we age.

Explore Dr. Cai's AFAR-supported research here

https://www.afar.org/grantee-spotlight-interviews/christoph-thaiss-spotlight

Grantee Spotlight Interview

Christoph Thaiss, PhD

Assistant Professor, University of Pennsylvania
McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss - 2023

What inspired you to pursue aging research?

Aging is the single biggest risk factor for the majority of the major human diseases. Therefore, if we make progress in understanding aging and how it regulates our propensity for disease, we have a big opportunity to address several important diseases at once.

In addition, aging is also a fascinating biological phenomenon that is pervasive in the animal kingdom but very heterogeneous between organisms, tissues, and cell types in the body.

Both the interesting biological challenge and its vast medical implications have inspired me to study aging.

In your view, what does AFAR mean to the field, and what does it mean, for you, to receive an AFAR grant now?

The AFAR grant serves as a catalyst for numerous new research directions in my lab. It enables us to ask bold and big questions--questions that do not follow the standard model of stepwise scientific progress where one result slowly builds on top of another, but rather questions that allow us to think more broadly and creatively.

I think this is exemplary of AFAR's general role in serving as a catalyzer for aging research that strives to achieve major breakthroughs in our understanding of this very complex biological phenomenon.

What is exciting about your research's potential impact?

The aging brain is often viewed as a black box that is quite inaccessible to therapeutic intervention. By focusing on the impact of the periphery on the brain, we hope to use the body's natural communication routes between organ systems to maintain brain health during aging. If successful, this strategy would open up an entirely new avenue to counteract diseases of the brain.

How would you describe your research to a non-scientist?

Brain aging often leads to cognitive decline, which can have devastating consequences. The loss of memories in old age robs us of some of the most essential aspects of the human experience. Our research aims to counteract age-associated cognitive decline by focusing on the communication channels between the body and the brain, particularly those originating in the gastrointestinal tract.

Explore Dr. Thaiss' AFAR-supported research here

https://www.afar.org/grantee-spotlight-interviews/emilie-t-reas-phd

GRANTEE SPOTLIGHT INTERVIEW

Emilie Reas, PhD

Professor, University of California - San Diego

McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss - 2022

What inspired you to pursue aging research?

My early scientific endeavors were motivated by a fascination with episodic memory, a cognitive function that serves a critical role in constructing our personal identity by integrating our past with the present and anticipated future. Given the importance of memory to the human experience, my doctoral work on the brain bases of normal memory sparked a particular curiosity about conditions in which memory deteriorates, including both aging and neurodegenerative disorders such as Alzheimer's disease. Struck by the surprisingly elusive nature of the brain changes leading to these prevalent conditions, I've endeavored to develop a research program that aims to both disentangle the multifactorial pathways underlying cognitive decline and to identify biomarkers of early Alzheimer's disease-related brain changes. The ultimate goal of my lab's research is to optimize tools to detect the earliest predictors of cognitive decline and to guide strategies for successful brain aging.

In your view, what does AFAR mean to the field, and what does it mean, for you, to receive an AFAR grant now?

Funding from AFAR has been uniquely instrumental in guiding my research trajectory and supporting my career development as an independent investigator. As a postdoctoral fellow transitioning from cognitive neuroscience to the field of aging research, AFAR supported an exploratory project which provided preliminary findings that served as the foundation for an NIH-funded career develop award and in turn, for my current research program. Now, with a rapidly evolving lab, this award from AFAR and the McKnight foundation will provide the opportunity and essential resources to extend our prior work by leveraging recent methodological and theoretical advances to more deeply probe the mechanisms underlying brain ang cognitive aging.

What is exciting about your research's potential impact?

One of the most promising aspects of my project is its potential to support a model of brain aging that unifies several established, yet still disconnected, risk factors and biological pathways. We know that cognitive decline with aging and dementia is very tightly linked to structural cellular changes such as loss of synapses, axons, and dendrites, and eventually cell death. It's also well accepted that both genetics and modifiable health factors, notably inflammation and vascular dysfunction, are intimately tied to the brain abnormalities underlying cognitive decline. Although we've identified several key pieces to the puzzle, we have yet to assemble those pieces into a cohesive mechanistic model of brain aging. By taking a multimodal approach that integrates advanced brain imaging, biofluid, cognitive, and genetic measures, our research aims to place a critical piece of this puzzle, namely an explanation for how inflammation can injure the brain in synergy with vascular dysfunction. Ultimately, we hope our results will provide an actionable neurobiological framework that helps to explain the avenues leading to cognitive decline, while also guiding targeted therapeutic approaches to preserve cognitive health into later life.

How would you describe your research to a non-scientist?

Broadly, my research program aims to optimize trajectories of brain aging by clarifying the risk factors for, and pathways towards, cognitive decline. A complementary goal is to develop more sentitive markers of early brain changes that precipitate cognitive decline in order to identify individuals at greatest risk for dementia. To this end, my lab employs a multimodal approach, integrating cutting-edge brain imaging methods with behavioral testing, genetics, and fluid measures. By focusing our research on human participants without manifest cognitive impairment, we hope that our work will translate directly to clinical settings for early disease detection and therapeutic intervention.

Explore more of Dr. Reas' AFAR-supported research here

https://www.afar.org/grantee-spotlight-interviews/tara-tracy-phd

GRANTEE SPOTLIGHT INTERVIEW

Tara Tracy, PhD

Assistant Professor, Buck Institute for Research on Aging

McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss - 2022

What inspired you to pursue aging research?

I was inspired to pursue aging research by my colleagues at the Buck Institute for Research on Aging who are at the forefront of investigating the biology of aging. Specifically, I have been intrigued by the factors that influence healthy aging through my extensive collaborations and interactions in the community of leading aging researchers at the Buck Institute. This has motivated me to initiate the proposed new research project in my lab to advance our understanding of synaptic mechanisms that influence cognitive decline in brain aging.

In your view, what does AFAR mean to the field, and what does it mean, for you, to receive an AFAR grant now?

I am honored to receive this AFAR grant award, and I am excited that it will allow me to expand my research program using innovative approaches to investigate how molecular mechanisms that impact synapse physiology drive memory loss in aging. In my view, AFAR has made major contributions to advancing, expanding, and driving innovation in the field of aging research through various and diverse granting mechanisms.

What is exciting about your research's potential impact?

Why some individuals are more prone to memory loss with age than others is not well understood. Our research is exciting because it can provide new insights into what is occurring within the neurons of individuals who are more vulnerable to memory loss in aging.

How would you describe your research to a non-scientist?

We are studying synapses, which are the small specialized structures that form where neurons connect with each other in the brain to transmit information. Synapses are critical for the encoding of new memories in the brain. KIBRA is a protein found in neurons that plays an important role in the normal function of synapses during the formation of new memories. In our ongoing research, we aim to establish how the levels of KIBRA protein at synapses can affect the susceptibility of an individual to memory loss in aging.

Explore Dr. Tracy's AFAR-supported research here

https://www.afar.org/grantee-spotlight-interviews/lindsay-de-biase-phd

GRANTEE SPOTLIGHT INTERVIEW

Lindsay De Biase, PhD

Assistant Professor, University of California, Los Angeles

McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss - 2021

What inspired you to pursue aging research?

The human brain with its complex cellular circuits is often compared to a very specialized biological computer. Yet, the brain faces the incredible challenge of needing to maintain its circuits over a very long operational life. You can't simply trade in your brain for an upgraded model every 5-10 years the way we do with computers. It's a fascinating challenge to try and understand how the different populations of cells in the brain work together to keep us thinking and engaging with our surroundings for 50, 70, 90 years. By studying aging, we of course hope that we can learn how to preserve the integrity of this organ that plays an outsize role in shaping our identity. But I also believe that we will uncover factors that promote cellular and circuit resilience that can have applications in many fields such as neurodegenerative disease, stroke, and brain injury.

In your view, what does AFAR mean to the field, and what does it mean, for you, to receive an AFAR grant now?

AFAR is a fantastic catalyst for the field of aging research. As a relatively new investigator, AFAR played an instrumental role in helping me to establish a research program that focuses on the role of non-neuronal cells in CNS aging. I received a Glenn Foundation and AFAR Grant for Junior Faculty that enabled us to gather preliminary data for our first NIH grant submissions. AFAR support also allowed us access to colonies of aging rodents maintained by the NIH, which is invaluable for basic researchers aiming to uncover the cellular and molecular mechanisms of CNS aging. AFAR also provided highly stimulating opportunities to interact with and learn from other aging researchers via their annual grantee symposium. This new source of support from the McKnight Brain Research Foundation / AFAR allows us to launch novel lines of CNS aging research and use cutting-edge approaches to link our cellular and molecular-level findings with cognitive performance and behavior. I am honored to receive this support and very excited by the potential of this new line of investigation to expand our understanding of how non-neuronal cells shape cognitive aging.

What is exciting about your research's potential impact?

I think our research is "outside the box" from a couple perspectives. First – we study non-neuronal cells, or glial cells. Neurons are electrically excitable and form information-storing circuits through their synaptic connections with one another. So it might seem counter-intuitive to try and understand cognition by looking at cells that are *not* electrically excitable and that *don't* form synapses. Yet, substantial evidence from the last 10-15 years shows that these glial cells can potently regulate the function of neurons and synapses in ways that have a big impact on behavior and cognition. This is an exciting frontier because glial cells are likely to be more therapeutically "tractable" than neurons. The second out-of-the-box piece of this research project is our study of glial interactions with the extracellular matrix. The role of the extracellular environment in synapse function and integrity has not received a lot of attention and this area is ripe for new discoveries.

How would you describe your research to a non-scientist?

We study non-neuronal, or glial, cells in the central nervous system. For many years these cells were thought to do little more than provide structural support for information-storing neurons in the brain. (The term glia derives from the Greek word for "glue"). Yet we now recognize that glial cells play essential roles in maintaining neuronal health and fine-tuning their function. The field is just at the beginning of mapping out exactly how these cells can regulate cognition and behavior and how they might be harnassed in a wide variety of therapeutic contexts.

AFAR turned 40 in 2021. What is your vision for the next 40 years of healthy aging?

As a neuroscientist, I often wish that I had more knowledge about aging of other organ systems and the dialog between the CNS and the rest of the body during aging. There is exciting headway being made in terms of increased interaction between aging researchers that study distinct organ systems, and exciting findings at the intersections of these fields. I think aging research will benefit immensely from further nurturing of cross-pollination between aging research disciplines. Many challenges persist in trying to translate basic research findings to the human CNS. I also hope to see substantial progress in the next 40 years in translational pipelines, fostered by greater dialog between clinicians and basic scientists as well as technical innovation. I also love seeing expanding knowledge about how non-pharmaceutical interventions (such as lifestyle changes) shape healthy aging. I hope as a human society we can support many individuals in pursuing such changes, especially those who may not have easy access to health care.

https://www.afar.org/grantee-spotlight-interviews/saul-villeda-phd

GRANTEE SPOTLIGHT INTERVIEW

Saul Villeda, PhD

Associate Professor, University of California, San Francisco

McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss - 2021

What inspired you to pursue aging research?

My interest in the fields of aging and rejuvenation is grounded in my fascination with development and tissue plasticity. The initial spark that led me to this field came as an undergraduate when I first learned about the discovery of the Spemann organizer. In this study, performed almost 100 years ago, scientists transplanted a small portion of a newt embryo onto another and induced organismal changes that resulted in the formation of a twin embryo. This fundamental concept that organismal changes could be influenced by inter-tissue interactions has molded my research program. Could latent plasticity remaining at old age mirror plasticity observed in development to rejuvenate aging tissues?

In your view, what does AFAR mean to the field, and what does it mean, for you, to receive an AFAR grant now?

AFAR serves as both the nexus and launching pad for the biology of aging research field. AFAR provides a mechanism in which innovative and oftentimes high-risk high-reward research is supported at the very early stages. To me, receiving an AFAR grant represents both validation and encouragement to pursue areas of research in which we seek to develop therapeutics that can treat cognitive decline in the aging brain by targeting molecular mechanisms of aging in blood independent of the brain itself.

What is exciting about your research's potential impact?

The proposed research aims to challenge long-standing views of brain aging as a rigid process, by identifying caloric restriction-induced blood factors as molecular targets to delay and potentially reverse age-related cognitive decline. The ability to counter brain aging through blood-based therapeutic interventions could enable the mitigation of vulnerability to dementia-related disorders in the elderly, fulfilling an unmet need that is growing more pressing as the human population ages.

How would you describe your research to a non-scientist?

My research is focused on understanding what drives functional and cognitive impairments in the aging brain, and importantly how the effects of aging can be reversed in the old brain. We focus our investigations on the beneficial effects of systemic interventions - including young blood administration, exercise, and caloric restriction – in animal models of brain aging. Our goal is to identify therapeutic targets in blood to prevent, ameliorate and reverse dementia-related neurodegenerative diseases in the elderly.

AFAR turned 40 in 2021. What is your vision for the next 40 years of healthy aging?

I turned 40 in 2021 too! My vision for the next 40 years of healthy aging involves the translation of lifestyle interventions, such as exercise and caloric restriction, into tractable therapeutic targets that can not only delay but restore function late in life. Given the unique trajectory for each aging individual, I believe decoding broad lifestyle interventions into combinatorial sets of molecular targets will enable a personalized medicine approach in which individual hallmarks of aging specific to each person can be ameliorated.

Annual Grantee Announcement Campaign on AFAR Social Media

In addition to news item on homepage, feature in monthly newsletter, and a press release, AFAR announces the recipients of each of our annual grant programs with a campaign on social media. From 2021-2023, each McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipient received their own post, linking to their research profiles on AFAR.org. These posts reach nearly 5.7k followers on X, 3.4k followers on Facebook, and 2.8K followers on LinkedIn. Please find below screen captures of the art and copy that appeared in the announcement campaign for each year's recipients. (Note: the examples below appeared on Facebook and were tailored for X and LinkedIn.)

For archives and updates, follow AFAR on X, Facebook, and LinkedIn.

https://www.facebook.com/100064839813834/posts/757421799762474/

https://www.facebook.com/100064839813834/posts/758049339699720/

American Federation for Aging Research
2,928 followers
1yr •

AFAR is pleased to announce the recipients of the 2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss: Emilie T. Reas, PhD, of UC San Diego, and Tara Tracy, PhD, of Buck Institute for Research on Aging. The grant provides up to two 3-year awards of $750,000 each to advanced Assistant Professors and recently appointed Associate Professors to lead transformative research in cognitive aging.
Learn more here about Dr. Reas' research here: https://bit.ly/3VD7IWO.
Learn more about Dr. Tracy's research here: https://bit.ly/3FvzOZ7.
Read a related press release here: https://bit.ly/3VR20ek.
#grant #fellow #grantee #2022grantee #grantanouncement #agingresearch #aging #cognition #cognitiveaging #brain #brainhealth

https://www.facebook.com/share/6zzViLHzDJVNG54G/

American Federation for Aging Research
2,928 followers
1yr •

AFAR is pleased to support Tara Tracy, PhD, of Buck Institute for Research on Aging, a 2022 McKnight Brain Research Foundation Innovator Award in Cognitive Aging and Memory Loss recipient. Dr. Tracy will research the role of KIBRA in age-related memory loss.
Learn more about Dr. Tracy's research here: https://bit.ly/3FvzOZ7
Read a related press release here: https://bit.ly/3VR20ek
#grant #fellow #grantee #2022grantee #grantanouncement #agingresearch #aging #cognition #cognitiveaging #brain #brainhealth

https://www.facebook.com/share/bKr9FVbPev4FFwmw/

American Federation for Aging Research
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AFAR congratulates Emilie Reas, PhD, of UC San Diego, on receiving the 2022 McKnight Brain Research Foundation Innovator Award in Cognitive Aging and Memory Loss. Dr. Reas will research the mediating role of bloodbrain barrier dysfunction in effects of systemic inflammation on brain microstructure and memory.

Learn more here about Dr. Reas' research here: https://bit.ly/3VD7IWO

Read a related press release here: https://bit.ly/3VR20ek

#grant #fellow #grantee #2022grantee #grantanouncement #agingresearch #aging #cognition #cognitiveaging #brain #brainhealth

https://www.facebook.com/share/dMAkQguKKcnsYXSz/

Annual Grantee Spotlight Interviews on AFAR Social Media

AFAR promotes the Grantee Spotlight Interviews on our social media. From 2021-2023, each McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipient received their own post. These posts reach nearly 5.7k followers on X, 3.4k followers on Facebook, and 2.8K followers on LinkedIn. Please find below screen captures of the art and copy that appeared in the announcement campaign for each year's recipients. (Note: the examples below appeared on Facebook and were tailored for X and LinkedIn.)

For archives and updates, follow AFAR on X, Facebook, and LinkedIn.

https://www.linkedin.com/posts/american-federation-for-aging-research_in-our-grantee-spotlight-interview-denise-activity-7211790803927511040-QoMT/?utm_source=share&utm_medium=member_desktop

https://www.linkedin.com/posts/american-federation-for-aging-research_in-our-grantee-spotlight-interview-christoph-activity-7212183240340619265-R3Xx?utm_source=share&utm_medium=member_desktop

PRESS RELEASES

AFAR has issued press releases to announce news of our collaboration with the McKnight Brain Research Foundation. Each release is blasted on EurekaAlert! Science Newswire and shared with all grantees' institutional communications offices. All releases are announced as News items on AFAR homepage and archived on AFAR website. Please find below links to releases to date, as well as pdfs of the distributed release:

June 25, 2024
Announcing Renewal of McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss
https://www.afar.org/imported/AFAR-Press-Release_McKnight-Innovator-Awards-Funding-Renewal_06.25.24.pdf

December 11, 2023
Announcing the 2024 Recipients of the McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss
https://www.afar.org/imported/AFAR-Press-Release_2023-MBRF-Innovator-Awards_12.11.23.pdf

December 7, 2022
Announcing the 2022 Recipients of the McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss
https://www.afar.org/imported/AFAR-Press-Release_2022-MBRF-Innovator-Awards_12.6.22.pdf

March 8, 2022
Announcing Inaugural Recipients of the McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss
https://www.afar.org/imported/AFAR-Press-Release_2021-MBFR-Grant-Recipients-Announced_Approved.pdf

May 20, 2021
Announcing establishment of McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss
https://www.afar.org/images/uploads/general/MBFR-Grant-Program-Announcement_05.20.21.pdf

June 25, 2024

Contact: John Chaich
john@afar.org

Research in Cognitive Aging and Age-Related Memory Loss Boosted through Renewed $4,626,500 Funding of Innovator Awards

Grant from the McKnight Brain Research Foundation to the American Federation for Aging Research extends support for groundbreaking studies across next five years

NEW YORK CITY and ORLANDO — The American Federation for Aging Research (AFAR) and the McKnight Brain Research Foundation (MBRF) are pleased to announce renewed funding of the **Innovator Awards in Cognitive Aging and Memory Loss,** a program that supports scientists who are pursuing groundbreaking studies in the field of cognitive aging.

The Innovator Awards program was launched in 2021 with a $4,615,000 million grant from the MBRF to AFAR. The successful program has supported six investigators to date, who each have received three-year awards of $750,000. This year, MBRF renewed its commitment with a $4,626,500 award to AFAR to expand the network of investigators who focus their research on cognitive aging and memory loss.

For the next three years, MBRF and AFAR will provide up to two, three-year awards of $750,000. One award will be made to support studies focusing on clinical translational research, and another award will support studies of the basic biological mechanisms underlying cognitive aging and age-related memory loss. The awards are intended for full-time independent investigators at the rank of Assistant Professor or Associate Professor (or equivalent) who have already demonstrated a firm commitment to cognitive aging research.

“The Innovator Awards program affirms the Foundation’s commitment to supporting the next generation of world-class research scientists in the field of cognitive aging,” said Michael L. Dockery, MD, MBRF Chair. “By supporting mid-career scientists who have shown the potential to become leaders in the field, we’re investing in research to help us better understand and ultimately alleviate the effects of cognitive decline and age-related memory loss.”

In the program’s first three years, funded investigators have furthered a range of research approaches and topics impacting cognitive aging and memory loss. Read research profiles on the past recipients here: 2023, 2022, and 2021.

“The renewed Innovator Awards help support proposals that are high risk/high gain in nature, which may be less suitable for conventional sources of funding. AFAR and MBRF expect that the proposed research will yield transformative discoveries,” says AFAR Executive Director Stephanie Lederman, EdM.

The Innovator Awards are reviewed by an esteemed committee comprised of leaders in cognitive aging research. The committee’s recommendations will be presented to MBRF and AFAR for final funding decisions.

The application window for the 2024 Innovator Awards is open now, and applications are due August 12. AFAR anticipates awarding the next two recipients in September.

Learn more about **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss** here.

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About AFAR
The American Federation for Aging Research (AFAR) is a national non-profit organization that supports and advances pioneering biomedical research that is revolutionizing how we live healthier and longer. For more than four decades, AFAR has served as the field's talent incubator, providing nearly $200 million to some 4,400 investigators at premier research institutions to date—and growing. In 2023, AFAR provided approximately $12,500,000 to more than 60 investigators. A trusted leader and strategist, AFAR also works with public and private funders to steer high quality grant programs and interdisciplinary research networks. AFAR-funded researchers are finding that modifying basic cellular processes can delay—or even prevent—many chronic diseases, often at the same time. They are discovering that it is never too late—or too early—to improve health. The science funded by AFAR is paving the way for innovative new therapies that promise to improve and extend our quality of life—at any age. Learn more at www.afar.org.

About the McKnight Brain Research Foundation
Founded in 1999, the McKnight Brain Research Foundation is the nation's only private foundation devoted exclusively to discovering the mysteries of the aging brain. Over the past two decades, the Foundation has funded more than $200 million in research specifically targeting cognitive aging and age-related cognitive decline and memory loss through direct contributions and strategic initiatives in partnership with the four McKnight Brain Institutes and the National Institute on Aging through the Foundation for the National Institutes of Health. Learn more about the Foundation at: www.mcknightbrain.org.

December 11, 2023

Contact: John Chaich
john@afar.org

The McKnight Brain Research Foundation and the American Federation for Aging Research Announce Recipients of the 2023 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss

Denise Cai (Mount Sinai) and **Christoph Thaiss (University of Pennsylvania)**
each receive $750,000 to lead transformative research in the field of cognitive aging

NEW YORK CITY and ORLANDO— The American Federation for Aging Research (AFAR) and the McKnight Brain Research Foundation (MBRF) are pleased to announce the 2023 recipients of **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss: Denise Cai, PhD** of the Icahn School of Medicine at Mount Sinai, and **Christoph Thaiss, PhD,** of the University of Pennsylvania.

Now in its third year, the Innovator Awards program funds research scientists pursuing groundbreaking studies in the field of cognitive aging.

Denise Cai, PhD, is an Associate Professor at the Icahn School of Medicine at Mount Sinai. Dr. Cai's project "Memory stability and flexibility across a lifetime" aims to identify biomarkers and behavioral markers that can predict age-related cognitive deficits and provide early intervention to prevent or slow age-related cognitive decline.

Christoph Thaiss, PhD, is an Assistant Professor at the University of Pennsylvania. Dr. Thaiss' project "Counteracting age-associated cognitive decline via gut-brain signaling" aims to develop a framework for how age-related diseases of the brain may be treated by means of peripheral intervention from the gastrointestinal tract.

Dr. Cai and Dr. Thaiss will each receive $750,000 for an award period of three years. The MBRF Innovator Awards in Cognitive Aging and Memory Loss are funded by a $4.5 million grant from the McKnight Brain Research Foundation that will support six investigators over a period of five years.

"The Innovator Awards are a primary example of the Foundation's commitment to supporting the next generation of world-class scientists dedicated to the field of age-related cognitive decline and memory loss," says Michael Dockery, MD, Chair of the McKnight Brain Research Foundation. "With Dr. Cai and Dr. Thaiss already demonstrating a strong commitment to the field, we are excited to support their efforts to uncover novel intervention and treatment methods to help people remain cognitively healthy later in life."

“AFAR has long supported the careers of talented investigators and research on cognitive health,” notes Stephanie Lederman, EdM, Executive Director, AFAR. “AFAR is pleased to continue our partnership with the McKnight Brain Research Foundation and proud to support these inspiring researchers.”

Learn more about **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss here.**

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About AFAR
The American Federation for Aging Research (AFAR) is a national non-profit organization that supports and advances pioneering biomedical research that is revolutionizing how we live healthier and longer. For more than four decades, AFAR has served as the field’s talent incubator, providing nearly $200 million to some 4,400 investigators at premier research institutions to date—and growing. In 2023, AFAR expects to provide approximately $12,500,000 to more than 60 investigators. A trusted leader and strategist, AFAR also works with public and private funders to steer high quality grant programs and interdisciplinary research networks. AFAR-funded researchers are finding that modifying basic cellular processes can delay—or even prevent—many chronic diseases, often at the same time. They are discovering that it is never too late—or too early—to improve health. The science funded by AFAR is paving the way for innovative new therapies that promise to improve and extend our quality of life—at any age. Learn more at www.afar.org.

About the McKnight Brain Research Foundation
Founded in 1999, the McKnight Brain Research Foundation is the nation’s only private foundation devoted exclusively to discovering the mysteries of the aging brain. Over the past two decades, the Foundation has funded more than $200 million in research specifically targeting cognitive aging and age-related cognitive decline and memory loss through direct contributions and strategic initiatives in partnership with the four McKnight Brain Institutes and the National Institute on Aging through the Foundation for the National Institutes of Health. Learn more about the Foundation at: www.mcknightbrain.org.

December 7, 2022

Contact: John Chaich
john@afar.org

The McKnight Brain Research Foundation and the American Federation for Aging Research announce Recipients of the 2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss

Emilie T. Reas (UCSD) and **Tara Tracy** (Buck Institute) receive $750,000 each to lead transformative research in the field of cognitive aging

NEW YORK and ORLANDO— The American Federation for Aging Research (AFAR) and the McKnight Brain Research Foundation (MBRF) are pleased to announce the 2022 recipients of **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss: Emilie T. Reas, PhD,** of the University of California San Diego (UCSD), and **Tara Tracy, PhD,** of the Buck Institute for Research on Aging.

Now in its second year, the Innovator Awards aim to build a cadre of outstanding research scientists across the United States to lead transformative research in the field of cognitive aging.

Emilie T. Reas, PhD, is an Assistant Professor, Neurosciences, at the University of California San Diego. With the support of this award, Dr. Reas will investigate the mediating role of blood-brain barrier dysfunction in effects of systemic inflammation on brain microstructure and memory. Dr. Reas' research program aims to optimize trajectories of brain aging by clarifying the risk factors for, and pathways towards, cognitive decline. A complementary goal is to develop more sentitive markers of early brain changes that precipitate cognitive decline in order to identify individuals at greatest risk for dementia. To this end, Dr. Reas' lab employs a multimodal approach, integrating cutting-edge brain imaging methods with behavioral testing, genetics, and fluid measures. By focusing this research on human participants without manifest cognitive impairment, Dr. Reas hopes that her research will translate directly to clinical settings for early disease detection and therapeutic intervention.

Tara Tracy, PhD, is an Assistant Professor at the Buck Institute for Research on Aging as well as an Adjunct Assistant Professor at the University of Southern California Leonard Davis School of Gerontology. With the support of this award, Dr. Tracy will investigate the role of KIBRA, a protein found in neurons that plays an important role in the normal function of synapses during the formation of new memories, in age-related memory loss. This builds on Dr. Tracy's research studying synapses, the small specialized structures that form where neurons connect with each other in the brain to transmit information. Synapses are critical for the encoding of new memories in the brain. In her ongoing research, Dr. Tracy aims to establish how the levels of KIBRA protein found in synapses can affect the susceptibility of an individual to memory loss in aging.

Dr. Reas and Dr. Tracy will each receive $750,000 for an award period of three years. The MBRF Innovator Awards in Cognitive Aging and Memory Loss are supported by a $4.5 million grant from the McKnight Brain Research Foundation and will support six investigators over a period of five years.

"The Innovator Awards in Cognitive Aging and Memory Loss are an extension of the Foundations mission to support the next generation of world-class scientists in the field of cognitive aging and memory loss," says Michael Dockery, MD, Chair of the McKnight Brain Research Foundation board of trustees. "Understanding cognitive decline as we age remains an understudied area of research, and with Dr. Reas and Dr. Tracy already showing the potential to become leaders in the field, we look forward to seeing the impact of their research in helping us better understand and alleviate the effects of age-related cognitive decline and memory loss."

AFAR has long supported the careers of talented investigators and research on cognitive health. "By providing research funding, AFAR and MRBF are building a cadre of outstanding research scientists across the United States who have the potential to lead transformative research in the field of cognitive aging," says Stephanie Lederman, EdM, Executive Director, AFAR.

Learn more about **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss** **here.**

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About AFAR
The American Federation for Aging Research (AFAR) is a national non-profit organization that supports and advances pioneering biomedical research that is revolutionizing how we live healthier and longer. For more than four decades, AFAR has served as the field's talent incubator, providing more than $193 million to nearly 4350 investigators at premier research institutions to date—and growing. In 2022, AFAR is expected to award over $11,000,000 to more than 60 investigators. A trusted leader and strategist, AFAR also works with public and private funders to steer high quality grant programs and interdisciplinary research networks. AFAR-funded researchers are finding that modifying basic cellular processes can delay—or even prevent—many chronic diseases, often at the same time. They are discovering that it is never too late—or too early—to improve health. This groundbreaking science is paving the way for innovative new therapies that promise to improve and extend our quality of life—at any age. Learn more at www.afar.org or follow AFARorg on Twitter and Facebook and American Federation for Aging Research on LinkedIn.

About the McKnight Brain Research Foundation
Founded in 1999, the McKnight Brain Research Foundation is the nation's only private foundation devoted exclusively to discovering the mysteries of the aging brain. Over the past two decades, the Foundation has funded more than $180 million in research specifically targeting cognitive aging and age-related cognitive decline and memory loss through direct contributions and strategic initiatives in partnership with the four McKnight Brain Institutes and the National Institute on Aging through the Foundation for the National Institutes of Health. Learn more about the Foundation at: www.mcknightbrain.org or follow McKnight Brain on Twitter and Facebook.

For Immediate Release:

Contact: John Chaich
john@afar.org

Inaugural Winners Selected for the 2021 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss

Lindsay De Biase (UCLA) *and* ***Saul Villeda (UCSF)*** *receive $750,000 each to lead transformative research in the field of cognitive aging*

NEW YORK and ORLANDO— The American Federation for Aging Research (AFAR) and the McKnight Brain Research Foundation (MBRF) are pleased to announce the 2021 recipients of **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss: Lindsay De Biase, PhD,** of the University of California Los Angeles (UCLA) and **Saul Villeda, PhD,** of the University of California San Francisco (UCSF).

Aiming to build a cadre of outstanding research scientists across the United States to lead transformative research in the field of cognitive aging, 2021 marked the inaugural year of the grant collaboration between AFAR and MBRF.

Lindsay De Biase, PhD is an Assistant Professor in the Department of Physiology in the David Geffen School of Medicine at UCLA. With the support of this award, Dr. De Biase will investigate the possibility that microglia shape synapse health during aging via modification of the extracellular matrix (ECM). The ECM is a meshwork of proteins and sugars woven tightly around neurons that potently regulates synapse stability. Recent studies and Dr. De Biase's preliminary data show that microglia express numerous genes involved in building up and breaking down the ECM and that they can engulf ECM components. Dr. De Biase will use multiple technical approaches to elucidate links between microglial-ECM interactions, synapse stability, and cognitive performance in aging mice and rats. The overarching goal of her research is to identify molecular pathways for therapeutic modulation of microglial-ECM interactions to preserve cognition.

Saul Villeda, PhD, is an Associate Professor in the Department of Anatomy in the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at the University of California San Francisco. With the support of this award, Dr. Villeda will investigate the rejuvenating potential of caloric restriction-induced blood factors on the aged brain at the cellular, molecular, and cognitive level. Caloric restriction counters age-related impairments in cognitive function in the aged brain. Dr. Villeda's lab and others have shown that systemic interventions, including administration of blood plasma derived from young or exercised aged animals rejuvenates cognition at old age. The rejuvenating effects of caloric restriction mirror those observed with a youthful circulation, raising the possibility that caloric restriction similarly functions through blood factors to exert its beneficial effects. The proposed studies aim to identify molecular mechanisms that can be targeted to promote cognitive rejuvenation at old age, with the potential for therapeutic implications in neurodegenerative disorders.

"I am honored to receive this support and very excited by the potential of this new line of investigation to expand our understanding of how non-neuronal cells shape cognitive aging," notes Dr. De Biase. "This new source of support from the McKnight Brain Research Foundation and AFAR allows us to launch novel lines of CNS aging

research and use cutting edge approaches to link our cellular and molecular-level findings with cognitive performance and behavior."

"This award provides a mechanism in which innovative and often times high-risk high-reward research is supported at the very early stages," states Dr. Villeda. "This new AFAR-MBRF program provides validation and encouragement to pursue areas of research in which we seek to develop therapeutics that can treat cognitive decline in the aging brain by targeting molecular mechanisms of aging in blood independent of the brain itself."

The MBRF Innovator Awards in Cognitive Aging and Memory Loss are supported by a $4.5 million grant from the McKnight Brain Research Foundation and will support six investigators over a period of five years.

"With our new Innovator Awards in Cognitive Aging and Memory Loss, MBRF is extending its mission of supporting research 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 and shown the potential to become leaders in the field," says Michael Dockery, MD, Chair of the McKnight Brain Research Foundation board of trustees. "We look forward to seeing the impact of Dr. De Biase and Dr. Villadela's research."

AFAR has long supported the careers of talented investigators and research on cognitive health. "By providing research funding, AFAR and MRBF are building a cadre of outstanding research scientists across the United States who have the potential to lead transformative research in the field of cognitive aging," says Stephanie Lederman, EdM, Executive Director, AFAR.

Learn more about **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss** **here.**

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About AFAR
The American Federation for Aging Research (AFAR) is a national non-profit organization that supports and advances pioneering biomedical research that is revolutionizing how we live healthier and longer. For four decades, AFAR has served as the field's talent incubator, providing more than $184 million to more than 4,200 investigators at premier research institutions nationwide. A trusted leader and strategist, AFAR also works with public and private funders to steer high quality grant programs and interdisciplinary research networks. AFAR-funded researchers are finding that modifying basic cellular processes can delay—or even prevent—many chronic diseases, often at the same time. They are discovering that it is never too late—or too early—to improve health. This groundbreaking science is paving the way for innovative new therapies that promise to improve and extend our quality of life—at any age. Learn more at www.afar.org or follow AFARorg on Twitter and Facebook.

About the McKnight Brain Research Foundation
Founded in 1999, the McKnight Brain Research Foundation is the nation's only private foundation devoted exclusively to discovering the mysteries of the aging brain. Over the past two decades, the Foundation has funded more than $180 million in research specifically targeting cognitive aging and age-related cognitive decline and memory loss through direct contributions and strategic initiatives in partnership with the four McKnight Brain Institutes and the National Institute on Aging through the Foundation for the National Institutes of Health, With this funding, we're supporting research and investigation to better understand and alleviate the effects of age-related cognitive decline and memory loss. Learn more about the Foundation at: www.mcknightbrain.org or follow McKnight Brain on Twitter and Facebook.

For Immediate Release:

Contact: John Chaich
john@afar.org

AFAR and the McKnight Brain Research Foundation launch new grant program in Cognitive Aging and Memory Loss

New program encourages outstanding mid-career scientists to lead transformative research in the field of cognitive aging.

NEW YORK and ORLANDO— The American Federation for Aging Research (AFAR) and the McKnight Brain Research Foundation (MBRF) are pleased to announce the launch of a new grant award program, **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss.**

The MBRF Innovator Awards in Cognitive Aging and Memory Loss are supported by a $4.5 million grant from the McKnight Brain Research Foundation and will support six investigators over a period of five years. Each year, MBRF and AFAR will provide up to two three-year awards of $250,000 annually. The total award amount of $750,000 over the three-year period will add substantial start-up support to help mid-career scientists develop and/or expand outstanding research programs in cognitive aging and memory loss.

The awards will be given in three grant cycles, in which each year, one award will be made to support studies focusing on clinical translational research and another award toward understanding basic biological mechanisms underlying cognitive aging and age-related memory loss.

"For most Americans, staying 'mentally sharp' as they age is a very high priority," said Michael Dockery, MD, Chair of the McKnight Brain Research Foundation board of trustees. "Even those not affected by Alzheimer's disease or other dementias will likely undergo cognitive changes due to the normal aging process. With the population of older adults growing rapidly in the United States and across the globe, it is critical that we support researchers dedicated to better understanding and alleviating the effects of age-related cognitive decline and memory loss."

AFAR has long supported the careers of talented investigators and research on cognitive health. "By providing research funding, AFAR and MRBF are building a cadre of outstanding research scientists across the United States who have the potential to lead transformative research in the field of cognitive aging," says Stephanie Lederman, EdM, Executive Director, AFAR.

With the new program, MBRF is extending 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 and shown the potential to become leaders in the field.

"Providing funding at the mid-career stage capitalizes on a unique opportunity to encourage leading scientists to continue embarking on independent careers that will lead to faster development of new ideas and approaches in cognitive aging research than is possible with traditional funding," notes Lederman.

"We are excited to partner with AFAR and look forward to seeing the impact of the research bolstered through the new Innovator Awards in Cognitive Aging and Memory Loss," Dockery added.

The recipients of the first award cycle will be announced by late 2021.

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About AFAR

The American Federation for Aging Research (AFAR) is a national non-profit organization that supports and advances pioneering biomedical research that is revolutionizing how we live healthier and longer. For four decades, AFAR has served as the field's talent incubator, providing more than $184 million to more than 4,200 investigators at premier research institutions nationwide. A trusted leader and strategist, AFAR also works with public and private funders to steer high quality grant programs and interdisciplinary research networks. AFAR-funded researchers are finding that modifying basic cellular processes can delay—or even prevent—many chronic diseases, often at the same time. They are discovering that it is never too late—or too early—to improve health. This groundbreaking science is paving the way for innovative new therapies that promise to improve and extend our quality of life—at any age. Learn more at www.afar.org or follow AFARorg on Twitter and Facebook.

About the McKnight Brain Research Foundation

Founded in 1999, the McKnight Brain Research Foundation is the nation's only private foundation devoted exclusively to discovering the mysteries of the aging brain. By supporting research and investigation, we're working to better understand and alleviate the effects of age-related cognitive decline and memory loss. Learn more about the Foundation at: www.mcknightbrain.org.

NEWSLETTER HIGHLIGHTS

AFAR produces a monthly e-newsletter, EncourAGE. It reaches close to 13k subscribers, comprised of members of the scientific community including grantees, donors, and general public.

AFAR has highlighted McKnight Brain Research Foundation-related news in several issues.

Please find below screen captures and hyperlinks to full issues of EncourAGE featuring McKnight Brain Research Foundation-related news:

Late June 2024:
Announcement of the McKnight Brain Research Foundation Innovator Awards Renewal

https://t.e2ma.net/webview/6hocix/b891c6f8066d2343c5e4b7d46f2fc018

The McKnight Brain Research Foundation Innovator Awards Renewed

McKNIGHT BRAIN RESEARCH FOUNDATION
Preserving memory, enhancing life

AFAR and the McKnight Brain Research Foundation (MBRF) are pleased to announce the renewal of the grant award program, **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss.**

The Innovator Awards program was launched in 2021, this year the MBRF renewed its commitment with a $4,626,500 award to AFAR to expand the network of investigators who focus their research on cognitive aging and memory loss.

Each year, MBRF and AFAR will provide up to two three-year awards of $750,000. One award will be made to support studies focusing on clinical translational research and another award will support studies understanding basic biological mechanisms underlying cognitive aging and age-related memory loss. The award targets full-time independent investigators at the rank of Assistant Professor or Associate Professor (or equivalent) who have already demonstrated a firm commitment to cognitive aging research.

Read research profiles on the past recipients here: 2023, 2022, and 2021.

Read our Grantee Spotlight Interviews with the 2023 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss here.

Read a related press release here.

December 2023:
Announcement of 2023 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss Recipients

https://t.e2ma.net/webview/6h01tv/9ece1abb57613f89d1d8c3b84c39bff4

Announcing 2023 Recipients: McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss

AFAR and the McKnight Brain Research Foundation are pleased to announce the 2023 recipients of the **Innovator Awards in Cognitivie Aging and Memory Loss**:

- **Denise Cai, PhD,** Associate Professor, the Icahn School of Medicine at Mount Sinai. Dr. Cai's funded project is titled "Memory stability and flexibility across a lifetime."
- **Christoph Thaiss, PhD,** Assistant Professor, University of Pennsylvania. Dr. Thaiss' funded project is titled "Counteracting age-associated cognitive decline via gut-brain signaling."

Now in its third year, the Innovator Awards program funds research scientists pursuing groundbreaking studies in the field of cognitive aging and memory loss. Each awardee receives $750,000 for an award period of three years.

Learn more about this AFAR grant program **here**, and read a press release about this year's awardees **here**.

McKNIGHT BRAIN RESEARCH FOUNDATION
Preserving memory, enhancing life

April 2023:
Grantee Spotlight interviews of 2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss Recipients

https://t.e2ma.net/webview/y3bnsp/51a4235e507ae46e0f7603deb90cdfb2

Grantee Spotlight Interviews


AFAR is pleased to share **Grantee Spotlight interviews** with the 2022 **McKnight Brain Research Foundation Innovator Award in Cognitive Aging and Memory Loss** recipients:

- **Emilie T. Reas, PhD**, University of California, San Diego
- **Tara Tracy, PhD**, Buck Institute for Research on Aging

In these brief interviews, the awardees explain their AFAR-supported research, inspiration to join the field, and more. **Read here.**

McKNIGHT BRAIN RESEARCH FOUNDATION
Preserving memory, enhancing life

March 2023:
Promotion of AFAR, McKnight Brain Research Foundation & Prevention Live Better Longer

https://t.e2ma.net/webview/6tpxso/dbc74033b2168b8dce58248e629e8d64

Upcoming Webinars

Our Live Better Longer webinar will be held on **Wednesday, April 26, 3-4pm ET**. 2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipients **Emilie Reas, PhD**, and **Tara Tracy, PhD** will join Prevention's Editor-in-Chief Sarah Smith to discuss **advances in brain health**. **RSVP here.**

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Prevention

McKNIGHT BRAIN RESEARCH FOUNDATION
Preserving memory, enhancing life

December 2022:
Announcement of 2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss Recipients

https://t.e2ma.net/webview/2yay9l/9e5c77e7af4299a8438a23aaa162667b

Announcing the McKnight Innovator Awards and Sagol GerOmics Award for 2022

AFAR is pleased to announce the latest 2022 grant recipients.

The **2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss** have been granted to:

- **Emilie T. Reas, PhD**, Assistant Professor, the University of California San Diego
- **Tara Tracy, PhD**, Assistant Professor, the Buck Institute for Research on Aging

Now in its second year, the Innovator Awards aim to build a cadre of outstanding research scientists across the United States to lead transformative research in the field of cognitive aging. The program provides up to two 3-year awards of $750,000 (USD) each to advanced Assistant Professors and recently appointed Associate Professors. One award will be made to support studies focusing on clinical translational research and another award toward understanding basic biological mechanisms underlying cognitive aging and age-related memory loss.

AFAR and MBRF's commitment to advancing research on cognitive aging were recently highlighted in a feature on Inside Philanthropy, available with a subscription here.

McKNIGHT BRAIN RESEARCH FOUNDATION
Preserving memory, enhancing life

March 2022:
Announcing the Inaugural Recipients of the 2021 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss

https://t.e2ma.net/webview/qlkr0e/29648d666430e074d893dc96d1f7607d

Announcing the Inaugural Recipients of the 2021 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss

AFAR and the McKnight Brain Research Foundation (MBRF) are pleased to announce the inaugural 2021 recipients of **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss: Lindsay De Biase, PhD, and Saul Villeda, PhD.**

Dr. De Biase is an Assistant Professor in the Department of Physiology in the David Geffen School of Medicine at the University of California Los Angeles. She will use her grant to investigate the possibility that microglia shape synapse health during aging via modification of the extracellular matrix (ECM). **Learn more about Dr. De Biase's research here.**

Dr. Villeda is an Associate Professor, Department of Anatomy, Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, at the University of California San Francisco. He will use his grant to investigate the rejuvenating potential of caloric restriction-induced blood factors on the aged brain at the cellular, molecular, and cognitive level. **Learn more about Dr Villeda's research here.**

This initiative is supported by a $4.5 million grant from the McKnight Brain Research Foundation and will support six investigators over a period of five years with the goal to build a cadre of outstanding research scientists across the United States to lead transformative research in the field of cognitive aging.

Read our Grantee Spotlight Interviews with the recipients here.

Learn more about this grant program here.

Read a related press release here.

McKNIGHT BRAIN RESEARCH FOUNDATION
Preserving memory, enhancing life

May 2021:
Announcing the Inaugural McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss

https://t.e2ma.net/webview/6pe6kc/f56432fb55c339882ebdd9efe73620c5

New Grant in Cognitive Aging and Memory Loss

McKNIGHT BRAIN RESEARCH FOUNDATION
Preserving memory, enhancing life

AFAR and the McKnight Brain Research Foundation (MBRF) are pleased to announce the launch of a new grant award program, **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss**. This new program will support six outstanding mid-career investigators over a period of five years, supporting studies focusing on clinical translational research and understanding basic biological mechanisms underlying cognitive aging and age-related memory loss.

Learn more about this new grant program here. Stay tuned for more information regarding program guidelines and application materials.

Website News Items

AFAR regularly reports on and/or tracks updates about McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipients as well as the MBRF/AFAR collaboration.

News items are shared on our homepage in a timely manner and then archived on our website. These items are further shared through AFAR's X, Facebook, and LinkedIn accounts.

Below, please see screen captures and hyperlinks for AFAR news and grantee news from 2021-2023.

June 24, 2024: Renewal News Item

https://www.afar.org/news/afar-and-the-mcknight-brain-research-foundation-mbrf-are-pleased-to-announce-the-renewal-of-the-mcknight-brain-research-foundation-innovator-awards-in-cognitive-aging-and-memory-loss

AFAR and the McKnight Brain Research Foundation (MBRF) are pleased to announce the renewal of the grant award program, The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss

AFAR and the McKnight Brain Research Foundation (MBRF) are pleased to announce the renewal of the grant award program, The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss.

AFAR NEWS

The Innovator Awards program was launched in 2021 with a $4,615,000 grant from the MBRF to AFAR. The successful program has supported six investigators to date, who have each received three-year awards of $750,000. This year, the MBRF renewed its commitment with a $4,626,500 award to AFAR to expand the network of investigators who focus their research on cognitive aging and memory loss.

Each year, MBRF and AFAR will provide up to two three-year awards of $750,000. One award will be made to support studies focusing on clinical translational research and another award will support studies understanding basic biological mechanisms underlying cognitive aging and age-related memory loss. The award targets full-time independent investigators at the rank of Assistant Professor or Associate Professor (or equivalent) who have already demonstrated a firm commitment to cognitive aging research.

The Innovator Awards are reviewed by an esteemed committee of leaders in cognitive aging research. The committee's recommendations will be presented to MBRF and AFAR for final funding decisions. AFAR anticipates awarding the next two recipients in September 2024. Applications are due August 12, 2024

Read research profiles on the past recipients here: 2023, 2022, and 2021.

Read our Grantee Spotlight Interviews with the 2023 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss here.

Read a related press release here.

March 21, 2024: 2022 Grantee Tara Tracy, PhD, featured in San Francisco Business Times

https://www.afar.org/news/grantee-news-2022-mcknight-brain-research-foundation-innovator-awards-in-cognitive-aging-and-memory-loss-recipient-tara-tracy-phd-selected-as-one-next-generation-of-biotech-superstars-publishes-research-on-new-strategies-for-addressing-alzheimers-an

Grantee News: 2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipient Tara Tracy, PhD featured as one "next generation of biotech superstars"; publishes research on new strategies for addressing Alzheimer's and dementia-related memory problems

On March 14, 2024, the San Francisco Business Times selected 2022 **McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss grantee** Tara Tracy, PhD in an article on the "**next generation of biotech superstars in the Bay Area**."

SAN FRANCISCO BUSINESS TIMES

JCI The Journal of Clinical Investigation

In addition to this acclaim, Dr. Tracy is the senior author of a research article recently published in the February 1st issue of **The Journal of Clinical Investigation**; the study proposes an alternate strategy for reversing the memory problems that accompany Alzheimer's disease and related dementias and builds on her **AFAR-supported research exploring** the role of KIBRA in age-related memory loss.

Read "KIBRA repairs synaptic plasticity and promotes resilience to tauopathy-related memory loss in The Journal of Clinical Investigation" **here**.

Hear more insights from Dr. Tracy in our Live Better Longer webinar "Advances in Brain Health" **here**:

February 1, 2024: Tara Tracy, PhD, published in The Journal of Clinical Investigation
https://www.jci.org/articles/view/169064

JCI The Journal of Clinical Investigation

KIBRA repairs synaptic plasticity and promotes resilience to tauopathy-related memory loss

Grant Kauwe,[1] Kristeen A. Pareja-Navarro,[1] Lei Yao,[1] Jackson H. Chen,[1] Ivy Wong,[1] Rowan Saloner,[2] Helen Cifuentes,[1] Alissa L. Nana,[2] Samah Shah,[1] Yaqiao Li,[3] David Le,[3] Salvatore Spina,[2] Lea T. Grinberg,[2,4] William W. Seeley,[2,4] Joel H. Kramer,[2] Todd C. Sacktor,[5] Birgit Schilling,[1] Li Gan,[6] Kaitlin B. Casaletto,[2] and Tara E. Tracy[1]

Authorship note: GK and KAPN contributed equally to this work.

Published February 1, 2024 - More info

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Abstract

Synaptic plasticity is obstructed by pathogenic tau in the brain, representing a key mechanism that underlies memory loss in Alzheimer's disease (AD) and related tauopathies. Here, we found that reduced levels of the memory-associated protein Kidney/BRAin (KIBRA) in the brain and increased KIBRA protein levels in cerebrospinal fluid are associated with cognitive impairment and pathological tau levels in disease. We next defined a mechanism for plasticity repair in vulnerable neurons using the C-terminus of the KIBRA protein (CT-KIBRA). We showed that CT-KIBRA restored plasticity and memory in transgenic mice expressing pathogenic human tau; however, CT-KIBRA did not alter tau levels or prevent tau-induced synapse loss. Instead, we found that CT-KIBRA stabilized the protein kinase Mζ (PKMζ) to maintain synaptic plasticity and memory despite tau-mediated pathogenesis. Thus, our results distinguished KIBRA both as a biomarker of synapse dysfunction and as the foundation for a synapse repair mechanism to reverse cognitive impairment in tauopathy.

December 11, 2023: Announcing the 2023 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipients

https://www.afar.org/news/announcing-the-2023-2023-mcknight-brain-research-foundation-innovator-awards-in-cognitive-aging-and-memory-loss-recipients

Announcing the 2023 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipients

The American Federation for Aging Research (AFAR) and the McKnight Brain Research Foundation (MBRF) are pleased to announce the 2023 recipients of **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss: Denise Cai, PhD** of Icahn School of Medicine at Mount Sinai, and **Christoph Thaiss, PhD,** of the University of Pennsylvania.

Now in its third year, the Innovator Awards aim to build a cadre of outstanding research scientists across the United States to lead transformative research in the field of cognitive aging.

Denise Cai, PhD, is an Associate Professor at the Icahn School of Medicine at Mount Sinai. Through the support of this award, Dr. Cai will research **memory stability and flexibility across a lifetime.**

Christoph Thaiss, PhD, is an Assistant Professor at the University of Pennsylvania. Through the support of this award, Dr. Thaiss will research **counteracting age-associated cognitive decline via gut-brain signaling**.

Dr. Cai and Dr. Thaiss will each receive $750,000 for an award period of three years. The MBRF Innovator Awards in Cognitive Aging and Memory Loss are supported by a $4.5 million grant from the McKnight Brain Research Foundation and will support six investigators over a period of five years.

Learn more about **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss** here.

Read a related press release on the 2023 awardees here.

November 21, 2023: Emilie Reas, PhD, Co-author publication in the Journal of Alzheimer's Disease

https://pubmed.ncbi.nlm.nih.gov/37955091/

Elevated Pure Tone Thresholds Are Associated with Altered Microstructure in Cortical Areas Related to Auditory Processing and Attentional Allocation

Linda K McEvoy [1] [2], Jaclyn Bergstrom [3], Donald J Hagler [4], David Wing [2], Emilie T Reas [5]

Affiliations + expand

PMID: 37955091 PMCID: PMC10793660 DOI: 10.3233/JAD-230767

Abstract

Background: Hearing loss is associated with cognitive decline and increased risk for Alzheimer's disease, but the basis of this association is not understood.

Objective: To determine whether hearing impairment is associated with advanced brain aging or altered microstructure in areas involved with auditory and cognitive processing.

Methods: 130 participants, (mean 76.4±7.3 years; 65% women) of the Rancho Bernardo Study of Healthy Aging had a screening audiogram in 2003-2005 and brain magnetic resonance imaging in 2014-2016. Hearing ability was defined as the average pure tone threshold (PTA) at 500, 1000, 2000, and 4000 Hz in the better-hearing ear. Brain-predicted age difference (Brain-pad) was calculated as the difference between brain-predicted age based on a validated structural imaging biomarker of brain age, and chronological age. Regional diffusion metrics in temporal and frontal cortex regions were obtained from diffusion-weighted MRIs. Linear regression analyses adjusted for age, gender, education, and health-related measures.

August 16, 2023: Saul Villeda, PhD, publication in Nature

https://www.nature.com/articles/s41467-023-39873-9

Article | Open access | Published: 16 August 2023

Platelet-derived exerkine CXCL4/platelet factor 4 rejuvenates hippocampal neurogenesis and restores cognitive function in aged mice

Odette Leiter, David Brici, Stephen J. Fletcher, Xuan Ling Hilary Yong, Jocelyn Widagdo, Nicholas Matigian, Adam B. Schroer, Gregor Bieri, Daniel G. Blackmore, Perry F. Bartlett, Victor Anggono, Saul A. Villeda & Tara L. Walker

Nature Communications **14**, Article number: 4375 (2023) | Cite this article

Abstract

The beneficial effects of physical activity on brain ageing are well recognised, with exerkines, factors that are secreted into the circulation in response to exercise, emerging as likely mediators of this response. However, the source and identity of these exerkines remain

December 7, 2022: Announcing the 2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipients

https://www.afar.org/news/announcing-the-2022-mcknight-brain-research-foundation-innovator-awards-in-cognitive-aging-and-memory-loss-recipients

Announcing the 2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss Recipients

AFAR and the McKnight Brain Research Foundation (MBRF) are pleased to announce the 2022 recipients of The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss:

- Emilie T. Reas, PhD, Assistant Professor, the University of California San Diego
- Tara Tracy, PhD, Assistant Professor, the Buck Institute for Research on Aging

Now in its second year, the Innovator Awards aim to build a cadre of outstanding research scientists across the United States to lead transformative research in the field of cognitive aging. The program provides up to two 3-year awards of $750,000 (USD) each to advanced Assistant Professors and recently appointed Associate Professors. One award will be made to support studies focusing on clinical translational research and another award toward understanding basic biological mechanisms underlying cognitive aging and age-related memory loss.

Learn more about the research Dr. Reas will advance with the support of this award here:

Learn more about the research Dr. Tracu will advance with the support of this award here:

Read a related press release here.

In addition, AFAR and MBRF's commitment to advancing research on cognitive aging were recently highlighted in a feature on Inside Philanthropy. Read with a subscription here.

March 7, 2022: Announcing the Inaugural Recipients of the 2021 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss

https://www.afar.org/news/announcing-the-inaugural-recipients-of-the-2021-mcknight-brain-research-foundation-innovator-awards-in-cognitive-aging-and-memory-loss

Announcing the Inaugural Recipients of the 2021 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss

AFAR and the McKnight Brain Research Foundation (MBRF) are pleased to announce the inaugural 2021 recipients of **The McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss: Lindsay De Biase, PhD,** and **Saul Villeda, PhD.**

Dr. De Biase is an Assistant Professor in the Department of Physiology in the David Geffen School of Medicine at the University of California Los Angeles. She will use her grant to investigate the possibility that microglia shape synapse health during aging via modification of the extracellular matrix (ECM).

Dr. Villeda is an Associate Professor, Department of Anatomy, Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, at the University of California San Francisco. He will use his grant to investigate the rejuvenating potential of caloric restriction-induced blood factors on the aged brain at the cellular, molecular, and cognitive level.

This grant is supported by a $4.5 million grant from the McKnight Brain Research Foundation and will support six investigators over a period of five years with the goal to build a cadre of outstanding research scientists across the United States to lead transformative research in the field of cognitive aging.

Learn more about the research that Dr. De Biase and Dr. Villeda will pursue with this award here.

Read our Grantee Spotlight Interviews with the recipients here.

Learn more about this grant program here.

Read a related press release here.

afar american federation for aging research

McKNIGHT BRAIN RESEARCH FOUNDATION
Preserving memory, enhancing life

News on Social Media

AFAR has created original content to announce news of McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipients as well as the MBRF/AFAR collaboration from 2021-2023.

These posts reach nearly 5.7k followers on X/Twitter, 3.4k followers on Facebook, and 2.8K followers on LinkedIn. Please find below a sampling. For archives and updates, follow AFAR on X, Facebook, and LinkedIn.

https://www.linkedin.com/posts/american-federation-for-aging-research_afar-and-the-mcknight-brain-research-foundation-activity-7211458616883642370-0hmm?utm_source=share&utm_medium=member_desktop

American Federation for Aging Research
Published by Hootsuite
· March 25 ·

On March 14, 2024, the San Francisco Business Times featured 2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss grantee Tara Tracy, PhD in a feature on the "next generation of biotech superstars in the Bay Area."
https://ow.ly/eU1C50QYNob
In addition to this acclaim, Dr. Tracy is the senior author of a research article recently published in the February 1st issue of the Journal of Clinical Investigation; the study proposes an alternate strategy for reversing the memory problems that accompany Alzheimer's disease and related dementias and builds on her AFAR-supported research exploring the role of KIBRA in age-related memory loss. Read more here: https://ow.ly/5bNG50QYN78

https://www.facebook.com/share/p/FT7JiBYKxrGAwJSy/

American Federation for Aging Research
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One month away! Join AFAR, Prevention, and McKnight Brain Research Foundation for "Advances in Brain Health"--the latest in our Live Better Longer webinar series. Free on Wednesday, April 26, 3-4pm ET. Featuring AFAR grantees Emilie T. Reas, PhD, and Tara Tracy, PhD, in conversation with Prevention's Editor in Chief, Sarah Smith. Learn more and RSVP: https://bit.ly/40pwGpF #cognition #alzheimers #brain #healthspan #aging #research Buck Institute for Research on Aging UC San Diego

https://www.linkedin.com/posts/american-federation-for-aging-research_cognition-alzheimers-brain-activity-7046844087370469376-QqQr?utm_source=share&utm_medium=member_desktop

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Two weeks away! Join AFAR, Prevention, and McKnight Brain Research Foundation for "Advances in Brain Health"--the latest in our Live Better Longer webinar series. Free on Wednesday, April 26, 3-4pm ET. Featuring AFAR grantees Emilie T. Reas, PhD, and Tara Tracy, PhD, in conversation with Prevention's Editor in Chief, Sarah Smith. Learn more and RSVP: https://bit.ly/40pwGpF
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Excited to hear from AFAR grantee Tara Tracy, PhD on Wednesday, April 26 from 3-4pm ET during "Advances in Brain Health," part of our Live Better Longer webinar series. Hosted by AFAR and Prevention with the McKnight Brain Research Foundation. Dr. Tracy is the recipient of the 2022 McKnight Brain Research Foundation Innovator Award in Cognitive Aging and Memory Loss, an AFAR grant program. Join us for this free, conversational webinar. Learn more and RSVP: https://bit.ly/40pwGpF
#cognition #alz #brain #healthspan #aging #research Buck Institute for Research on Aging

https://www.linkedin.com/posts/american-federation-for-aging-research_cognition-alz-brain-activity-7052279991341867009-Czyp?utm_source=share&utm_medium=member_desktop

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#cognition #alz #brain #healthspan #aging #research

https://www.linkedin.com/posts/american-federation-for-aging-research_cognition-alz-brain-activity-7051555274335117312-gC_1?utm_source=share&utm_medium=member_desktop

Grantee Institutions Reporting

AFAR works with the communications offices of each grantee's institutions to encourage them to share news of their researcher's award through their communications channels such as websites, newsletters, and social media.

Please find below screen captures and links to reporting from institutions of several recipients in the first and second cohorts of the McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipients to date.

February 1, 2024: Buck Institute News Item on Tara Tracy, PhD, Publication

https://www.buckinstitute.org/news/buck-scientists-discover-a-potential-way-to-repair-synapses-damaged-in-alzheimers-disease/

by Buck Institute

FEBRUARY 1, 2024 , NEWS

Buck Scientists Discover a Potential Way to Repair Synapses Damaged in Alzheimer's Disease

Dr. Tara Tracy

While newly approved drugs for Alzheimer's show some promise for slowing the memory-robbing disease, the current treatments fall far short of being effective at regaining memory. What is needed are more treatment options targeted to restore memory, said Buck Assistant Professor Tara Tracy, PhD, the senior author of a study that proposes an alternate strategy for reversing the memory problems that accompany Alzheimer's disease and related dementias.

Since most current research on potential treatments for Alzheimer's focuses on reducing the toxic proteins, such as tau and amyloid beta, that accumulate in the brain as the disease progresses, the team veered away from this route to explore an alternative. "Rather than trying to reduce toxic proteins in the brain, we are trying to reverse the damage caused by Alzheimer's disease to restore memory," said Tracy. The findings appear in the February 1 issue of *The Journal of Clinical Investigation*.

The work hinges on a protein called KIBRA, named because it is found in the kidney and the brain. In the brain, it is primarily localized at the synapses, which are the connections between neurons that allow memories to be formed and recalled. Research has shown that KIBRA is required for synapses to form memories, and Tracy's team has found that brains with Alzheimer's disease are deficient in KIBRA.

"We wondered how the lower levels of KIBRA affected signaling at the synapse, and whether understanding that mechanism better could yield some insight into how to repair the synapses damaged during the course of Alzheimer's disease," said Buck Staff Scientist Grant Kauwe, PhD, co-first author of the study. "What we identified is a mechanism that could be targeted to repair synaptic function, and we are now trying to develop a therapy based on this work."

The team first measured the levels of KIBRA in the cerebrospinal fluid of humans. They found that higher levels of KIBRA in the cerebrospinal fluid, but lower levels in the brain, corresponded to the severity of dementia.

November 21, 2023: UC San Diego News Item on Emilie Reas, PhD, Publication in the Journal of Alzheimer's Disease

https://today.ucsd.edu/story/hearing-loss-is-associated-with-subtle-changes-in-the-brain

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Hearing Loss is Associated with Subtle Changes in the Brain

Increased dementia risk associated with hearing impairment may come from compensatory brain changes

Researchers are trying to understand the association between hearing loss and increased risk of dementia. Photo credit: iStock/image_jungle

August 16, 2023: UCSF Press Release on Saul Villeda, PhD, publication in Nature
https://www.eurekalert.org/news-releases/998560

NEWS RELEASE 16-AUG-2023

Blood factor can turn back time in the aging brain

Peer-Reviewed Publication

UNIVERSITY OF CALIFORNIA - SAN FRANCISCO

Blood Factor Can Turn Back Time in the Aging Brain

Platelets are behind the cognitive benefits of young blood, exercise and the longevity hormone klotho

In a remarkable convergence, scientists have discovered that the same blood factor is responsible for the cognitive enhancement that results from young blood transfusion, the longevity hormone klotho, and exercise.

In a trio of papers appearing in *Nature*, *Nature Aging* and *Nature Communications* on August 16, 2023, two UCSF teams and a team from the University of Queensland (Australia), identify platelet factor 4 (PF4) as a common messenger of each of these interventions.

As its name suggests, PF4 is made by platelets, a type of blood cell that alerts the immune system when there is a wound and helps to form clots. It turns out that PF4 is also a cognitive enhancer. Under its influence, old mice recover the sharpness of middle age and young mice get smarter.

"Young blood, klotho, and exercise can somehow tell your brain, "Hey, improve your function," said Saul Villeda, PhD, associate director of the UCSF Bakar Aging Research Institute and the senior author on the *Nature* paper. "With PF4, we're starting to understand the vocabulary behind this rejuvenation."

Villeda led the study on young blood, which was published in *Nature*. Dena Dubal, MD, PhD, UCSF professor and David A. Coulter Endowed Chair in Aging and Neurodegenerative Disease, led the study on klotho, which was published in *Nature Aging*. Tara Walker, PhD, professor of neuroscience at the University of Queensland, led the study on exercise, which was published in *Nature Communications*.

May 15, 2023: UCSF News Item on Saul Villeda, PhD, the 2023 Byers Award recipient

https://www.ucsf.edu/news/2023/05/425361/does-exercise-rejuvenate-blood-improve-cognitive-function

Campus News • May 15, 2023

Does Exercise Rejuvenate Blood, Improve Cognitive Function?

Saul Villeda Delivers 2023 Byers Award Lecture on Reversing Aging's Effects on the Brain

By Ariel Bleicher

We've all been there. You walk out of the office after a long workday, look out over a sea of cars, and wonder, "Now where the heck did I park?"

When you're young, remembering comes easy. "Oh, yeah," you quickly deduce, "over there, by that coffee cart, where I bought a cappuccino and a blueberry muffin." But as you get older, your recall gets slower and less certain. More and more, you find yourself wandering aimlessly while clicking the unlock button on your key fob in hopes of hearing your car's familiar beep.

"That's your brain on aging," neuroscientist **Saul Villeda**, PhD, said during an honorary lecture about his work as the 2023 Byers Award recipient. He delivered the talk, titled "Blood Work and the Brain: Deciphering the Language of Cognitive Rejuvenation," on April 24.

April 4, 2023: Scientist Spotlight: Tara Tracy, PhD

https://www.buckinstitute.org/blog/scientist-spotlight-tara-tracy/

Scientist Spotlight: Tara Tracy, PhD

Turning obstacles into opportunities

Tell Buck assistant professor Tara Tracy, PhD, that she can't do something and it will only make her work harder to prove you wrong. This quality has served her well in her choices for her career path, in her research pursuits and in spearheading an initiative to support women in science.

A pivotal moment that pointed her toward a science career was ironically not a success but a missed opportunity. She still vividly remembers from her freshman year of high school a competitive internship at Rockefeller University, a welcome respite from her underfunded and overcrowded New York City public school. She did not get the internship.

"I felt like it was the golden ticket to go where they have the best science in the world," she says. "I will always remember that feeling of missing out." The sting of that rejection served as an early source of motivation. "If something bad happens, or somebody tells me I can't do something, it just makes me want to work harder," she says. "That is how I have acted throughout my career."

Despite not having many science resources in her high school, Tracy was always drawn to the field of biology, specifically how the brain works. After graduating with a Neuroscience and Behavior major from Wesleyan University, she earned her PhD at UC Berkeley. There she studied a wide range of topics in neuroscience, focusing on how synapses develop at the molecular level.

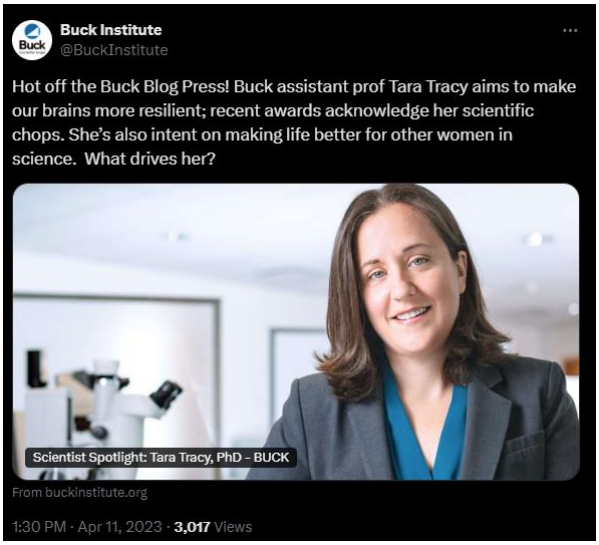
She decided to do something really different from her basic research in neurobiology for her postdoctoral training. She focused on human neurological diseases during a fellowship at the Gladstone Institute of Neurological Disease and UC San Francisco, studying Alzheimer's disease. "What is funny is that at that time, it felt like a hurdle to cross to change like that," she says. "But I did it anyway and it turned out OK."

Tracy's success at a less traditional career pathway spurred her yet again to pursue a different direction for a faculty position, to focus on aging at the Buck, joining in 2018.

"Alzheimer's research runs in parallel with aging research," she says. "There is obviously overlap between them, but only recently has there been more integration of the fields." Researchers, such as Tracy and others at the Buck, help to bridge the disciplines. "It has been really cool to be a part of integrating these fields," she says.

Tracy carries the same resolve in her career decisions to her research projects. "If somebody tells me a project won't work, often I will do it anyway," she says. "I love the challenge. I get so driven by that way of thinking."

The risks appear to have paid off. She currently combines her foundation in both basic and translational neuroscience to explore what happens in neurological disease processes, especially Alzheimer's disease, aiming to repair the damage and restore memory. For her work, Tracy won one of the two 2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss.



April 4, 2022: UCLA News Item Announcing Award

https://newsroom.ucla.edu/dept/faculty/de-biase-2021-mcknight-brain-research-foundation-award

FACULTY BULLETIN BOARD

Lindsay De Biase honored by McKnight Brain Research Foundation

Louise Kim
April 4, 2022

Share

Lindsay De Biase has been awarded a 2021 McKnight Brain Research Foundation Innovator Award in Cognitive Aging and Memory Loss. She is one of two scientists who will each receive $750,000 to lead transformative research in the field of cognitive aging.

De Biase is an assistant professor in the departments of physiology and neurobiology at the David Geffen School of Medicine at UCLA. Her research interests include the causes and effects of microglial regional specialization within basal ganglia circuits.

The grant will allow De Biase to study whether microglia shape synapse health during aging due to changes in the extracellular matrix — a network of proteins and sugars woven around neurons that regulates synapse stability. Recent studies show that microglia express numerous genes involved in building up and breaking down the extracellular matrix and that they can overwhelm those components.

De Biase will search for links between the microglial and extracellular matrix interactions, synapse stability, and cognitive performance in aging mice and rats. Her overalll goal is to find ways to preserve cognition.

UCLA

Lindsay De Biase

Media Contact

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DSampson@mednet.ucla.edu

Webinar

AFAR and **Prevention Magazine** host a regular conversation series, Live Better Longer. AFAR experts join Editors from Prevention to discuss the research-backed science driving wellness choices and innovative therapeutics to extend our years of health at any age.

The webinars attract both Prevention subscribers and AFAR supporters; an average of 400 attend. The webinars are promoted on AFAR social media and e-blasts, and recordings are shared via email with RSVPs, on AFAR social media, and archived on the AFAR website.

The 2022 McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss recipients, **Emilie T. Reas, PhD**, and **Tara Tracy, PhD**, shared insights in a Live Better Longer webinar on April 26, 2023, titled "Advances in Brain Health."

Please find below a linked recording:

https://vimeo.com/823097577

The webinar is archived on AFAR's website here.

SCIENTIFIC PRESENTATIONS

Since our last progress report, Dr. Daniel Gray, the lead postdoctoral fellow contributing to this research presented posters with study findings at the Glial Biology Gordon Conference (Ventura, CA, March 2023), the Neuroimmune Interactions Keystone Symposium (Whistler, BC, Canada, May 2023) and the Society for Neuroscience (SFN) Annual Meeting (Washington, DC, November 2023). Postbaccalaureate fellow Abigail Gutierrez (former undergraduate researcher in our lab) presented study findings at the UCLA Brain Research Institute Annual Neuroscience Poster Day (November 2023). I gave talks that included portions of our research from this study at the Glial Biology Gordon Conference (Ventura, CA, March 2023), the Parkinson's Gordon Conference (Les Diablerets, Switzerland, May 2023) and Neuroscience Seminars at University of Cincinnati (February 2023), NIA/NIDA Intramural Research Programs (April 2023), Brown University (April 2023), and University of Lausanne (May 2023).

TRAINING

Daniel has become extremely well versed in working with mice and, as will be evident in data described below, has successfully implemented very nuanced behavioral paradigms to tease out early stages of cognitive decline in late middle-aged mice. In addition, Daniel has built impressive expertise in analyzing complex proteomics data sets. Finally, he has greatly expanded his imaging repertoire, carrying out high resolution imaging with top-of-the-line Zeiss, Olympus, and Leica microscopes. He has expanded his image analysis capabilities in FIJI, Imaris, via custom scripts in MatLab for assessment of live imaging videos of microglial cell process movements. Building these skills is an impressive feat for a scientist who had largely been working with macaques carrying out *in vivo* electrophysiology. As a key part of Daniel's training, he is applying for career transition grants that will hopefully support final phases of his postdoctoral research and enhance his competitiveness on the job market in 1-2 years' time. Daniel has been fully independent in generating the ideas and first drafts of these grants, and only subsequently receiving my input and suggestions. Undergraduate students Claribel Charway and Abigail Gutierrez, who were contributing to this project under Daniel's guidance, completed their undergraduate training. Claribel successfully transitioned to gap year research at Columbia University in pursuit of her goal of future admission to MD/PhD programs. Abigail Gutierrez, has continued working in our lab as a postbaccalaureate fellow/research technician in pursuit of her goal of future admission to MD/PhD programs. Daniel has begun mentoring two new undergraduate researchers, Mia Donato and Aitana Allen-Perez, and has continued to show an excellent ability to help his team of undergraduate students establish a foundational experimental and critical reasoning skills and foster their independence and interest in pursuing additional training in research.

AWARDS

Dr. Gray received the 2023 Boyer/Parvin Postdoctoral Research Award from the UCLA Molecular Biology Institute for his work on this project and presented a seminar on his research to the UCLA community. This award also included $4000 in travel funds that supported his presentation at SFN. This award was also strong validation that Daniel has built a potent suite of molecular biology skills to complement his previous training and expertise in analysis of cognitive aging in non-human primates. We also received an NIH R01 diversity supplement to support postbaccalaureate training for Abigail Gutierrez (former undergraduate researcher in our lab).

SCIENTIFIC PROGRESS

For the most recent funding period, we would like to highlight the following progress:

1) Unbiased proteomic analysis of changes in ECM composition during aging (relevant to Aim 3). As described in our previous progress report, we generated what, to our knowledge, is the first proteomic mapping of ECM composition in multiple brain regions during aging. We have now completed analysis of all samples and continue to find key changes in ECM proteoglycans with aging that were more prominent in the midbrain compared to striatum (**Fig. 1**). In particular, hyaluronan binding proteins (HAPLN1-4), which anchor glycoproteins and proteoglycans to hyaluronan scaffolds, were increased in the midbrain with aging. We have also leveraged weighted gene correlation network analysis (WGCNA) and downstream pathway analysis (Metascape) to understand how the status of matrix proteins relates to the overall tissue proteome in each brain region (**Fig. 2**). This analysis revealed two gene modules (yellow and brown) that were strongly

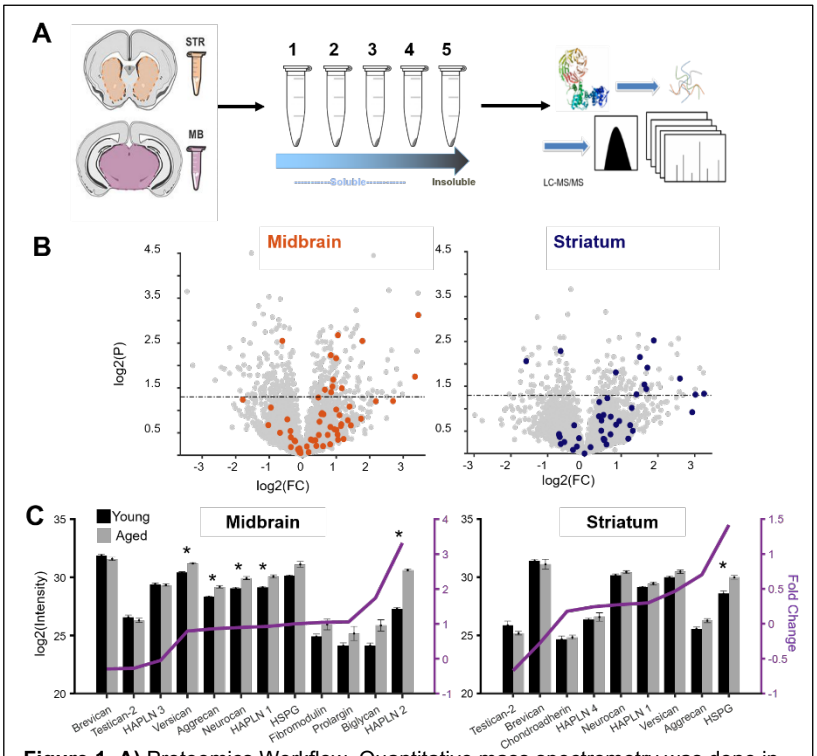


Figure 1. A) Proteomics Workflow. Quantitative mass spectrometry was done in collaboration with the UCLA Proteomic Research center. **B)** Volcano plots of midbrain and striatum samples. Core matrisome proteins are denoted in orange/blue. **C)** Age comparisons of log-normalized intensity values of ECM proteoglycans in the midbrain and striatum (black axis), and the fold change of these comparison (purple axis). * $p < 0.05$

associated with status of hyaluronan binding proteins and other proteoglycans. Expression patterns of genes in this module were also tightly related to brain region. Separate gene modules (blue and cyan) were not aligned with brain region but were linked to status of immune function genes such as members of the complement cascade. Interestingly, the status of numerous synapse relevant genes was strongly aligned with the yellow and brown modules, not the blue and cyan modules. This indicates that the local status of synaptic proteins is more strongly associated with local status of ECM components and not local status of complement proteins. This is a key observation because the complement cascade has been implicated in declining synaptic integrity and microglial phagocytic removal of synapses in numerous contexts.

We have also analyzed the status of ECM collagens and found that collagens are more abundant in the midbrain compared to striatum and several collagens increased with aging (*not shown*). Analysis of glycoproteins, revealed that laminins were initially found at lower levels in the striatum, but were more significantly increased during aging compared to the midbrain (*not shown*). **Together with histological analyses described in the previous progress report showing that hyaluronan networks undergo larger age-associated changes in the VTA compared to the NAc, and that microglial contact with hyaluronan networks changes during aging, these data support the idea that there are critical differences in the ECM and glial-ECM interactions across brain regions that are important for synapse integrity.**

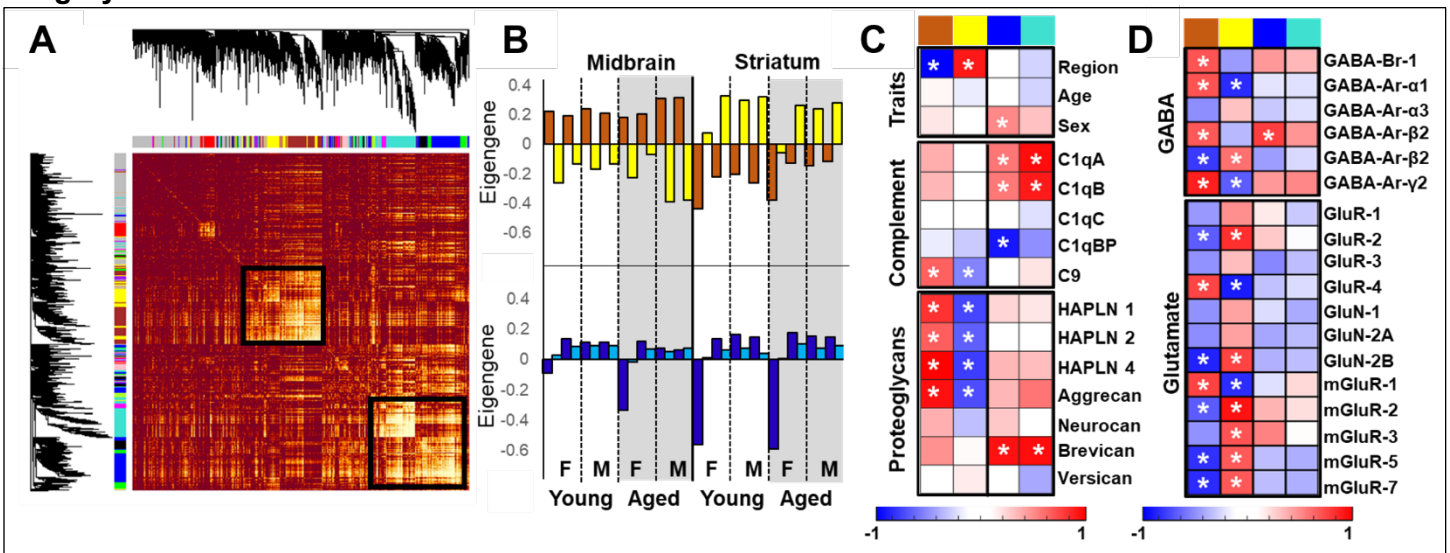


Figure 2. A) Weighted Gene Coexpression Network Analysis (WGCNA) topological overlap matrix. Black boxes denote brown/yellow and blue/turquoise protein modules. **B)** Eigengene values of brown/yellow and blue/turquoise modules for each animal. **C)** Module-trait relationships between brown/yellow and blue/turquoise modules suggests that ECM proteoglycan abundance is associated with the brown/yellow module. **D)** GABA and glutamate receptor abundance was also associated with the brown/yellow module. * $p < 0.05$

In future experiments, we will use this workflow to carry out proteomic mapping of the ECM and synapse integrity in behaviorally-characterized aging mice.

2) Manipulation of microglia and hyaluronan networks to reveal how microglia-ECM interactions impact synapses (relevant to Aims 2 and 3). Using immunostaining for Homer2 as well as hyaluronan scaffolds, we found that hyaluronan is frequently associated with homer 2, particularly near to proximal dendrites and somas of dopamine neurons (**Fig. 3**). **This supports the idea that there are key interactions between the ECM and synapses in these brain regions and that the local status of the matrix during aging will impact synapse function.** Quantification of these ECM-hyaluronan interactions in multiple brain regions in young and aging mice is ongoing. For transgenic manipulation of microglia, we are currently using *CSFR1*$^{\Delta FIRE/\Delta FIRE}$ mice, which lack microglia, and *CX3CR1*$^{EGFP/EGFP}$ mice, which lack the microglial fractalkine receptor. Data from our lab show that *CSFR1*$^{\Delta FIRE/\Delta FIRE}$ mice have deficits in developmental synaptogenesis and we and others have observed behavioral deficits in these mice. However, the status of the ECM and its relation to circuit function has not been analyzed in these mice. Knockout of the microglial fractalkine receptor (CX3CR1) has been associated with deficits in synaptic plasticity but status of the ECM and its relation to circuit function has not been analyzed in these mice. We have almost completed imaging and analysis of tissue from these mice and are quantifying the status of hyaluronan networks, hyaluronan-synapse interactions, and the overall status of synaptic integrity in multiple brain regions. For manipulation of the hyaluronan scaffolds we are using the compound 4-methylumbelliferone (4-MU) to deplete hyaluronan scaffolds from the brain, as described in our previous progress report. This compound is quite bitter and we did not have success in delivering it to mice in the normal chow. We eventually found that mice will consume the compound mixed with small quantities of peanut butter and that a 6 week exposure to the compound significantly depletes hyaluronan scaffolds from the brain (**Fig. 4**). In tissue from 4MU-treated and control mice, we are quantifying the impact of disrupting hyaluronan scaffolds on microglial morphology, microglial-synapse interactions, and overall synapse integrity. Future experiments will determine the impact of 4MU treatment on microglial cell process motility, gene expression, and behavior in young and aging mice.

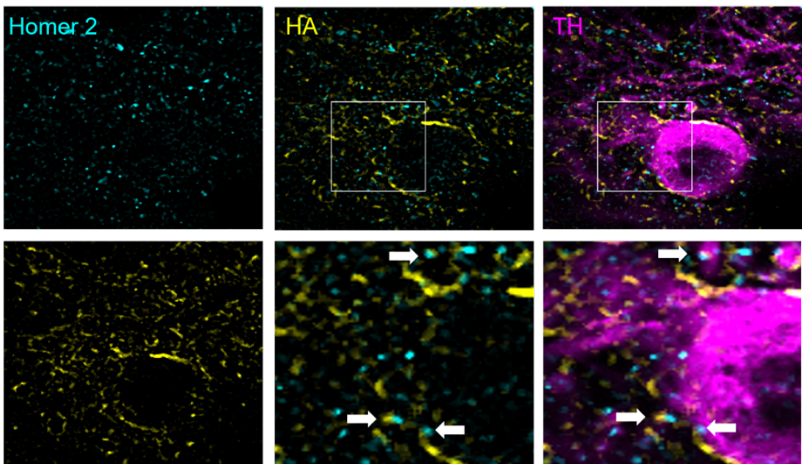


Figure 3. Immunostaining for synaptic marker Homer 2 and hyaluronan scaffolds (HA). *White arrows* highlight colocalizations of Homer 2 and hyaluronan that are frequently observed in close proximity to the surface of dopamine neurons, labeled via staining for tyrosine hydroxylase (TH).

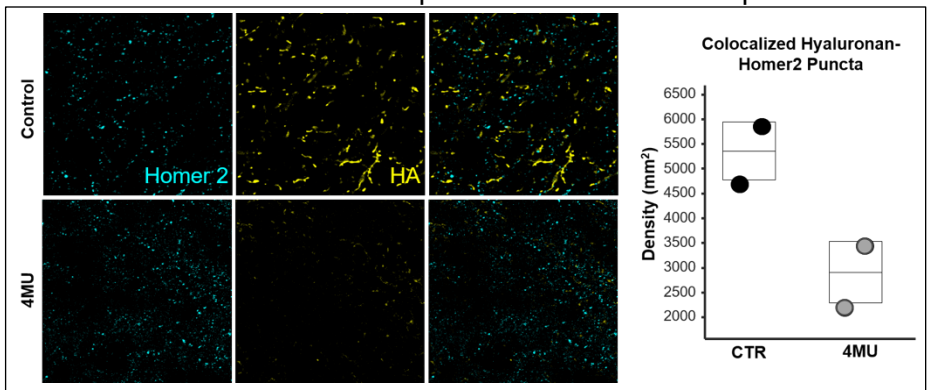


Figure 4. High magnification confocal images showing depletion of hyaluronan scaffolds in VTA following 6 weeks treatment with 4MU. Initial quantification indicates a substantial decrease in Homer 2 labeled synapses colocalized with hyaluronan, suggesting that these synapses may now be more labile.

3) Assessment of spatial and reward-based learning in young adult and aging mice (relevant to Aims 2 and 3). We have now moved six full cohorts of young and aged mice through our learning paradigm, described in our original proposal and in further detail in our 2022 progress report. Addition of data from larger numbers of mice has confirmed that young (3-5mo) and late middle aged (16-18mo) mice learn the behavior similarly (**Fig. 5**) and that late middle-aged mice exhibit deficits in performance with longer delays between encoding and retrieval portions of the behavior. For each cohort of mice run through this behavioral paradigm, we continue to include and analyze sedentary controls - young and old mice that remained in their home cages within the vivarium for the time it takes their behavior counterparts to complete the behavior paradigm. An additional component of the experiment design that we have incorporated is to euthanize 50% of the mice that undergo behavioral training 90min after the final behavioral session and 50% of the mice 48hrs following the final behavioral session. This has enabled cFOS staining to reveal behaviorally-induced patterns of neuronal

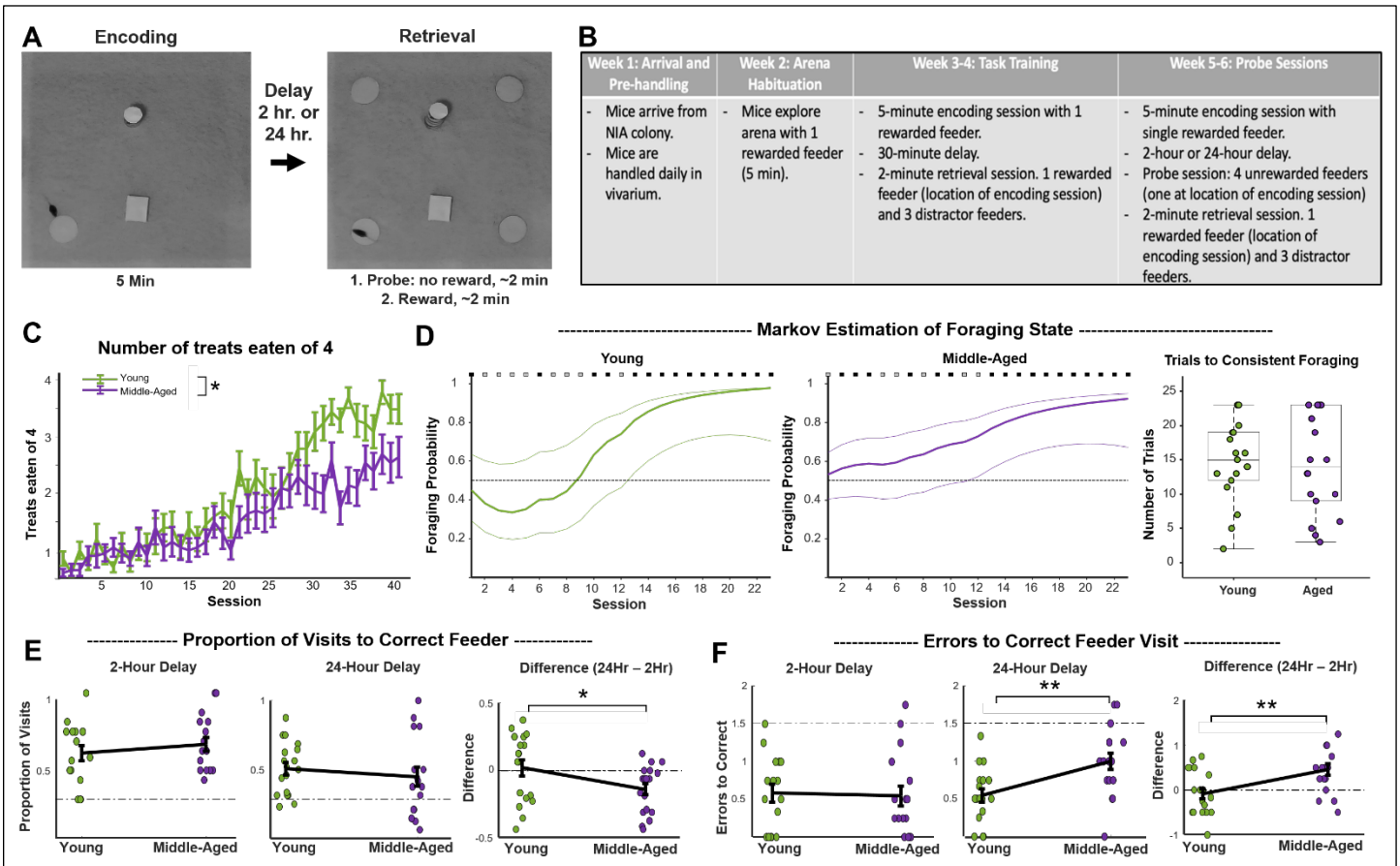


Figure 5. A) Schematic of foraging-based spatial reference memory task. **B)** Table depicting the behavioral testing paradigm. **C)** Number of treats eaten out of 4 across sessions for young (3-5 months; green) and late middle-aged (16-18 months; purple) mice. **D)** Representative learning curves from hidden-Markov modelling estimation of the animal's foraging status (left, middle). The number of trials to consistent foraging behavior was not different between young and middle-aged mice (right). **E)** Proportion of visits to correct feeder and **F)** number of errors before visiting the correct feeder during probe trials following a 2 or 24 hour delay. The right panel in **E** and **F** depict difference measures (24 Hr. - 2 Hr.). * $p < 0.05$, ** $p < 0.01$

activation in well-trained mice (*not shown*). It will also allow future analysis of the relationship between neuronal activation and local ECM/synapse status. In addition to analyzing reward-based learning and memory, we are extracting information (*not shown*) about anxiety-like trends (amount of time spent in the arena periphery vs. center) and potential indicators of cognitive flexibility (number of errors that involve going to the location that was rewarded in the behavior session immediately prior). **Successful implementation of this behavioral paradigm positions us as one of few labs in the world equipped to reveal the relationship between molecular status of the glia-ECM-synapses and preservation or decline of cognition during aging.**

4) Relationship between behavioral performance and ECM (relevant to Aims 2 and 3). In tissue collected from behaviorally-characterized mice, we have carried out immunostaining, high magnification confocal imaging, and analysis of hyaluronan networks in multiple brain regions (**Fig. 6**). This analysis revealed that, in the VTA, there was a trend toward increased density of hyaluronan fibrils in middle-aged sedentary mice.

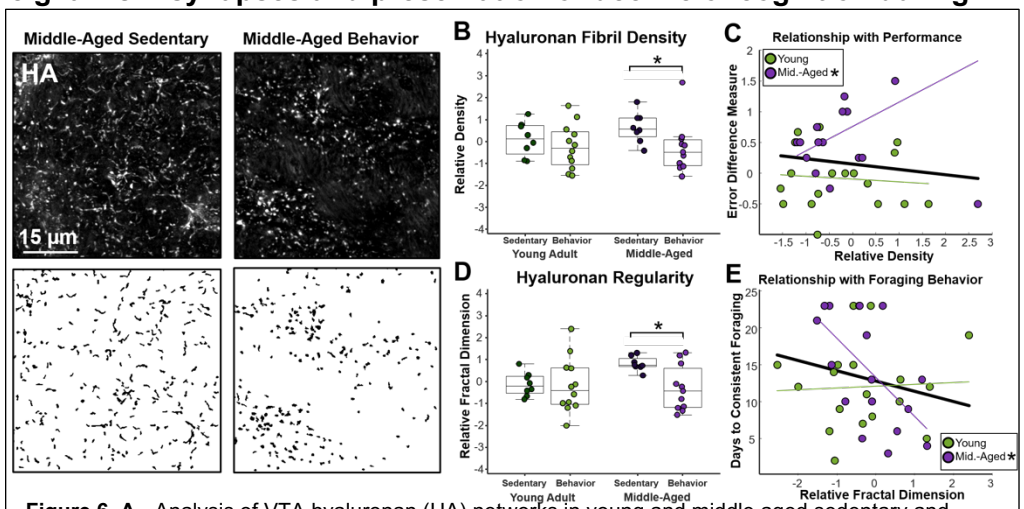


Figure 6. A - Analysis of VTA hyaluronan (HA) networks in young and middle aged sedentary and behavior-trained mice. **B,C** – reduced HA fibril density is associated with better behavioral performance in middle aged mice. **D,E** – more regular HA tissue distribution is associated with better behavioral performance in middle aged mice.

However, middle-aged mice that underwent behavioral training showed significantly reduced hyaluronan fibril density, with levels similar to those of young mice that underwent behavioral training. Middle-aged sedentary mice also showed trends toward loss of the regularity of hyaluronan distribution in the tissue, something that was not observed in the middle-aged behavior mice. Finally, in young mice that underwent behavior training, there was no clear correlation between status of hyaluronan networks and behavioral performance. In middle-aged mice, however, higher density of hyaluronan fibrils or loss of hyaluronan tissue distribution (as was observed in the sedentary mice) was correlated with worse behavioral performance. **These findings show for the first time that status of VTA hyaluronan networks is linked to reward-based learning and behavior in middle-aged mice. They also raise several intriguing possibilities. 1) They suggest that behavioral engagement itself can modify some ECM changes that begin to emerge with age in sedentary mice. 3) They suggest that, while ECM status may be less essential for optimal cognition in young mice, aging mice that maintain or re-establish a youthful ECM state perform the best. In other words, ECM status may enable middle-aged mice to continue performing well cognitively, even in the face of all the other cellular and molecular changes in the aging CNS. This would make ECM status a critical substrate of cognitive reserve or resilience.** Analysis of hyaluronan networks in additional brain regions, including critical downstream projection regions from the VTA is ongoing.

5) Relationship between behavioral performance and ECM (relevant to Aims 2 and 3). In tissue collected from behaviorally-characterized mice, we have carried out immunostaining, high magnification confocal imaging, and analysis of microglial density and morphology in multiple brain regions (**Fig. 7**). This analysis revealed significant increases in the territory and ramification of VTA microglia in young behaviorally-trained mice compared to young sedentary controls. Importantly, these changes were evident when mice were euthanized 90min following the final behavior session, but not when they were euthanized 48hrs after the final behavioral session. **This indicates that these changes in VTA microglial morphology are dynamic and transient changes associated with behavior.** In middle-aged mice, no differences in microglial territory or ramification were observed between sedentary and behaviorally-trained mice, regardless of euthanasia time. **This suggests that behaviorally driven microglial remodeling is lost as mice age.** In general, VTA microglial density was elevated in middle-aged compared to young mice, consistent with previous findings in the lab. Surprisingly, there were hints of increased microglial density in behaviorally-trained middle-aged mice compared to sedentary middle-aged mice, although these differences were not maintained if mice were euthanized 48hrs following the final behavioral session. **This raises the possibility that some degree of microglial turnover occurs with behavioral engagement.** Analyses to link these metrics of microglial morphology and density with behavioral

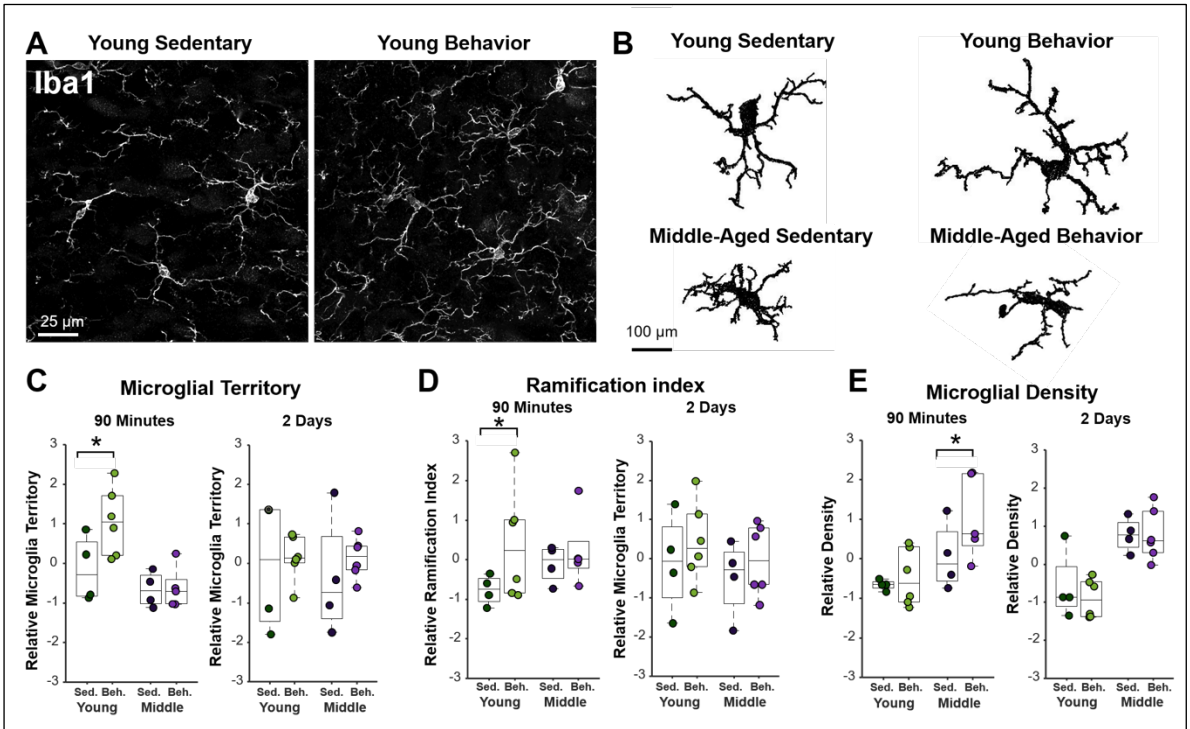


Figure 8. A,B – Immunostaining of VTA microglia and reconstruction of microglial morphologies in sedentary and behaviorally trained mice. **C-E** – features of microglial morphology and density in relation to age, behavioral status, and time of euthanasia.

performance are ongoing. Analysis of microglial morphology and density in additional brain regions is also ongoing.

EXPERIMENTAL GOALS FOR THE NEXT FUNDING PERIOD

- We will complete analyses of hyaluronan networks / microglial attributes / synapse status in multiple brain regions from tissue already collected from behaviorally-characterized mice.
- We will carry out spatial transcriptomic analysis of tissue already collected from behaviorally characterized mice.
- We will run additional cohorts of mice through behavior to collect tissue for proteomic analysis.
- We will carry out behavior on 4MU treated mice that have had depletion of hyaluronan networks as well as *CSFR1*$^{\Delta FIRE/\Delta FIRE}$ mice and *CX3CR1*$^{EGFP/EGFP}$ mice.

PLANS FOR ADDITIONAL FUNDING

I have submitted several disease foundation LOIs to seek support for the future directions of this research. I will also apply for a Larry Hillblom Network Grant (Jan 2024), together with collaborators, to explore the relationship of gait and changes in cognition. In particular, we would hope to test the hypothesis that glial-ECM interactions are essential cellular and molecular players that determine gait-cognition links during aging. We anticipate preparing and submitting an NIH R01 with data from this study serving providing essential rationale and proof of feasibility in June or October of 2024.

PLANS FOR SCIENTIFIC MANUSCRIPTS. We are currently preparing a manuscript describing data from #1 and #2 and anticipate that this will be accessible on BioRxIV and submitted to a journal by the end of January 2024. With growing interest in studying brain ECM in a variety of contexts, we are also planning to prepare a techniques-based manuscript detailing the tissue processing and analysis methods we have used to study the brain ECM in the context of aging. We anticipate preparing and submitting a manuscript detailing the reward-based behavior paradigm and our findings concerning how microglial-ECM-synapse interactions impact cognitive preservation in the fall / early winter of 2024.

Villeda, Saul, 2022, McKnight Innovator Award

LAY SUMMARY OF PROGRESS

Evidence indicates that caloric restriction can counter age-related decline in neurogenic and cognitive processes in the aged brain. Despite the evident benefit of caloric restriction, its application is hindered in the elderly by technical barriers. The research described in this progress report aims to challenge prevalent views of brain aging as a rigid process by investigating the potential of circulating blood factors to confer benefits of caloric restriction while circumventing pre-existing limitations in the elderly. Behavioral data generated in my lab indicate that late-onset, short-term caloric restriction initiated late in life in aged mice can rejuvenate cognitive function in the aging hippocampus – a brain region highly vulnerable to the effects of aging. Furthermore, using systemic administration of blood plasma derived from late-onset, short-term caloric restricted aged mice, we demonstrate that the benefits of caloric restriction on hippocampal-dependent learning and memory can be transferred to *ad libitum* fed aged mice through circulating factors in blood. Studies building on this foundational evidence will have significant translational potential, identifying molecular pathways that could be targeted for novel therapies to restore age-related cognitive dysfunction and potentially treat dementia-related neurodegenerative disorders.

SPECIFIC AIMS/OBJECTIVES

The goal of the proposal is to investigate the rejuvenating potential of calorie restriction (CR)-induced blood factors on the aged hippocampus at the molecular, cellular, and cognitive level. *We hypothesize that the rejuvenating effects of CR on cognitive function can be transferred through circulating blood factors.* We are testing this theory with two Specific Aims:

1. Determine molecular mechanisms downstream of CR that underlie cognitive rejuvenation in the aged brain.
2. Investigate the rejuvenating potential of CR-induced blood factors on cognitive function in the aged brain.

ACCOMPLISHMENTS/RESEARCH PERFORMED

The following data has been generated by my research group in support of the specific aims highlighted in the objectives of the project.

Late-onset, short-term CR improves hippocampal-dependent learning and memory in aged mice. Previously, our lab assessed the potential of short-term CR to rescue age-related impairments in hippocampal-dependent learning and memory using novel object recognition (NOR) behavioral paradigms. Preliminary data included in our original submission demonstrated that CR aged animals exhibited enhanced object and spatial learning and memory compared to *ad libitum* (AL) aged mice. These behavioral data indicated that short-term, late-onset CR is sufficient to rejuvenate hippocampal-dependent cognitive function at old age. To build upon these preliminary data, we have performed a more extensive cognitive assessment of hippocampal-dependent learning and memory in CR aged mice using NOR, radial arm water maze (RAWM) and contextual fear conditioning behavioral paradigms (**Figure 1**).

Aged (22-month-old) mice (late-onset) were subjected to a 30% reduction in daily caloric intake for 4 weeks (short-term). Age-matched aged mice placed on AL diet served as control. Changes in hippocampal-dependent learning and memory were measured using NOR, RAWM, and contextual fear conditioning (**Figure 1A**). For NOR, during the training phase a subject is allowed to interact with

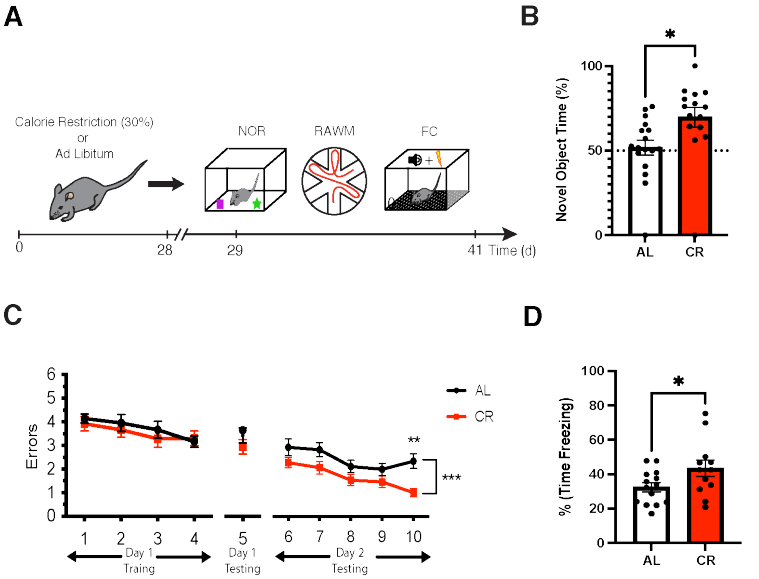


Figure 1. Short-term, late-onset calorie restriction improves cognitive function in aged mice. A. Novel object recognition (NOR), radial arm watermaze (RAWM), and fear conditioning (FC) used to assess hippocampal-dependent learning and memory in aged (22 months) mice following short-term (4 weeks) caloric restriction (CR, 30% decrease in food intake) initiated late in life (21 months) or ad libitum (AL) feeding. **B.** Object recognition memory assessed by NOR as percent time spent exploring a novel object 24 hours after training. **C.** Spatial learning and memory assessed by RAWM as number of entry errors committed during each block of the training and testing phases. **D.** Contextual fear memory was assessed by quantify the percent freezing time 24 hours after training. N=14 mice per group. Data represented as mean ± s.e.m; *P<0.05; **P<0.01; t-test (**b,d**), (two-way ANOVA with Šídák's correction for multiple comparisons **c**).

two identical objects in the exploration arena during the training phase. During the testing phase 24 hours later, the subject is placed back into the arena and one of the familiar objects is replaced with a novel object. Exploration time with the familiar and novel object is then quantified using the Smart Video Tracking Software (Panlab; Harvard Apparatus). Consistent with preliminary data, aged mice that underwent late-onset, short-term CR spent significantly more time with the novel object compared to AL control aged mice (**Figure 1B**).

For the RAWM paradigm, a pool of water was divided into 6 arms with a platform placed in a goal arm that was kept constant. A series of spatial cues surrounded the pool such that animals used spatial orientation to learn the location of the platform. During the training phase on day one, mice were trained for 15 trials, with trials alternating between a visible and hidden platform. During the testing phase on day two, mice were tested for 15 trials with a hidden platform. Entry into an incorrect arm was scored as an error, and errors were averaged over training blocks (three consecutive trials). In the RAWM, all aged mice showed similar spatial learning capacity. However, late-onset, short-term CR aged mice committed fewer errors compared to AL control aged mice (**Figure 1C**).

For the contextual fear-conditioning paradigm, mice learned to associate the environmental context (a fear conditioning chamber) with an aversive stimulus (a mild foot shock; unconditioned stimulus). Conditioned fear was measured following each chamber exposure as freezing behavior using a FreezeScan video tracking system and software (Cleversys, Inc). On day one each mouse was placed in a fear-conditioning chamber and allowed to explore for two minutes before delivery of a 30-second tone (70 dB) ending with a two-second foot shock (0.6mA). Two minutes later, a second CS-US pair was delivered. On day two each mouse was placed in the fear-conditioning chamber containing the same exact context, but with no administration of a CS or foot shock. All aged mice exhibited similar baseline freezing (data not shown). Interestingly, late-onset, short-term CR aged mice demonstrated increased freezing in contextual memory testing compared to AL control aged mice (**Figure 1D**). 24 hours after behavior was completed, one brain hemisphere was collected and processed for histological analysis. And the contralateral hemisphere was processed for transcriptional profiling and biochemical analysis. Together, these behavioral data further validate that late-onset, short-term CR is sufficient to rejuvenate hippocampal-dependent learning and memory in aged mice.

Systemic administration of blood plasma derived from late-onset, short-term CR aged mice improves hippocampal-dependent learning and memory in AL aged mice. To investigate the role of CR-induced circulating blood factors in rejuvenating the aged brain, blood plasma was isolated from aged mice that either underwent late-onset, short-term CR or were fed AL diet. Aged mouse blood was collected by intracardial bleed and followed by centrifugation at 1,000 g for 10 minutes for plasma preparation. Plasma was aliquoted for systemic administration studies and for future mass spectrometry analysis. Prior to use for systemic administration, plasma was dialyzed using 3.5-kDa D-tube dialyzers (EMD Millipore) in saline to remove any remaining anticoagulant. Subsequently, aged AL mice were systemically treated with either CR or AL control blood plasma (100 µL/injection) via intravenous tail vein injection eight times over 24 days. Hippocampal-dependent function was then assessed using NOR and RAWM (**Figure 2A**).

Remarkably, systemic administration of CR blood plasma was sufficient to reverse age-related cognitive decline at old age. For NOR, aged mice that received blood plasma from late-onset, short-term CR aged mice spent significantly more time with the novel object compared to aged mice that received blood plasma from aged AL mice (**Figure 2B**). For RAWM paradigm, aged mice receiving systemic administration of CR or AL aged blood plasma showed similar spatial learning capacity. However, during the testing phase, aged mice

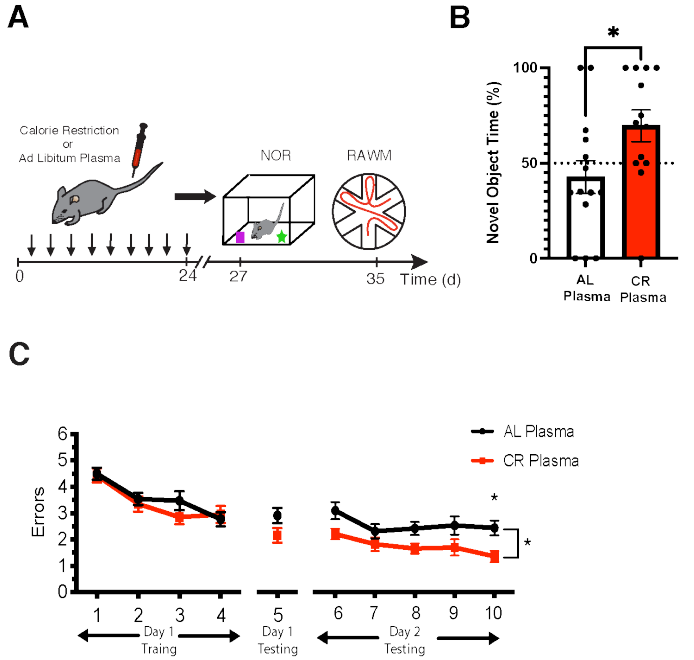


Figure 2. Systemic administration of calorie restriction-induced blood factors improves cognitive function in aged mice. A. Plasma was collected from aged (22 months) mice on CR or AL diet and administered to aged mice on AL diet 8 times over 24 days (100 µl per intravenous injection). Hippocampal-dependent learning and memory was then assessed with NOR and RAWM. **B.** Object recognition memory assessed by NOR as percent time spent exploring a novel object 24 hours after training. **C.** Spatial learning and memory assessed by RAWM as number of entry errors committed during each block of the training and testing phases. N=14 mice per group. Data shown as mean±s.e.m.; *P<0.05, **P<0.01, t-test (B); two-way ANOVA with Šídák's correction for multiple comparisons (C).

receiving CR aged blood plasma committed fewer errors compared to aged mice receiving AL aged blood plasma (**Figure 2C**). 24 hours after behavior was completed, one brain hemisphere was collected and processed for histological analysis. And the contralateral hemisphere was processed for transcriptional profiling and biochemical analysis. Collectively, these behavioral data indicate that the benefits of late-onset, short-term CR on cognitive function can be transferred through circulating factors in blood at old age.

NEW FUNDING
1. NIH/NIA R01AG077770: Pro-youthful role of Gpld1 on regenerative and cognitive function in the aged brain.
2. NIH/NIA R01AG077816: Systemic mechanisms of brain rejuvenation.

Grant recipient: Reas, Emilie T.

Award: 2022 McKnight Brain Research Foundation Innovator Award in Cognitive Aging and Memory Loss

Project progress

Over the prior reporting period, we have focused efforts on participant recruitment, data collection of imaging, biofluid, genetic, and cognitive data, and optimizing our MRI data processing pipeline. To date, we have enrolled 52 cognitively normal older adults from the UC San Diego Shiley-Marcos Alzheimer's disease Research Center (ADRC) and surrounding community, who have undergone MRI scanning and cognitive testing, and provided blood and saliva samples. We have optimized our image processing pipeline for sensitivity to age-related blood-brain barrier (BBB) dysfunction, resulting in a highly efficient image processing stream. Upon finalizing this refined pipeline, we conducted preliminary analysis of available imaging, genetic, and cognitive data, which are under review for publication. Aims over the final project period include development of the microstructural brain age score, measurement of inflammatory plasma markers, and integrative analysis across MRI, biofluid, genetic, and cognitive measures.

Specific Aims and objectives

Biological aging is associated with various chronic diseases and debilitating conditions, including cognitive decline and Alzheimer's disease (AD). A common thread to most age-related disorders is systemic inflammation, suggesting that strategies to control inflammation may be promising therapeutic targets for AD or related diseases of "inflammaging." Despite mounting evidence implicating neuroinflammation in AD pathogenesis, the avenue by which peripheral inflammation impairs brain function, and the role of early inflammatory changes in the AD cascade, remain unclear. A candidate link between systemic inflammation and neurodegeneration is the blood-brain barrier (BBB), which maintains brain homeostasis by providing a tightly regulated protective interface with peripheral circulation. The BBB becomes dysfunctional in the presence of chronic inflammation, and increased BBB permeability has been observed in both aging and AD. The proposed project will test the overarching hypothesis that systemic inflammation accelerates microstructural brain aging, a process mediated by BBB breakdown and modified by AD risk. Plasma inflammatory protein measurement, the multicompartment diffusion MRI technique restriction spectrum imaging (RSI), dynamic contrast-enhanced MRI, and cognitive testing will be conducted on 150 older adults free of dementia. This project will leverage a cohort that is well characterized by demographic, clinical, neuropsychological, genetic, and biofluid data, together with the most advanced MRI methods to assess subtle abnormalities in regional BBB permeability and brain microstructure. First, we will examine whether circulating inflammatory factors are associated with more severe microstructural brain aging, as measured by RSI, and with memory impairment (Aim 1). Second, we will assess whether BBB permeability mediates effects of inflammation on microstructural brain aging and memory deficits (Aim 2). Finally, using the AD polygenic hazard score, a validated genetic marker of preclinical AD, we will determine if AD risk modifies associations of systemic inflammation on brain aging or memory and mediation by BBB breakdown (Aim 3). Ultimately, findings will help to bridge the still elusive link of inflammaging with cognitive decline and neurodegeneration. It will further inform the role of neurovascular dysfunction in mediating the deleterious effects of systemic inflammation on brain health and guide strategies for early prevention or treatment of age-related cognitive decline and dementia.

Major activities and results

During the second year of this award, major activities focused on 1) participant recruitment and data collection, 2) finalizing our image processing pipeline, and 3) preliminary analysis of MRI, cognitive, and genetic data.

Objective 1: Participant recruitment and data collection. Participant recruitment has been fruitful, with 35% (*N*=52) of our target sample enrolled despite initial setbacks due to lower-than-expected enrollment from the UC San Diego Shiley-Marcos ADRC longitudinal study cohort meeting inclusion criteria. We have since implemented strategies for community engagement, including flyering throughout the broader San Diego region, outreach through social media, and most recently, leveraging a UCSD-sponsored health registry (Data Extraction Concierge Service). With these additional resources in place, we remain optimistic to achieve target enrollment by project end. Demographic characteristics for currently enrolled participants are shown in **Table 1**. Participants had a mean age of 75 at time of MRI, are equally represented by men and women, were intentionally enriched for AD genetic risk, highly educated, and performed within expected ranges for age on

tests of cognitive testing.

TABLE 1. Participant characteristics (*N*=52)	
Age	74.9 ± 7.6
Sex (*N* (%) Female)	26 (50%)
Education (years)	16.9 ± 2.1
APOE4 carrier (high AD genetic risk, *N* (%))	23 (44%)
MMSE (global cognition)	29.1 ± 1.2
Trails B (executive function)	82.2 ± 32.0
Animal naming (verbal fluency)	22.5 ± 4.7
CVLT (verbal memory) learning	47.7 ± 11.5
CVLT (verbal memory) delayed recall	10.6 ± 3.9

Objective 2: Development of an integrated image processing pipeline. A major accomplishment of this reporting period was completion of a streamlined workflow for MRI data quality control and processing. We recently upgraded our automated structural and diffusion MRI processing pipeline, which improved image registration, artifact removal, and delineation of tissue boundaries. In parallel, we extensively tested alternative model parameters using the ROCKETSHIP software for DCE MRI data processing, determining optimal settings for an arterial input function, smoothing, and minimum signal thresholding. We also validated methods for both region-of-interest and voxel-wise statistical analysis of multi-modal MRI data.

Objective 3: Data analysis. Preliminary analysis of imaging and genetic data from the first 44 cognitively normal participants of this project has been conducted and submitted for publication. Analyses revealed that individuals with elevated genetic risk for AD have increased BBB permeability across the cortical gray matter (**Figure 1**). Furthermore, BBB leakage was associated with microstructural damage to the entorhinal cortex, a site of early AD-related neurodegeneration, particularly for those with higher AD genetic risk or AD pathology (**Figure 2**). Although we previously observed strong correlations between brain microstructure and cognition, counter to our hypothesis BBB permeability was unrelated to cognitive function. These findings received favorable initial review at the journal *Alzheimer's & Dementia*, where our resubmitted manuscript is under review.

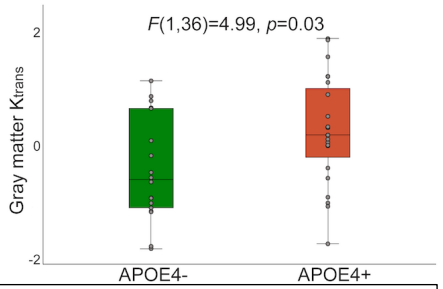


***Figure 1**. Gray matter BBB permeability is higher for older adults with increased AD genetic risk.*

Over the final year of this project, we plan to address the remaining study aims by integrating inflammatory biomarkers and developing the microstructural brain age score. Stored plasma samples are currently being prepared for shipment to Alamar Biosciences, for measurement of the NULISA Inflammation 250 panel. Concurrently, we are developing a diffusion MRI (RSI) based brain age score on an independent sample of approximately 40,000 participants from the UK Biobank. MRI data are undergoing processing, after which we will apply a machine learning algorithm to develop a brain age score, which will be used in comparative analyses against BBB permeability and inflammatory factors.

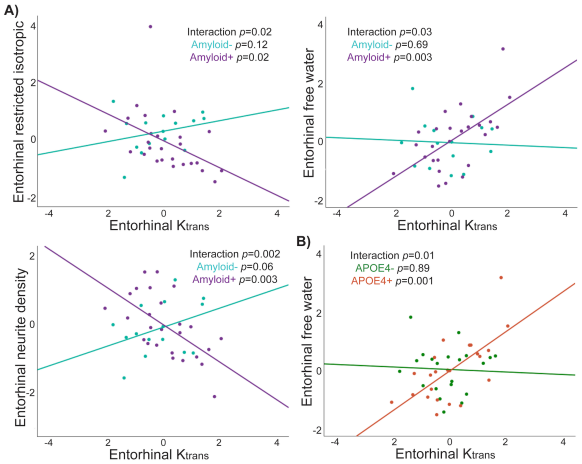


***Figure 2**. Entorhinal BBB permeability correlates abnormal microstructure for those with high AD genetic risk or AD pathology.*

Changes to research plan

As noted in our prior progress report, we have decided to use the UK Biobank dataset, rather than the originally proposed Rancho Bernardo Study dataset, to derive the microstructural brain age score, to improve generalizability and rigor. Additionally, due to concerns over sample batch effects with the proposed Olink assay, we have decided to use the Alamar NULISA assay for inflammatory markers.

Presentations and publications

A manuscript reporting preliminary data from this project is under review at *Alzheimer's & Dementia*. In addition, results presented at this summer's Alzheimer's Association International Conference incorporated data from cognitively normal controls collected under this project:

> Reas ET, Alderson-Myers A, Solders S, Shen Q, Wang X, Rivera CS, Banks SJ, Graves JS. (2024). Blood-brain barrier breakdown and abnormal brain microstructure in older adults with COVID-19-related cognitive impairment are modified by sex and *APOE4*. Poster presented at the Alzheimer's Association International Conference, Philadelphia, July 28-August 1, 2024. *Alzheimer's & Dementia*.

Overall impressions

Highlights of this reporting period include ongoing data collection, finalizing our multimodal MRI data processing pipeline, and preliminary data analysis. Interim analyses, expected to be published soon, demonstrate BBB breakdown in normal aging linked to AD genetic risk and microstructural abnormalities. The final project period will focus on continued data collection, measurement of inflammatory plasma markers, and development of the microstructural brain age score.

New funding

Since the prior progress report, Dr. Reas has assumed the role of Biomarker Core Co-leader (Imaging lead) of the UC San Diego Shiley-Marcos ADRC, supported by NIA P30 AG062429. She is also PI on a submitted NIH R01 (AG091503) that is expected to be awarded this winter, entitled "Blood-brain barrier and microstructural brain biomarkers of ARIA and treatment outcomes with anti-amyloid immunotherapy for Alzheimer's disease." If funded, this project will leverage the neuroimaging methods refined under the current award to examine changes in BBB permeability and brain microstructure accompanying monoclonal anti-amyloid therapy for AD.

Tara E. Tracy
2022 recipient of the McKnight Brain Research Foundation Innovator Award in Cognitive Aging and Memory Loss
Title: Role of KIBRA in Age-Related Memory Loss

SUMMARY
We have made progress on both aims of the project in this reporting period. The goal of Aim 1 is to establish how KIBRA levels affect cognition and neuronal function in aged mice. We have generated cohorts of mice for experiments the have different levels of KIBRA protein expressed in their brain due to the deletion of either one or both copies of the gene that encodes KIBRA. We performed a series of behavior tests on aged wildtype mice, mice with reduced KIBRA protein levels (KIBRA heterozygous knockout mice), and mice lacking KIBRA protein (KIBRA homozygous knockout mice). One of the tests assessed pattern separation memory, which is a type of memory that involves recalling the difference between two very similar but distinct experiences. Our results thus far suggest that aged mice with reduced KIBRA protein levels are more susceptible to pattern separation memory impairment compared to mice that have normal levels of KIBRA protein in the brain. On the other hand, we did not find on effect of KIBRA protein levels in aged mice during a test of working memory, indicating that KIBRA levels may affect specific types of memory with age. The goal of Aim 2 is to establish how KIBRA levels affect human neuron function. To address this aim we worked with Applied StemCell to design an approach to knockout the gene that encodes KIBRA in human induced pluripotent stem cells (iPSCs). The iPSCs that were generated using this strategy will next be screened to identify a clone that is deficient in KIBRA protein. Then we will differentiate the KIBRA deficient iPSCs into human neurons for experiments described in Aim 2. We also designed and confirmed a strategy using RNA interference (RNAi) to knockdown the expression of KIBRA protein in human neurons as an alternative approach to address the goal of Aim 2. In the next reporting period, we will continue to use the transgenic mice and the human iPSC lines that we generate to model the effects of KIBRA deficiency on aging to achieve the goals of the project.

SPECIFIC AIMS
Aim 1: Determine the extent to which KIBRA levels confer susceptibility to age-related synaptic and cognitive decline in mice. We hypothesize that neurons with less KIBRA levels confer greater susceptibility to synaptic and memory decline in aging.

Aim 2: **Determine the role of KIBRA in synapse function and plasticity in human neurons.**
We hypothesize that KIBRA is for required the postsynaptic signaling that modulates for synapse strength in human neurons.

EXPERIMENTS PERFORMED
A postdoctoral fellow, Dr. Mahima Sharma, was recruited to work on the experiments for this award, and due to some delays related to obtaining a work visa she started working on the projects in June 2023. For Aim 1, we performed behavior experiments on mice to determine the age-dependent effect of KIBRA levels on memory. We assessed the memory performance of 14–16-month-old KIBRA heterozygous knockout (KIBRA +/-) mice compared to non-transgenic (ntg) littermate control mice in the object-context discrimination test of pattern separation memory, the Y-maze test of working memory, the Morris water maze (MWM) test of spatial memory, and in a contextual fear conditioning paradigm. Following behavior testing, the mice were euthanized, perfused with saline, and the brains were collected. Half of each brain was fixed for immunohistochemistry and half of the brain was frozen for biochemical analyses. Behavioral testing of a second cohort of 10–12-month-old mice with KIBRA homozygous knockout (KIBRA -/-), KIBRA +/-, and ntg littermate mice is currently ongoing. The mice have thus far been tested in the object-context discrimination test of pattern separation memory, the Y-maze test of working memory, and the Barnes maze test of spatial memory.

For Aim 2, we collaborated with Applied StemCell to design a CRISPR/Cas9 strategy to engineer KIBRA knockout human induced pluripotent stem cells (iPSCs). Guide RNAs (gRNAs) were originally targeted to the 7th exon of WWC1. Efficient cutting was not achieved using the first gRNAs targeting exon 7. Thus, new gRNAs were designed to target the 8th exon of WWC1. After transfection of cells with new gRNAs targeting exon 8, pooled analyses were performed to confirm the efficiency of cutting by Cas9. To generate monoclonal iPSC lines with KIBRA -/- and KIBRA +/- genotypes, 384 single cells were selected from the transfected pool for screening.

In addition to working towards generating a KIBRA knockout iPSC line, we identified a short hairpin RNA (shRNA) sequence to knockdown KIBRA protein levels in cells. We next generated a lentiviral vector with the

shRNA sequence which can be used to express the KIBRA shRNA in human iPSC-derived neurons. We have begun testing the effect of lentiviral-based KIBRA shRNA expression in human iPSC-derived neurons.

RESULTS

We previously found that KIBRA +/- transgenic mice did not have impaired pattern separation memory in the object-context discrimination test at 7-9 months of age, however at 14-16 months old the KIBRA +/- had impaired memory in contextual fear conditioning. During this reporting period, we tested another cohort of ntg and KIBRA +/- littermate mice in a series of tests of hippocampus-dependent memory at 14-16 months old. Interestingly, we found that although KIBRA +/- maintained pattern separation memory at 7-9 months old (Figure 1A), their pattern separation memory was impaired in 14–16-month-old mice (Figure 1B). These findings support that reduced KIBRA protein levels cause susceptibility to memory decline during aging. Our preliminary results showed that aged KIBRA +/- mice have impaired learning and memory in the contextual fear conditioning test. We have repeated the contextual fear conditioning test in a new second cohort of aged ntg and KIBRA +/- littermate mice and found a similar effect (Figure 1C and 1D). Notably, the aged KIBRA +/- mice completed a similar proportion of spontaneous alternations in the Y-maze compared to ntg controls (Figure 1E), suggesting that their working memory was not affected.

The aged ntg and KIBRA +/- mice were also tested in the Morris water maze test of spatial learning and memory. Both ntg and KIBRA +/- mice showed spatial learning during several days of hidden platform training, however, during the probe trial neither ntg nor KIBRA +/- mice showed significant effects in the % time spent in the target quadrant making it unclear whether or not the ntg or KIBRA +/- mice retained spatial memory (data not shown). While it is difficult to determine the reason for this unexpected effect, we speculate that the mice employed a search strategy based on thigmotaxis during the probe trial which is not considered a hippocampus-dependent strategy (1). Considering that we have previously tested other mouse strains successfully in the probe trial of the Morris water maze, we suspect that thigmotaxis may be a strategy used specifically by the mouse strain background of our KIBRA deficient mice. Thus, we plan to move forward with using a different type of spatial memory test in subsequent behavior cohorts. We are currently testing a cohort of aged ntg, KIBRA +/-, and KIBRA -/- mice in the Barnes maze test of spatial memory. The same cohort has also been tested in the object-context discrimination test and Y-maze. We will analyze these data during the next reporting period. Thus far, our results for Aim 1 support that the reduction of KIBRA levels in aged mice has a detrimental impact on pattern separation memory and contextual memory, without a substantial effect on working memory.

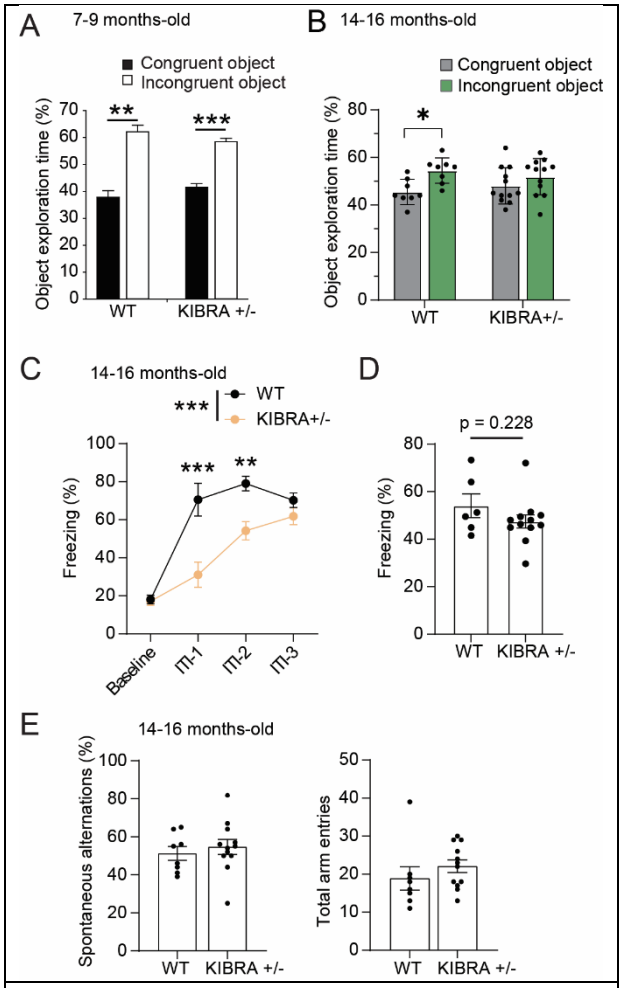


Figure 1. Behavioral analyses of KIBRA +/- mice showed age-dependent effects of KIBRA on memory. (**A and B**) Mice were subjected to the object-context discrimination test of pattern separation memory. (**A**) Preliminary data was acquired from adult mice (7-9 months old; **p < 0.01, *** p<0.001, paired student's t-test). (**B**) Aged mice (14-16 months old) were tested during this reporting period (n= 8-12 mice per group; *, p < 0.05, paired Student's *t*-test). (**C**) Freezing was measured in14-16 months old mice during inter trial intervals (ITI) throughout training to assess contextual fear learning (n= 6-12 mice per group; **, p < 0.01, ***, P < 0.001, two-way repeated measures ANOVA). (**D**) Time spent freezing 24 hours after learning (Student's t-test). (**E**) Working memory was assessed in the Y-maze test by measuring the fraction of spontaneous alternations.

For Aim 2 we have collaborated with Applied StemCell to generate the KIBRA heterozygous and homozygous knockout human iPSCs. Multiple gRNAs were tested to enhance the efficacy of CRISPR editing within the WWC1 gene that encodes KIBRA. Three gRNAs, gRNA #6, 7, and 8, were identified that target exon 8 of WWC1 (Figure2A). When the gRNAs were transfected into cells together with Cas9, the pooled cells were sequenced by Sanger sequencing to reveal that there were insertions and deletions within the pooled cell population that could represent KIBRA knockout cells (Figure 2B and 2C). From pooled transfected human iPSCs, 384 single

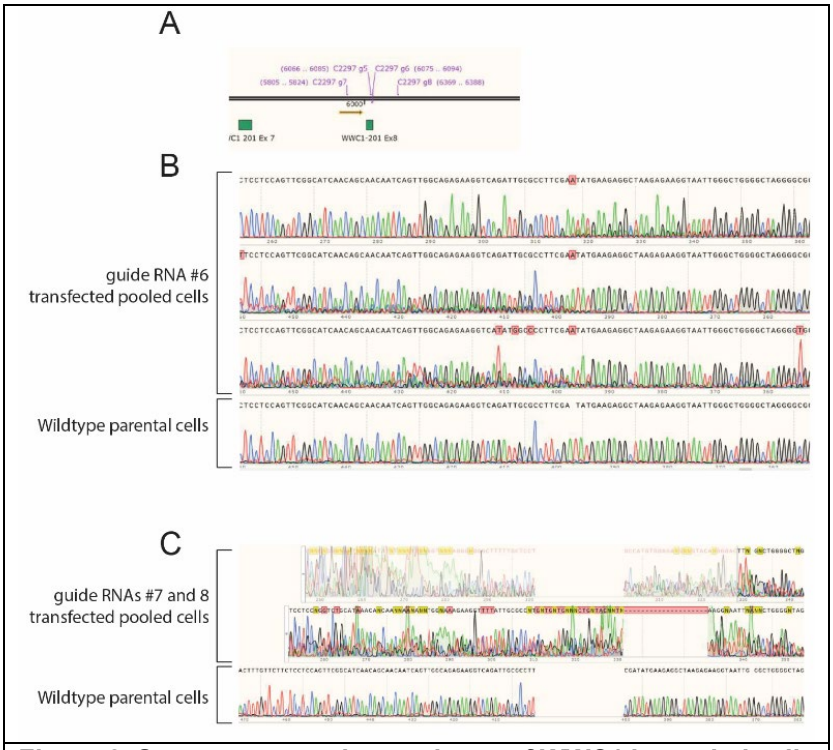


Figure 2. Sanger sequencing analyses of WWC1 in pooled cells following CRISPR/Cas9 editing. (**A**) Guide RNAs (gRNAs) were designed to target exon 8 in the WWC1 gene that encodes KIBRA. (**B**) One base pair addition in the sequence of pooled cells transfected with gRNA #6 indicates a frameshift in the coding sequence compared to the parental cell line. (**C**) Deleted base pairs in the sequence of pooled cells transfected with gRNAs #7 and 8 compared to the parental cell line.

iPSCs were selected, and they are currently growing into clonal colonies which will be sequenced individually to identify monoclonal KIBRA heterozygous and homozygous knockout iPSC lines. We have confirmed that KIBRA protein can be detected by western blot of human iPSC-derived neuron lysate (Figure 3A), and human KIBRA is similar in size to mouse KIBRA. To establish another approach to knockdown KIBRA protein levels in human neurons we designed a KIBRA shRNA that reduces the levels of KIBRA overexpressed in HEK293 cells (Figure 3B). We then made a lentivirus containing the KIBRA shRNA that we plan to use to infect human neurons. We will use both the KIBRA knockout cell lines and lentiviral-based KIBRA shRNA infection in the next reporting period to investigate the effect of KIBRA deficiency on synapse physiology and plasticity in human neurons.

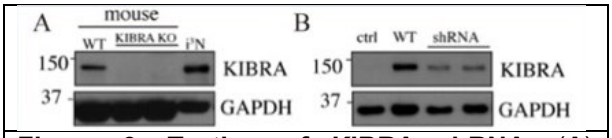


Figure 3. Testing of KIBRA shRNA. (**A**) Immunoblot showing that KIBRA protein is detected in human iPSC-derived neurons (i^3N) and it is similar in size to KIBRA protein expressed in mouse brain. (**B**) Immunoblot from HEK293 cells expressing human KIBRA protein with or without KIBRA shRNA.

Presentations

- Invited speaker, Symposium on Neuromodulation, University of Virginia, VA (2023)
- Invited speaker, Verge Genomics, CA (2023)
- Invited speaker, AFAR Prevention Live Better Longer webinar, (2023)
- Poster presentation, Neurodegenerative Diseases: Biology and Therapeutics Conference, Cold Spring Harbor Laboratory, NY (2022)
- Invited speaker, Bay Area Alzheimer's Researchers' Symposium, Stanford University, CA (2022)

Publications

1. Kauwe G*, Pareja-Navarro KA*, Chen J, Wong I, Saloner R, Cifuentes H, Nana AL, Shah S, Li Y, Le D, Spina S, Grinberg LT, Seeley WW, Kramer JH, Sacktor TC, Schilling B, Gan L, Casaletto KB, **Tracy TE**. KIBRA repairs synaptic plasticity and promotes resilience to tauopathy-related memory loss. ***Journal of Clinical Investigation***, *in press* (*Co-first author).
2. Udeochu J*, Amin S*, Huang Y*, Fan L, Torres ER, Carling GK, Liu B, McGurran H, Coronas-Samano G, Kauwe G, Mousa GA, Wong MY, Ye P, Nagiri RK, Lo I, Holtzman J, Corona C, Yarahmady A, Gill MT, Raju RM, Mok SA, Gong S, Luo W, Zhao M, **Tracy TE**, Ratan RR, Tsai LH, Sinha SC, Gan L (2023). Tau-activation of microglial cGAS-IFN reduces MEF2C-mediated cognitive resilience. ***Nature Neuroscience***. 26 (5):737-750 (*Co-first author).

Funding

No new funding was received during the first year of this award.

Promotions/Honors

Selected by NIH as a standing member of the Neuronal Communications (NC) Study Section

Reference

1. Gehring TV, et al. Detailed classification of swimming paths in the Morris Water Maze: multiple strategies within one trial. *Scientific reports.* 2015;5:14562.

Scientific report narrative

"Counteracting age-associated cognitive decline via gut-brain signaling"

McKnight Brain Research Foundation Innovator Award in Cognitive Aging and Memory Loss

Christoph A. Thaiss, PhD

First budget period (2023-2024)

Summary

The overall goal of this proposal is to identify new ways to counteract brain aging and cognitive decline. Age-associated memory loss is devastating for affected individuals and greatly impacts the quality of life for a substantial portion of the elderly population. What is really remarkable about the phenomenon of age-associated cognitive decline is how variable it is in the population. Some individuals maintain fully intact memories at old age, while others experience severe cognitive decline and an inability to form and retrieve memories. What causes this heterogeneity is largely unclear. Our study focuses on an innovative explanation for this phenomenon. We specifically focus on factors outside of the brain. During the first year of this study, we have made significant progress toward understanding a pathway that originates in the gastrointestinal tract, contributes to age associated cognitive decline, and can be targeted to counteract memory loss in aging animals.

Scientific progress

As part of this project, we have recently developed an experimental pipeline to study the bidirectional communication between the gut and the brain, which will facilitate all parts of the proposed study.

Our investigations are facilitated by a serendipitous discovery which allows us to experimentally uncouple biological age from cognitive age: We cohoused young (2-months-old) and aged (20-months-old) mice in the same cage, which is not typically done in aging research. Numerous studies have documented changes in the intestinal microbiome during aging[8-14], but cohousing resulted in an equilibration of the microbial communities between young and old mice that resembled the "old-like" state (**Fig. 1a**). We then investigated the phenotypic consequences of cohabitation between young and aged mice. Remarkably, one month of cohousing with aged mice impaired the short-term memory of young mice in the novel object recognition task (**Fig. 1b**). The impact of the aged microbiome on learning and memory was likewise observed in the Barnes maze assay, a long-term spatial learning and memory task (**Fig. 1c**).

We sought to disentangle the impact of cohousing on intestinal microbial community composition from its social effects. To this end, we colonized young (2-month-old) germ-free mice with fecal microbiome samples obtained from either young (2-month-old) or aged (20-month-old) donors. Microbiome transplantation recapitulated the composition of donor microbiomes in the recipients (**Fig. 2d**), thus establishing age-associated microbiome alterations in young mice without cohousing. As in the cohousing setting, accelerating microbiome aging in young mice abolished learning and memory performance in the novel object recognition and Barnes maze tasks (**Fig. 2e, f**).

Learning and memory, and in particular the novel object and Barnes maze paradigms, are highly dependent on the hippocampus[15,16]. In response to stimuli, hippocampal neurons can form memory ensembles, known as "engrams," which store information about the trigger and can be activated upon re-exposure to the stimulus[17,18]. Importantly, hippocampal engram formation declines with age, and this loss is accelerated by neurodegeneration[18]. We thus explored whether microbiome aging impacted hippocampal function.

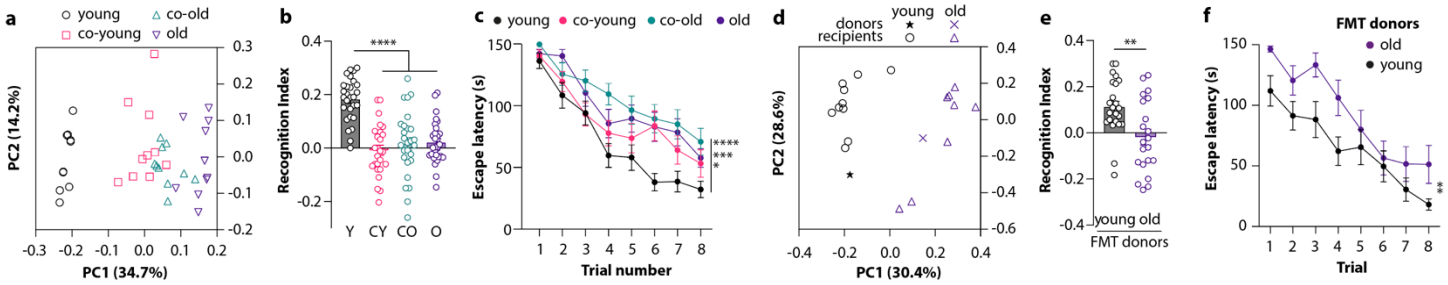


Fig. 1 | Microbiome impact on age-associated cognitive decline. **a-c**, PCoA plot of Bray-Curtis microbiome dissimilarity (a), novel object recognition (NOR) (b), and Barnes maze escape latency (c) in young (2 months) and old (20 months) mice after 1 month of cohousing. Y = young, CY = cohoused young, CO = cohoused old, O = old. **d-f**, PCoA plot of Bray-Curtis microbiome dissimilarity (d), NOR (e), Barnes Maze escape latency (f) in germ-free mice 1 month after fecal microbiota transfer (FMT) from young and old donors. * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001

Staining for the immediate-early gene cFos, a marker of neuronal activation, revealed that multiple hippocampal regions (CA3, CA1, and dentate gyrus) showed impaired activation in response to novelty exposure in aged mice as well as cohoused young mice (**Fig. 2a, b**). These findings highlight impaired hippocampal activity in response to age-associated microbiome perturbations. But how does the brain "know" about alterations in the gut milieu?

We speculated that neuronal connections between the gut and the brain, through vagal or spinal afferents, may be involved in the transduction of age-associated intestinal signals to the brain. To test this hypothesis, we took advantage of the fact that a large fraction of both vagal and spinal afferents expresses the vanilloid receptor TRPV1. We chemogenetically activated TRPV1^{+} neurons in young mice and in young mice cohoused with aged mice[6]. Remarkably, activation of sensory neurons fully restored hippocampal cFos activity and cognitive performance in cohoused young mice, while not altering the novel object recognition ability of young controls (**Fig. 2c-e**).

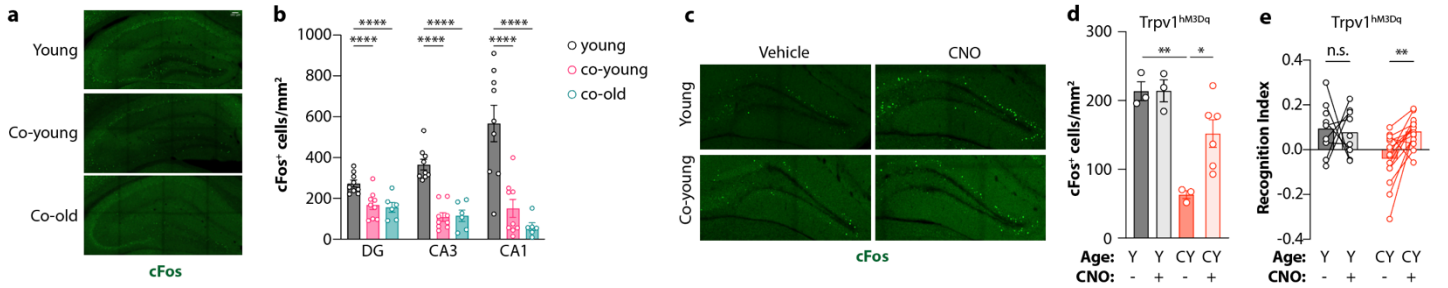


Fig. 2 | Reversal of aged microbiome-brain interactions. **a-d**, Representative images (a, c) and quantifications (b, d) of cFos^{+} neurons in the hippocampus of cohoused mice (a, b) and in cohoused *Trpv1*$^{AAV\text{-}hM3Dq}$ mice receiving CNO for chemogenetic activation of sensory neurons (c, d). Novel object recognition (e) in cohoused *Trpv1*$^{AAV\text{-}hM3Dq}$ mice. Mice received daily i.p. injections of CNO (1 mg/kg) for 5 days. * p<0.05, ** p<0.01, **** p<0.0001

Collectively, these results demonstrate that we have made major progress toward the goals of this project. They also enable us to mechanistically tackle the remaining objectives that we are pursuing with this study.

Career development activities

The AFAR McKnight Brain Research Foundation Innovator Award in Cognitive Aging and Memory Loss has brought visibility to our work and enabled several networking activities in the field of aging, cognitive decline, and brain resilience. It has also resulted in the invitation to a FASEB conference on the topic of "Cellular and Molecular Mechanisms of Brain Aging" which will take place on September 15, 2024 - September 19, 2024. A trainee working on the project will likewise attend the conference to interact with leaders in the field and foster future career opportunities.

Presentations and publications

The work described here has been presented at the following conferences:

- 88th Cold Spring Harbor Laboratory Symposium on Quantitative Biology “Brain Body Physiology”
  May 29 - June 3, 2024
- Keystone Symposium “Neuroimmune Interactions: Nervous System and Immune Cell Heterogeneity in Health and Disease”
  June 3-6, 2024

Overall impressions

The AFAR McKnight Brain Research Foundation Innovator Award in Cognitive Aging and Memory Loss has been transformative for my lab’s ability to study the brain-extrinsic pathways that lead to cognitive resilience during aging. My lab does not traditionally study aging, but the support of the AFAR McKnight award has resulted in significant exposure and involvement in the aging community. The progress we have made in the first year of the grant strongly enhances the feasibility of our remaining goals for the second and third year of the study.

New funding and promotions

The AFAR McKnight award is still the only source of funding for this project.
An R01 submission to the NIH/NIA is planned based on the results obtained from this study so far, in order to secure future funding for this line of research.

McKNIGHT BRAIN RESEARCH FOUNDATION
Preserving memory, enhancing life

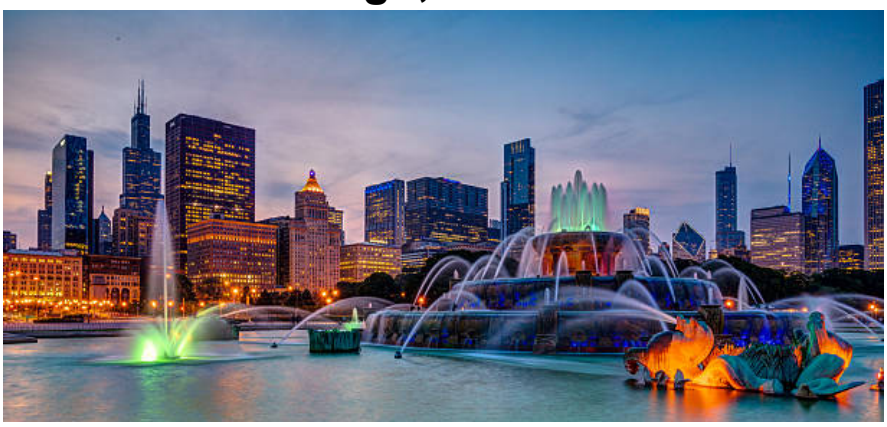
SAVE-THE-DATE

MCKNIGHT BRAIN RESEARCH FOUNDATION POSTER RECEPTION

In conjunction with SfN

SUNDAY, October 6, 2024
5:00 - 7:00 P.M.

Hilton Chicago
Williford ABC 3rd Floor
720 S Michigan Avenue
Chicago, IL 60605



Questions:
poster_session@mcknightbrain.org
Vicki Hixon

McKnight Brain Research Foundation

Poster Reception
Chicago, IL
October 6, 2024

	Alpha First Author Last Name	Institute	Abstract Title
1	Adamson, Ashley	UAB	The role for cell cycle regulators in trichloroethylene-induced Parkinson's dement
2	Balsamo, Barbara	Gainesville	Alpha-Synuclein Aggregation Impairs Executive Function in Aging: Insights from a Prefrontal Cortex Mouse Model study
3	Banerjee, Anisha	UAB	Targeting AD-pathology by increasing Angiotensin (1-7) via genetically modified probiotic in TgF344-AD rats
4	Barnes, Carol	Arizona	Relationships between cognition, MRI-based regional gray matter volume and amyloid and tau histopathology across the lifespan of male and female rhesus macaques
5	Baumgartner, Nina	UAB	The rostral lateral septum drives estrous cycle state-dependent suppression of cued threat memory
6	Bolaram, Anudeep	UAB	Neural Mechanisms of Adolescent Sustained Attention
7	Brunson, Jackie	UAB	Examination of Motility and Neuronal Morphology in Variants Associated with MAPK8iP3-related Disorders
8	Chawla, Monica	Arizona	Identification of novel activity-related transcripts using laser capture microdissection and RNA sequencing
9	Chen, Yu Jung	Arizona	Arc mRNA expression pattern in the CA1 subregion of rat hippocampus following spatial behavior
10	Claar, Robert	Gainesville	Fronto-limbic activity and functional connectivity in post-traumatic stress disorder and mild traumatic brain injury
11	Cook, Anna	UAB	Progranulin insufficiency and TDP-43 overexpression interact to worsen phenotypes in a mouse model of Frontotemporal Dementia
12	Cooper, Mary	UAB	Alzheimer's Disease Clock Gene Expression Alterations in Parvalbumin Interneurons
13	Davis, Natalie	UAB	Loss of Alzheimer's disease risk factor BIN1 in inhibitory neurons induces network hyperexcitability and behavioral abnormalities
14	Eickstead, Cameryn	UAB	Violence Exposure, Psychosocial Stress, and Prefrontal Cortex Reactivity
15	Faraji, Mojdeh	Gainesville	Age associated changes in brain phospholipids are mitigated by vagus nerve stimulation
16	Fox, Stephanie	UAB	Block of Sortilin Binding in Progranulin Gene Therapy Increases Progranulin Levels and Corrects Lipid Abnormalities, Behavioral Phenotypes, and Neurodegeneration Biomarkers in Progranulin Deficient Mice

17	Gazarov, Emely	Gainesville	Effects of chronic cannabis smoke exposure on peripheral and brain inflammatory markers and tau pathology in mice
18	Grey, Devon	UAB	Adolescent neural reactivity to stress varies with dietary nutrients
19	Hill, Clune	Gainesville	Exploring the Impact of Reward Objects on Mnemonic Discrimination and Aging: Insights from Rodent Model
20	Jeyagopal, Swetha	Gainesville	Cognitive effects of intra-striatal injection of α-synuclein preformed fibrils in young versus aged rats
21	Johnson, Megan	Arizona	A large normative aging dataset for the characterization of verbal memory performance across the lifespan
22	Jones-Muhammad, Maria	UAB	The Ketogenic diet modifies O-GlcNAc transferase expression in neurons and astrocytes within the aged hippocampus
23	Juhasz, Joshua	Gainesville	Accuracy of BrainAGE Estimates Produced by Machine Learning Algorithms
24	Krumm, Zachary	Gainesville	Assessing The Impact of the GLP-1 Receptor Agonist Exendin-4 On Reward-Mediated Behaviors
25	Kumar, Sreehari	UAB	Sex-specific multisystem alterations in metabolome in aged TgF344-AD rats
26	Ling, George Cowart, Hannah	UAB	Dynamics of Default Mode Network Activity Linked to Processing Speed in Cognitively Healthy Oldest-Old
27	Lovett, Sarah	Gainesville	Unveiling the dynamics of hippocampal theta wave propagation in freely moving rats
28	Mallepalli, Suresh	Miami	Role of cofilin in recurrent hypoglycemia exposure-linked stroke risk in insulin-treated diabetic rats
29	McCuiston, Mary	UAB	Effects of ketone diester supplementation on fear extinction impairments in the TgF344AD rat model of Alzheimer's disease across the lifespan
30	McDermott, Kelsey	Arizona	Changes in noradrenergic receptor density in hippocampus across the lifespan of the rhesus macaque
31	Mikhail, Karim	UAB	Effects of Alzheimer's disease risk factor BIN1 on L-type voltage-gated calcium channel surface localization in neurons
32	Nakamura, Megan (Broersma, Faith)	Gainesville	Electrophysiological Signatures of Novel Language Learning in the Earliest Stages
33	Ngwu-Hyacinth, Ogechukwu	UAB	A novel multi-modal magnetic resonance imaging technique to measure the concentration and ratio of iron products in a phantom of cerebral cavernous malformation
34	Ojeda, Ana	Gainesville	Employing sexually dimorphic risk for metabolic syndrome to identify Alzheimer's disease risk promoting or protective genes
35	Qiu, Alina	Gainesville	Stopping Before the Finish Line: Exploring Differences in Dropout and Readmission Rates for Older Adults in Substance Use Disorder Treatment
36	Raciti, Federica Maddalena	Miami	Auditory and Vestibular Consequences of Mild Traumatic Brain Injury
37	Rehni, Ashish K.	Miami	Recurrent hypoglycemia exposure results in cognitive impairment via increased platelet dysfunction in aged insulin-treated diabetic male rats

38	Rodriquez, Jose	Gainesville	Effects of chronic vagus nerve stimulation in aging
39	Sangaletti, Rachele	Miami	Exploring the link between blast-induced hearing loss and the progression of Alzheimer's disease
40	Silva, Giovana	Gainesville	The Importance of Tissue Identity in MRI-derived tDCS Models
41	Smith, Gabrielle	UAB	Development of SLC6A1 Knock-out Zebrafish and Drug Screening Pipelines to Identify Treatments for SLC6A1 Neurodevelopmental Disorders
42	Srivathsa, Sahana	Arizona	Investigating age-related changes of mPFC neural responses to ventral hippocampus stimulation
43	Tadepalli, Aniketh	UAB	Block of sortilin binding in progranulin gene therapy enhances rescue of microgliosis and microglial lipofuscinosis in progranulin-deficient mice
44	Tellez, Alexa Jo	UAB	Ovarian Hormones Tune Amygdala Inhibition to Drive Anxiety-Like Behavior Across the Reproductive Cycle
45	Titus, Ann	Gainesville	Identifying peripheral immune response signature dependent on Parkinson's disease progression
46	Tuckey, Ryan	UAB	MD simulations of rare Alzheimer's disease–associated APOE isoforms, such as APOE3- Christchurch, highlight unique structural, conformational, and dynamical features
47	Zempare, Marc	Arizona	CRISPR screening of genes associated with neuronal pentraxin 2 gene expression in human iPSC-derived glutamatergic excitatory neurons
48	Zequeira, Sabrina	UFL	Differential effects of chronic oral THC consumption in young and aged rats
49			
50			