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

Tuesday, March 28, 2023
5:00 pm ET – 6:00 pm ET

Members Attending:	Dr. Madhav Thambisetty, Committee Chair; Dr. Mike Dockery, MBRF Chair; Dr. Sue Pekarske, Trustee
Also Attending:	Dr. Lee Dockery, Chair Emeritus; Ms. Melanie Cianciotto, Corporate Trustee; Dr. Angelika Schlanger, Executive Director
Not in Attendance:	Dr. Patricia Boyle, Trustee; Dr. Richard Isaacson, Trustee

AGENDA

5:00 pm ET	1.	Call to Order/Roll Call	Dr. Madhav Thambisetty
ACTION	2.	Approval of Minutes, January 20, 2023	Dr. Madhav Thambisetty
	3.	Updated Activity Timeline	Dr. Madhav Thambisetty
	4.	Pilot Grant Applications a. Discussion of submitted proposals	Dr. Madhav Thambisetty
ACTION		b. Approval of select proposals	
	5.	Current Grants/Programs a. MBRF Innovator Awards in Cognitive Aging and Memory Loss (AFAR) Update	Dr. Madhav Thambisetty
ACTION		b. MBRF Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss (ABF) ii. Proposed changes for 2023 iii. Review and approval of RFA for 2023	
	6.	Cognitive Aging Summit IV Planning Update a. March 20, 2023 meeting with FNIH and NIA	Dr. Madhav Thambisetty
ACTION **6:00 on ET**	7.	Adjourn	Dr. Madhav Thambisetty

MINUTES
MCKNIGHT BRAIN RESEARCH FOUNDATION (MBRF)
RESEARCH COMMITTEE
CONFERENCE CALL
January 20, 2023

The Research Committee of the MBRF was called to order at 4:00 pm EST on January 20, 2023, by Dr. Madhav Thambisetty.

The following members were present:

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

The following members were absent:
Dr. Mike Dockery, MBRF Chair
Dr. Richard Isaacson, 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 October 17, 2022, Meeting

The minutes of the October 17, 2022, Research Committee Meeting (Attachment 1) were reviewed and approved as amended. The changes are:

Item 4 a, the last sentence should read "The committee discussed how to formalize the suggestions to ensure due consideration of applicants proposing clinical translational projects."

Action Item 1: The minutes of the October 17, 2022, Research Committee Meeting were approved as amended (Attachment 1).

3. Updated Activity Timeline

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

4. Current Grants/Programs

a. MBRF Innovators Awards in Cognitive Aging and Memory Loss

The committee received the draft RFA for the MBRF Innovators Awards in Cognitive Aging and Memory Loss (Attachment 3) for information. The 2023 application deadline is July 1, 2023. The anticipated award announcement date is September 15, 2023, with an award start date of October 1, 2023.

The committee discussed the feedback from AFAR regarding the match requirement. They feel making the match less restrictive for smaller candidates would allow for a broader, more diverse pool of candidates, including investigators from smaller institutions. Dr. Thambisetty reminded the committee the MBRF has already amended the match requirement by allowing for an in-kind contribution. He also shared that the match is a strong demonstration from an institution that they are committed to the candidate. When AFAR was asked how we could increase the number of applicants they shared that it is their experience that access to funding would be more equitable if the match requirement were adjusted down. The committee discussed how this may be unfair to those that have already submitted applications and that the awards have not yet completed a three year cycle. The committee also discussed how a limited number of applications for the MBRF Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss were received. We don't really know if the match is the main challenge to increasing the application pool. The committee agreed that more information is needed before a change to the match requirement can be made and that this should be discussed further at the February 16, 2023, Board of Trustees' meeting.

Dr. Thambisetty and Dr. Schlanger shared proposed changes to the 2023 grant cycle, including a full two weeks for the MBRF to review the proposed slate of awardees; adding more clinically-focused reviewers to the review committee; and separating out the ranking process into two categories—basic science and clinical translational research—to ensure that the grant guidelines are met. AFAR has agreed to implement these changes.

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

Dr. Thambisetty shared with the committee that the proposed changes to the RFA and task of reviewing applications has been shared with Jane Ransom at the ABF. The proposed changes included asking for two weeks for the MBRF to review the slate of applications, equitable distribution of reviewer assignments, adding an additional non-MBRF reviewer and stronger language in the RFA to further indicate the applications

relating solely to Dementia/Alzheimer's Disease will not be considered. There also needs to be further and broader outreach. ABF will share their marketing plan with the MBRF. ABF intends to do a soft launch sometime before May. Dr. Schlanger will ask if the draft RFA will be available to share with the trustees at the February 16, 2023, Board of Trustees' meeting.

c. FNIH/NIA 2022 Research Partnership in Cognitive Aging Report

The committee received the 2022 Research Partnership in Cognitive Aging report (Attachment 4) prepared by the FNIH/NIA for information. The committee felt the MedEx study was a significant study and noted that it will be extended through a new NIH award, "Resilience and Brain Health of Older Adults During the COVID-19 Pandemic."

5. Pilot Grants – Leadership Council Update

Dr. Thambisetty provided an update on the status of the pilot grants. Dr. Mike Dockery emailed Dr. Ron Lazar on January 2, 2023, to provide an overview of the Inter-Institutional Bioinformatics, Neuroimaging and Cognitive Assessment and Brain Aging Registry cores as well as the Cognitive Aging and Memory Intervention Core (CAMI). Dr. Dockery also stressed the importance of reconstituting the CAMI Core Committee to get the program back on track and develop ideas and plans about further options for the unspent funds from the first three Cores or new collaborative proposals. He also shared the MBRF would not be in favor having fellow or junior faculty members driving this process.

6. Cognitive Aging Summit Planning Update

A planning meeting with the FNIH and NIA is scheduled for January 31, 2023. Drs. Mike Dockery, Lee Dockery, Madhav Thambisetty and Angelika Schlanger will participate in the planning session and hope to provide an update at the February 16, 2023, Board of Trustees' meeting.

7. Adjourn

Dr. Thambisetty asked if there was any further discussion. Hearing none, he called for adjournment of the meeting at 5:10 p.m. EST.

Summary of Action Items:

Respectfully Submitted,

Melanie A. Cianciotto
Corporate Trustee

Research Committee Activity Timeline

2022-2023

Updated March 13, 2023

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	DONE February 5, 2020 DONE June 15, 2020 DONE Feb. 26, 2021 Annual Reports were reviewed by the Trustees on Feb. 9, 2022	Reviewers presented at Feb. 2021 Trustees Meeting. Follow up letters were written and sent to each of the MBIs. All Requests of MBIs have been addressed by MBIs. MBRF/MBI Task Force was established April 2021 to streamline Annual Report Recommendations. Recommendations were reviewed Oct 28, 2021 by Trustees. New Template was used for 2021 Annual Reports
	Review of all New Funding Requests from MBIs. Most Funding Requests should be reviewed by the Interventional Core Committee of the MBIs first.	UM submitted a request for $200,000 for Neurocognitive Post-Doctoral Fellowship over the next two years Christian Agudelo, MD, was selected	October 23, 2019 Trustees voted to fund -- payable over two years. Position Start Date – July 2020	The notification letter mentioned that future funding should come from other sources (See "The Evelyn F. McKnight Neurocognitive Clinical Scholar in Brain Health and Aging" on page two)

		UA submitted a request for $244,400 for UM's participation in the Precision Aging Demonstration Pilot	The proposal was reviewed and approved by the Trustees on Feb 5, 2020. The budget was revised and approved June 2020	Dr. Mike Dockery notified UA of the Trustees' approval Trustees were notified of the revised budget and approved no-cost revisions
		A Funding Request "Centralized, telephone-based, computer-assisted…Spanish" for $129,000 was submitted in April 2021 by Dr. Ron Lazar	Reviewed by Cmte in July and not recommended	This request was reviewed by the Trustees in July 2021 and was denied. Suggestion was provided to Dr. Lazar to work though MBI Core Committee if he chooses to resubmit.
		UM submitted a request for $ 3 million to endow a Neurocognitive Training Fund in Brain Health and Aging. UM submitted a request for $250,000 to co-fund a fellowship over 5 years – The Evelyn F. McKnight Neurocognitive Clinical Scholar in Brain Health and Aging"	July 1, 2021 October 2021 Research Cmte reviewed on October 21, 2021; Recommended funding; Trustees reviewed and approved funding October 28, 2021 Grant Notification Memorandum was dated Nov. 10, 2021	This request was denied by Trustees on July 28, 2021, but Dr. Lee Dockery was asked to pursue conversations with UM about how they might proceed. Dr. Dockery had several conversations and exchanges with UM with ideas for strengthening the program infrastructure. A memorandum notifying UM of the approval for 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 sent by Dr. Mike Dockery to UM and agreed to and signed by Drs. Sacco and Rundek.

"Encourage and assess research at the McKnight Brain Institutes (MBIs)" continued	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 at each Trustees' Meeting ON HOLD DUE TO UNIVERSITY TRAVEL RESTRICTIONS	Approved in 2009 In the amount of $100,000 Approximately $30,000 remains in the fund
	Inter-institutional Block Grants	Cognitive Aging Core Working Groups	N/A	5 Areas: Brain and Cognitive Health Cognitive Aging & Memory Cognitive Testing Battery Epigenetics MRI standardization
	Inter-institutional Block Grants	Bio-Informatics Core (Epigenetics)	Funding period: 9/1/2013-8/31/2015	Tom Foster, UF still lead scientist.
	Inter-institutional Block Grants	Neuroimaging Core	Funding period: 1/1/2015 to 12/31/2017 $931,759.00	
	Inter-institutional Block Grants	Cognitive Assessment and Brain Registry Core	Funding period: 9/1/2015-8/31/2017 Request for another extension was approved at the Feb 5, 2020, Trustees' meeting.	No-cost Extension Request submitted for April 30, 2021. Trustees approved the extension.
	Review of Pilot Grants (Funding Requests and Progress Reports)	1)A Novel Invention Tool – Levin 2)Revitalizing Cognition in Older Adults – Bowers	1)Funding Period: 5/1/2018-4/30/2020 2)Funding period: 5/1/2018-4/30/2020	1)Funding for 2-years for total of $120,000 2)Funding for 2-years for total of $120,000

				No-cost Extension Request submitted and approved for April 30, 2021.
		3)Transcutaneous Vagal Nerve Stimulation and Cognition Training – Williamson/Alexander	3)Approved July 2019 Funding period: 10/1/2019-9/30/2021 Deadline was extended	3)Funding for 2-years for total of $120,000
			Request for no-cost Extension	Trustees approved at their August 29, 2022 meeting
	Applications for 2021 Pilot Grants	5 Letters of Intent were Submitted	Research Cmte Reviewed LOIs for 2020 Jan. 29, 2021.	Trustees approved 3 grants
		3 Grants were approved	Feb. 26, 2021	
		With Dr. Gomes-Osman's subsequent departure from UM, the Core Committee recommended the next application in line to replace Dr. Gomes-Osman's. This was submitted by Dr. Sonya Kaur "Sleep Intervention…"	The Research Cmte did not recommend funding the next-in-line proposal in its July 2021 meeting "Reuniting the Brain and Body to Understand Cognitive Aging: The Nexus of Geroscience and Neuroscience" pilot grant August 2022	The Trustees denied funding and setting this precedent in its July 2021 meeting. Dr. Rundek was notified. Interim Report submitted. Trustees reviewed and approved on August 29, 2022
	Checked RFA for 2022 before it was posted to be sure it stresses Junior Faculty. It does.	Drs. Lazar and Levin shared that only 1 LOI was received for 2022 funding cycle.	January 31, 2022 Leadership Council Meeting attended by Drs. Thambisetty and Mike Dockery and A. Porter	Several reasons for only 1 LOI were cited. The Leadership Council drafted a new RFA to address these reasons and broaden the scope of the research for Trustee review at their February meeting

			February 23, 2022 September 12, 2022	Dr. Mike Dockery, on behalf of the Trustees, responded to the LC and the members of the Core Committee that they did not wish to change the focus of the pilot grant program by changing the RFA Dr. Mike Dockery, on behalf of the Trustees, and Angelika Schlanger attended the Leadership Council meeting and asked the Council to follow up with the MBRF on the status of the Cognitive Aging and Memory Intervention Core Workgroup, in terms of its membership and plans to respond to the Memo from February 23, 2022.
	Applications for 2023 Pilot Grants	5 Applications Submitted on February 7, 2023 via Ron Lazar and Bonnie Levin	Research Committee will review on March 28, 2023	
"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	Fund balance of $1 million from 2nd five-year partnership returned to MBRF Report received on all FNIH/MBRF activities RFA posted: "Network for Identification, Evaluation, and Tracking	DONE August 2019 FNIH Report in October 2019 had an error. A corrected report resubmitted on Feb. 5, 2020.	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) 2014 Partnership renewal funded one 5-year project for $15 million with $5 M from MBRF and $10 M from NIA

	3rd cycle approved 2019 to begin Spring of 2020	of Older Persons with Superior Cognitive Performance for Age" FNIH Report submitted For information only	Posted Feb 2020; Deadline LOI Sept. 1; Application October 1, 2020 First payment was made to FNIH by March 31, 2021. Will continue until 2025 Dr. Molly Wagster will be attending the March 23-25 Inter-institutional Meeting at UA. The Trustees have invited her to present at their meeting on March 23, and to the idea of inviting the grantees for a video presentation. Dr. Julie Gerberding, Julie Wolf-Rodda, FNIH, and Dr. Molly Wagster, NIA, attended MBRF Trustees Meeting on October 27, 2022, in DC	Valerie connected with Julie Wolf-Rodda and Molly Wagster on promoting STARRS study. NIA will provide $14M to be pooled with MBRF $5 M. A 2.8 Match. RFA was shared with Communications Working Group for posting and with Leadership Council. Two grants were provided from the Research Partnership ""Network for Identification, Evaluation and Tracking of Older Persons with Superior Cognitive Performance for their Chronological Age" to Dr. Thomas Perls, Boston University, and Dr. Emily Rogalski. Julie Wolf-Rodda, FNIH, Dr. Molly Wagster, NIA, and other members of the FNIH and NIA teams met by Zoom with Drs. Mike Dockery, Lee Dockery, Madhav Thamibisetty and Angelika Schlanger on January 31 and March 20, 2023 to being planning the next Cognitive Aging Summit.

"Identify opportunities…to foster greater interest in cognitive aging and age-related memory loss (in the scientific community)"	MBRF Innovators Awards in Cognitive Aging and Memory Loss The McKnight Brain Research Foundation committed $4.5 million over the next five years to support outstanding mid-career scientists committed to researching the basic biological mechanisms underlying cognitive aging and memory loss.	Program was Approved by the Trustees Potential administrative and/or funding partners were approached American Federation of Aging Research (AFAR) was identified as an excellent partner organization. AFAR presented a proposal and draft contract for review Revised Agreement signed between AFAR and the MBRF	October 14, 2020 December 2020 January 2021 February 2021 July 15, 2021 August 2021 Mid Oct. 2021 Dec. 15, 2021 March 2022 August 2, 2022 September 19, 2022 December 7, 2022	AFAR Review Committee: Chair: Dr. Anna Maria Cuervo Members: Dr. Rafa de Cabo Dr. Thambisetty Dr. Boyle and Dr. Roz Anderson 2021 LOI Deadline – 9 LOIs Received LOI Review – 7 applicants asked to submit full application Application Deadline Award Announcement 2022 *LOI Submission and review was eliminated due to the small number of applicants in 2021* Application Deadline Application Review – 4 applied. Award Announcement
	Reserve & Resilience Workshop 2019 Reserve & Resilience Workshop Pilot Grants 2020	Over 300 Attendees (8 MBI researchers) Organizers requested $30,000 to support (1 – 3) pilot grants	September 9 and 10th, 2019 Bethesda In-Person Meeting CHANGED TO VIRTUAL MTG September 14 and 15, 2020; Report Submitted Jan. 2021 Oct 31/Nov 1 Bethesda	This is an outcome from Cog. Aging Summit III held in 2017. Research Committee approved support in first and second years. Dr. Stern requested support for the Final R & R Workshop to take place Oct. 31/Nov. 1 in Bethesda.

	Final Reserve & Resilience Workshop 2021		Meeting will be a hybrid – part virtual and part person. The program is posted on reserveandresilience.com. Of note, Jen Bizon and Tom Foster are panelists.	He did not request a specific amount but support MBRF provided last year was $30,000. Committee supports recommendation to fund at no more than $30,000.
"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)	2021-2022 MBRF Reviewers are Dr. Boyle, Dr. Thambisetty, and Dr. Isaacson	Reviewers meet in Dec. Two Scholars are selected and alternates were identified. Awardees are notified in January. Funding starts July 1 of each cycle	<u>First Scholarships Awarded</u> January 2018 (McConnell, Albert) <u>Second Scholarships</u> Awarded January 2019 (Camargo, Sedaghat) <u>Third Scholarships</u> Awarded January 2020 (Baxter, Getz)
	McKnight Brain Research Foundation Clinical Translational Research Scholarship with American Academy of Neurology (AAN) and American Brain Foundation (ABF) (continued)		Edits to 2021 RFA were made and approved by Research Cmte. RFA was posted as of July 4, 2020, on AAN site. Advertising followed 2019 Plan for 2020 Award and begin in August, 2020. 8 applications for 2021 were received. October 14, 2020, Renewal for next five years was approved by the Trustees	<u>Fourth Scholarships</u> were Awarded in January 2021 to Dr. Wendy Yau Wai-Ying (Brigham and Women's) and ~~Dr. Matthew Burns (UF)~~ Dr. Reem Waziry (Publicly announced in April 2021 (Dr. Matthew Burns [UF] received a K-Award from NIA and had to decline the McKnight Scholarship.) <u>Fifth Scholarships</u> Advertising was conducted in August and September 5 Applications received Oct. 1. Review was in Dec. 2021

		Members of the 2022-23 Review Committee include Dr. Madhav Thambisetty and Dr. Patricia Boyle	2022-23 Deadlines September 1, 2022 Application Deadline November 3, 2022 Review Committee Meets January 9, 2023 Notification of Recipients Spring 2023 Announcement of Recipients	Sixth Scholarships New 2022-23 RFA Draft was reviewed and has been posted and advertised - 9 applications were reviewed 2023 Scholars Announced (Drs. Eva Klinman, MD, PhD and Sheena Baratano, MD, PhD)
"Encourage young investigators…" Continued	Poster Reception at 2019 Society for Neuroscience annual meeting (Chicago) MBRF/MBI Poster Reception 2020 Society for Neuroscience (SfN) annual meeting in DC October 24 – 28, 2020 canceled due to DC pandemic closing guidelines Society for Neuroscience will meet in San Diego Nov 12 - 16		October 20, 2019 August 29, 2022 September 5, 2022 September 1, 2022	First Poster Reception held in 2008. (50 submissions received) Sponsored by MBRF. Hosted by Directors of MBIs. Submissions open to researchers at MBIs and invited guests only MBRF Trustees Decided not to host the MBRF/MBI Poster session at the 2022 meeting. Dr. Mike Dockery updated the Leadership Council on Sept. 12, 2022 by Zoom. Dr. Mike Dockery wrote to the Leadership Council to ensure it will take place in 2023. Ms. Porter wrote to Dr. Molly Wagster to alert her that the poster reception will not take place this year.

To: The McKnight Brain Research Foundation Board of Trustees

From: Bonnie Levin, PhD
Ronald M. Lazar, PhD

Date: February 6, 2023

Re: McKnight Research Foundation (MBRF) Cognitive Aging and Memory Intervention Core Pilot Grants: 2022-2024 Cycle

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The Intervention Core has completed its assessment of reviews for the 2022-2024 cycle of Pilot Grants, and its recommendations are below:

A Review of the Process

We began formulating the guidelines of the RFP in the Fall 2021, which was approved by the Trustees on 11/16/2021, and distributed to all of the MBI's several days later. The deadline for a Letter of Intent (LOI) was 12/31/2021 and the full application was due on 3/1/2022. As of January 1, 2022, we received only one LOI. We approached the Trustees with a broader set of proposal guidelines to increase the number of applications, but they felt that the original scope was the best fit for the stated goals of the Intervention Core. As a result, a new RFP with the original guidelines was re-issued on 3/29/2022, with an LOI due on 5/15/2022 and the full application, if invited, due on 7/1/2022. We then received five LOI's, and all applicants were invited to submit full proposals.

We received all five full proposals by the first week in July. Because some of the applications described projects that were out of the purview of MBI faculty, we needed to solicit outside referees. This introduced unique challenges because we were asking non-MBI reviewers to volunteer their time and expertise. For this reason, it took several months to identify and receive reviews. In the end, we received the final review on 12/31/2022, and we are forwarding the five applications, the 11 reviews and their associated scores, and our recommendations here for consideration by the Board of Trustees.

Scores and Recommendations

1. Scoring Criteria: The reviews largely followed the format of an NIH grant review, ranging from 1 (Best) to 9 (Worst), using the criteria below for judging the overall impact of a project, if funded.

Impact	Score	Descriptor	Additional Guidance on Strengths/Weaknesses
High	1	Exceptional	Exceptionally strong with essentially no weaknesses
	2	Outstanding	Extremely strong with negligible weaknesses
	3	Excellent	Very strong with only some minor weaknesses
Medium	4	Very Good	Strong but with numerous minor weaknesses
	5	Good	Strong but with at least one moderate weakness
	6	Satisfactory	Some strengths but also some moderate weaknesses
Low	7	Fair	Some strengths but with at least one major weakness
	8	Marginal	A few strengths and a few major weaknesses
	9	Poor	Very few strengths and numerous major weaknesses

We did not require scores for individual NIH criteria (Significance, Investigators, Innovation, Approach, Environment) or those specific to this funding mechanism (level

of collaboration between McKnight Brain Institutes, potential for clinical translational impact of the intervention on cognitive aging and memory, Potential for NIH funding). Nevertheless, we asked for comments on all elements, which are included in the attached copies of the 11 reviews. At least two reviews were requested for each application.

2. Scores

The chart below gives the scores from reviewers and the mean for each of the five applications, designated by the corresponding PI and Institution:

	Scores			
Applicant	**Reviewer 1**	**Reviewer 2**	**Reviewer 3**	**Mean Score**
Kaur (Miami)	5	5		5
Lubin (UAB)	2	4		3
Pehlivanoglu (FL)	4	7		5.5
Pilonieta (UAB)	7	6		6.5
Signorile (Miami)	3	3	3	3

3. Recommendations and Rationale

Our goal was to fund at least one junior investigator and, if possible, one clinical and one translational neuroscience application. We recognize a junior investigator is more likely to submit a less competitive application compared to an experienced scientist. We believe, however, that it is important to encourage and nurture less experienced investigators, mentor them through the grant process, and provide a platform for them to showcase their work.

We therefore recommend to the Trustees pilot funding for the Signorile and Kaur proposals. Signorile (Miami and FL), a senior investigator, proposes to implement a YogaCue program that includes highspeed intervals to address cardiovascular fitness, and multi-directional responses to visual and auditory cuing, with pattern recognition and retention to address multiple cognitive domains. They will use changes in the retinal microvasculature and capillary function and targeted cognitive testing to assess the success of the YogaCue program. Kaur, a junior investigator, plans to examine the feasibility and tolerability of timed, bright light exposure therapy to enhance circadian function and cognition in the oldest old. We believe that this proposal was reviewed as if from a senior investigator and therefore judged it more harshly than warranted for a junior clinical scientist. We think that her proposed intervention is extremely novel and has potential for a clinical use.

As a condition of accepting this award, we will require pilot grant recipients to serve as future reviewers for this funding mechanism, ensuring a more expedited review process in upcoming grant cycles.

If appropriate, we would be pleased to meet with the Trustees during their consideration of these recommendations.

Respectively submitted,
Bonnie Levin, PhD
Ronald M. Lazar, PhD

Department of Health and Human Services
Public Health Services

Grant Application

Do not exceed character length restrictions indicated.

LEAVE BLANK—FOR PHS USE ONLY.

Type	Activity	Number
Review Group		Formerly
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*

Feasibility of a timed bright light exposure therapy to improve circadian functio

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☒ NO ☐ YES
(If "Yes," state number and title)
Number: Title:

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. eRA Commons User Name
Kaur, Sonya, Sarjit	Ph.D	SSKAUR1

3c. POSITION TITLE
Assistant Professor

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Neurology

3f. MAJOR SUBDIVISION
Neuropsychology

3d. MAILING ADDRESS *(Street, city, state, zip code)*
1120 NW 14th Street
Suite #1369
Miami, Florida 33136

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 305-243-7529 FAX:

E-MAIL ADDRESS:
ssk109@med.miami.edu

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt	If "Yes," Exemption No.
☐ No ☒ Yes	☒ No ☐ Yes	

4b. Federal-Wide Assurance No.	4c. Clinical Trial	4d. NIH-defined Phase III Clinical Trial
	☐ No ☒ Yes	☐ No ☒ Yes

5. VERTEBRATE ANIMALS ☒ No ☐ Yes — 5a. Animal Welfare Assurance No

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
06/01/23	06/01/25				

9. APPLICANT ORGANIZATION
Name University of Miami
Address
1120 NW 14th Street
Miami, Florida 33136

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☐ State ☐ Local
Private: → ☒ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
DUNS NO. Cong. District

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name Sophia Borges
Title Senior Sponsored Programs Specialist
Address 1120 NW 14th ST, Room 1373, Miami, FL 33136
Tel: 305-243-5976 FAX: 305-243-7081
E-Mail: slb223@med.miami.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name
Title
Address
Tel: FAX:
E-Mail:

14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)* DATE

Use only if preparing an application with Multiple PDs/PIs. See http://grants.nih.gov/grants/multi_pi/index.htm for details.

Contact Program Director/Principal Investigator (Last, First, Middle): Kaur, Sonya, Sarjit

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle) Gamble, Karen	3b. DEGREE(S) PhD	3h. NIH Commons User Name KLGAMBLE
3c. POSITION TITLE Professor	3d. MAILING ADDRESS *(Street, city, state, zip code)* 1719 6th Avenue South Birmingham, AL 3529 th 4	
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT Psychiatry and Behavioral Neurology		
3f. MAJOR SUBDIVISION		
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS: karengamble@uabmc.edu	

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name
3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*	
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT		
3f. MAJOR SUBDIVISION		
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:	

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name
3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*	
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT		
3f. MAJOR SUBDIVISION		
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:	

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name
3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*	
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT		
3f. MAJOR SUBDIVISION		
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: FAX:	E-MAIL ADDRESS:	

PROJECT SUMMARY (See instructions):

The goal for this project is to examine the feasibility and tolerability of timed bright light exposure therapy to enhance circadian function and cognition in the oldest old. A major strength of this study is that it will leverage McKnight Brain Aging Registry (MBAR) data that has not yet been examined. Older age is associated with sleep disruption; in fact more than half of adults over the age of 65 years report at least one sleep complaint [1]. In the oldest old, sleep disruption is associated with increased risk of mortality [2] and physical functioning[3]. Sleep disruption also has strong associations with worse cognitive function [4]: Poor sleep has been identified as an independent predictor of executive dysfunction in older adults [4, 5] and sleep wake disturbances are seen in 25-40% of patients with dementia [6]. While there is preliminary evidence showing that changes in select cognitive correlates of poor sleep may be reversible with pharmacological intervention [7] , the efficacy of behavioral sleep interventions in enhancing cognition has not been demonstrated. This is particularly true for the oldest old, the fastest growing segment of the US population who are highest risk of cognitive decline and dementia [8, 9] who may be sensitive to negative side effects of pharmacological sleep interventions. It is assumed that interventions directed towards improving sleep will produce a concomitant positive change in cognition among the oldest old; however, there is a paucity of research evaluating whether sleep interventions in fact lead to enhanced cognitive performance. Given that cognitive function is the most important predictor of functional ability and quality of life in older adults [10], it is critical to develop and study the impact of targeted interventions. It is hoped that successful completion of this project will provide crucial pilot data to examine feasibility and tolerability among healthy oldest old who have not experienced cognitive decline but show variability in memory performance and to show effect sizes needed determine sample size and design characteristics for a larger career development award, such as an NIH K23 mentored research grant or McKnight Brain Research Foundation American Academy of Neurology Career Development Award.

RELEVANCE (See instructions):

This project will leverage the rich but underutilized data from the multi-site McKnight funded MBAR oldest old study. We hope to provide early evidence of light intervention for improving circadian rhythm dysfunction and cognition in a cognitively intact but vulnerable population with some variability in memory.

PROJECT/PERFORMANCE SITE(S) (if additional space is needed, use Project/Performance Site Format Page)

Project/Performance Site Primary Location		
Organizational Name: University of Miami		
DUNS:		
Street 1: 1140 NW 14th St	Street 2:	
City: Miami	County:	State: Florida
Province:	Country:	Zip/Postal Code: 33136
Project/Performance Site Congressional Districts:		

Additional Project/Performance Site Location		
Organizational Name: University of Alabama at Birmingham		
DUNS:		
Street 1: 1720 University Blvd	Street 2:	
City: Birmingham	County:	State: Alabama
Province:	Country:	Zip/Postal Code: 35294
Project/Performance Site Congressional Districts:		

SCIENTIFIC/KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s)/Principal Investigator(s). List all other key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Sonya Kaur	SSKAUR1	University of Miami	PI
Karen Gamble	KLGAMBLE	UAB	PI
Bonnie Levin	BONNIE_LEVIN	University of Miami	Mentor

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project
Alberto Ramos	University of Miami	Mentor

Human Embryonic Stem Cells ☒ **No** ☐ **Yes**

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

Program Director/Principal Investigator (Last, First, Middle): Kaur, Sonya, Sarjit

DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY	FROM	THROUGH
	06/2023	06/2024

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Sonya Kaur	PD/PI	1.5	1.5			17,000		17,000
TBD (UAB)	RA					17,500		17,500
SUBTOTALS →						34,500		34,500

CONSULTANT COSTS	
EQUIPMENT *(Itemize)* Re-Timer glasses for 2 sites Blue light blocking glasses	5,000
SUPPLIES *(Itemize by category)* Cognitive test materials Licenses for actiwatch	4,000
TRAVEL Travel for meetings	5,000
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS Opthalmology eye examinations	10,000
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)* Participant transportation costs	1,500

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$** 60,000
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$** 60,000

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only*.	34,500	48,500			
CONSULTANT COSTS					
EQUIPMENT	5,000				
SUPPLIES	4,000				
TRAVEL	5,000	5,000			
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS	10,000	5,000			
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES	1,500	1,500			
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	60,000	60,000			
F&A CONSORTIUM/ CONTRACTUAL COSTS					
TOTAL DIRECT COSTS	60,000	60,000			

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD	**$** 120,000

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Sonya Kaur, Ph.D., Principal Investigator (effort = 1.5 calendar month in the Year 01, 2.4 calendar months in the Year 02). Dr. Kaur will be responsible for the overall coordination and supervision of all aspects of the study. This includes hiring, training, and supervising staff/students; recruiting study participants; coordinating treatment and assessment components; scheduling and staff assignments; and data management. In addition, she will conduct all cognitive assessments pre and post intervention for study team members, assist with statistical analyses, and be responsible for reporting the study's findings.

B. OTHER PERSONNEL

TBA Research Assistant, University of Alabama at Birmingham (effort = 1.8 calendar months in Year 01 , 2.4 calendar months in Year 02). This individual will complete cognitive assessments, call participants and enter data at UAB under the supervision of Dr. Gamble, PI.

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

C. EQUIPMENT - $5000 is requested for Re-Timer glasses and blue light blocking glasses for the intervention.
$4000 is requested for cognitive test supplies.

D. TRAVEL - $5000 per year is requested for travel to University of Miami for investigators to meet and set up procedures prior to implementation of the study protocol.

E. PARTICIPANT /TRAINEE SUPPORT COSTS
$1,500 per year are requested for participant transportation costs.

F. OTHER DIRECT COSTS

F.1 Materials and Supplies

None

F. 3. Consultants

F.5. Subawards/Consortium/Contractual Costs

None

PROJECT SUMMARY

The goal for this project is to examine the feasibility and tolerability of timed bright light exposure therapy to enhance circadian function and cognition in the oldest old. A major strength of this study is that it will leverage McKnight Brain Aging Registry (MBAR) data that has not yet been examined. Older age is associated with sleep disruption; in fact more than half of adults over the age of 65 years report at least one sleep complaint [1]. In the oldest old, sleep disruption is associated with increased risk of mortality [2] and physical functioning[3]. Sleep disruption also has strong associations with worse cognitive function [4]: Poor sleep has been identified as an independent predictor of executive dysfunction in older adults [4, 5] and sleep wake disturbances are seen in 25-40% of patients with dementia [6]. While there is preliminary evidence showing that changes in select cognitive correlates of poor sleep may be reversible with pharmacological intervention [7] , the efficacy of behavioral sleep interventions in enhancing cognition has not been demonstrated in older individuals. This is particularly true for the oldest old, the fastest growing segment of the US population who are highest risk of cognitive decline and dementia [8, 9] and are disproportionately susceptible to negative side effects of pharmacological sleep interventions. ***It is assumed that interventions directed towards improving sleep will produce a concomitant positive change in cognition among the oldest old; however, there is a paucity of research evaluating whether sleep interventions in fact lead to enhanced cognitive performance****.* Given that cognitive function is the most important predictor of functional ability and quality of life in older adults [10], it is critical to develop and study the impact of targeted interventions. It is hoped that successful completion of this project will provide crucial pilot data to examine feasibility and tolerability among healthy oldest old who have not experienced cognitive decline but show variability in memory performance and to show effect sizes needed determine sample size and design characteristics for a larger career development award, such as an NIH K23 mentored research grant or McKnight Brain Research Foundation American Academy of Neurology Career Development Award.

SPECIFIC AIMS

Aim 1: To examine the feasibility and tolerability of a timed bright light intervention therapy in healthy oldest old with circadian rhythm disruption (i.e. intermediate or delayed sleep timing as measured by sleep diary and actigraphy data). We will utilize the rich data collected as part of the inter-institutional McKnight Brain Aging Registry (MBAR) and offer the intervention to a subset of participants with intermediate or delayed sleep time as derived from previously collected wrist actigraphy data. We will collect data on compliance with the intervention through daily telephone surveys, wrist actigraphy and self-reported tolerability.

Aim 2: We will collect effect sizes for post-intervention changes in measures of memory and executive function after 3 weeks of intervention and after 6 months. Based on the well-documented association between poor sleep and cognitive function [5, 11], we hypothesize that participants will exhibit improvements in memory and executive function immediately after the intervention and at 6 month follow-up. Effect sizes from these analyses will be used to generate power calculations for a larger grant.

Aim 3: As an exploratory aim, we will examine if participants report improved subjective fatigue and gait speed after 3 weeks of intervention and after 6 months. Based on our own prior studies demonstrating strong associations with sleep quality and measures of frailty in younger, cognitively unimpaired adults[12], we hypothesize that participants will report improved fatigue and gait speed immediately after the intervention and at 6 month follow-up.

SIGNIFICANCE

Cognitive function is the most important predictor of nursing home admissions, functional independence and quality of life in older adults[10]. Poor sleep quality has consistently been associated with incident dementia and declines in memory and executive function [4, 5, 13-16]. Given that 28.3% of adults in the United States report insufficient sleep, [17], it is critical to identify and evaluate the efficacy of interventions aimed at ameliorating the cognitive sequelae associated with poor sleep. This is particularly salient for the oldest old, the fastest growing demographic in the US and yet the most understudied. It is also well documented that the oldest old shows a heightened vulnerability to side effects associated with sleep medication and would thus strongly benefit from behavioral interventions. **While there are studies demonstrating the efficacy of bright light therapy in improving sleep timing and consolidation in older age, including those with dementia , there is no research to date on the oldest old. Further, there is little known regarding the effects of light intervention therapy on neuropsychological outcomes.** This may be particularly pertinent for the

oldest old, who continue to experience a heightened risk of developing cognitive impairment and dementia with increasing age [9]. We aim to address this critical gap in the literature and leverage the infrastructure and rich participant data in the MBAR by offering *a non-invasive, inexpensive, easily accessible, safe home-based bright light therapy intervention* to a subset of participants who demonstrate intermediate or delayed sleep timing.

Prevalence and public health impact of late life cognitive decline

It has been projected that the number of new cases of neurodegenerative dementia will increase 3.7 times within the next 40 years [18]. By 2047, it is projected that one in every 45 Americans will have neurodegenerative dementia [19]. Interventions that delay the disease onset by as little as two years could reduce the number of projected new cases by 1.94 million [19]. In addition, approximately 30% of adults aged 65 and older will experience cognitive decline or dementia after a stroke [20] The elderly population (aged 65 and older) is projected to reach 70 million by 2030 [19]. 13.93% of the elderly population in the United States had a diagnosis of any dementia, including vascular dementia in 2002 [19]. In the oldest old, dementia prevalence is estimated to increase by 18.2% per year [9]. As dementia leads to significant public health costs in the form of nursing home admissions, adult day care and respite services for caregivers [21], it is crucial to develop and evaluate safe, targeted preventative efforts and promote healthy cognitive aging.

Sleep quality is implicated in cognitive dysfunction

The association between sleep quality and cognitive dysfunction is well established [4, 13, 22]. Poor sleep quality has consistently been linked with increased risk for incident dementia [14-16, 23]. In addition, measures of sleep quality such as sleep duration and efficiency predicted better scores on measures of global cognitive function [24]. Furthermore, subjective complaints of poor sleep predicted declines in global cognitive functioning in older adults after 8 years. In younger adults, sleep deprivation is associated with reduced response speeds that were equivalent to legally prescribed levels of alcohol intoxication [25]. Chronic sleep restriction is also associated with poorer performances on measures of alertness, vigilance, working memory and arithmetic [26]. Given that the relationship between sleep and cognition thus appears robust across the lifespan, efficacious sleep interventions such as bright light therapy plausible early intervention to prevent or reverse cognitive decline in the oldest old who exhibit delayed sleep timing and/or high levels of wake time after sleep onset.

Sleep quality is a predictor of physical functioning, including fatigue and gait speed.

Our previous study using the McKnight Frailty Registry has demonstrated a strong association between sleep quality, physical frailty (including fatigue and gait speed) and cognitive function in middle aged and older adults [12]. In community dwelling older adults, gait speed is also associated with increased sleep fragmentation [27]. There is growing recognition that the etiology of fatigue and slowed gait speed in older adults is characterized by basal ganglia degeneration, which is thought to disrupt striato-cortical and striato-thalamo-cortical pathways involved in initiating and sustaining self-motivation, internal cueing for goal directed tasks and regulating energy expenditure and perception[28, 29]. Given that circadian function is in part governed by basal ganglia structures including the globus pallidus and the nucleus accumbens [30], *it is reasonable to suggest that interventions aimed at improving circadian rhythm function could also improve other health outcomes such as fatigue and slowed gait functions that are affected by disruption of basal ganglia pathways.*

Sleep interventions have potential to improve cognitive function

Behavioral interventions such as Tai Chi have been effective in improving sleep quality and global cognition in older adults [31]. Other treatments such as laughter therapy have shown promise in improving symptoms of insomnia, sleep quality and mood in older adults without significant benefit on cognitive function [32]. In addition, adherence to continuous partial airway pressure (CPAP) therapy among patients with obstructive sleep apnea has predicted improvements on measures of attention, short term memory, learning, planning and verbal fluency [33, 34]. Sustained, long term use of CPAP therapy in individuals with Alzheimer's Disease and obstructive sleep apnea has been demonstrated to slow declines in global cognitive functioning [35]. In addition, one month of CPAP therapy is associated with hypertrophic changes in the thalamus with concomitant improvements in verbal memory [36]. While there is mixed evidence for the efficacy of bright light therapy on cognitive function, most studies have focused on institutionalized older adults with moderate to severe dementia [37]. *There is a paucity of studies examining cognitively unimpaired or mildly impaired older adults. This is particularly true with regards to the oldest old, who have traditionally not been involved in clinical trial research.*

INNOVATION

The current study is highly innovative. Firstly, we intend to leverage the resources in the well characterized MBAR study that has been largely unexamined thus far. This data base contains extensive subjective and

objective measures of sleep, including self-report questionnaires, wrist actigraphy and sleep diary data. All participants also have cognitive assessment data available at baseline. .Secondly, examining healthy the oldest old individuals will provide unique insights on the efficacy of light therapy to further enhance cognition in a super aging cohort. Thirdly, our delivery of the intervention via telehealth modalities will provide unique insights on the feasibility and tolerability of telehealth technology in the oldest old. Since the coronavirus disease 19 (COVID 19) pandemic in 2020, there has been renewed interest in safe, effective home based treatments.

APPROACH

The specific aims of this project will be accomplished by collecting qualitative data on the feasibility and tolerability of a 3 week bright light therapy intervention. Specifically, participants will be provided with a commercially available home wearable light therapy device (Re-Timer, Adelaide, AU), with proven efficacy at improving sleep and circadian function in younger adults [38]. Participants will be instructed to wear the device within 30 minutes of waking in the morning for 90 minutes daily. A battery of neuropsychological tests will be administered via telemedicine modalities pre- and post intervention and after 6 months with special emphasis on memory, attention, processing speed and executive function, all of which are vulnerable in adults with poor sleep [33]. Participants will also complete daily sleep diaries, validated sleep questionnaires and 7 days of wrist actigraphy pre- and post intervention and after 6 months.

RESEARCH DESIGN AND METHODS

The study will be conducted in accordance with the Helsinki Declaration of 1975 and with approval from the local Institutional Review Board. Participants will undergo health assessment, sleep assessment and neuropsychological evaluation pre- and post intervention as well as after 6 months.

Study population

10 participants will be recruited from the multi-site MBAR study at the University of Miami and University of Alabama at Birmingham.

Inclusion criteria: Participants will be included in the study if they exhibit an intermediate or delayed sleep time. For the purpose of this study, chronotype will be calculated using the mid sleep time of work free days [39]. Intermediate or delayed sleep time is defined as mid sleep time of 3:00 am or later, which is the published population mean for this age group [40]. In addition, participants will be included if they are aged >85 years, no major physical disability, independent in basic and instrumental activities of daily living.

Exclusion criteria: MBAR patients have been rigorously screened for severe medical and psychiatric disorders. In addition, participants will be excluded if they have a history of retinal disorder, and more recent events that include eye surgery stroke, seizure disorder, moderate to severe traumatic brain injury, and moderate to severe cognitive impairment (score of <20 on the Montreal Cognitive Assessment). In addition, participants will be excluded if they are taking prescribed medication for sleep.

Procedures

Month	Study Events
1	Research assistant training, recruitment and pre-intervention visits
2-20	Complete recruitment & pre-intervention visits, initiate monitoring and follow-up
20-24	Complete data analysis, present results at McKnight Inter-Institutional meeting, prepare NIH proposal

Potential participants who meet the above criteria will be invited to participate in a pre-screening visit which will include routine eye examination to rule out retinal disorders that could lead to sundowning. Participants will attend a baseline and post-evaluation as well as a 6 month follow-up visit. At each visit participants will complete cognitive, sleep and health assessment measures and actigraphy data will be downloaded. The procedural timeline for the study is presented in table 1.

Intervention

Participants who are eligible and consent to the study will be provided with Re-timer glasses, an innovative new technology that delivers bright light therapy through eyeglasses with proven efficacy in multiple populations [38], including older adults [41]. Re-Timers emit a blue-green 500-nm dominant wavelength, ultraviolet-free light in portable, lightweight glasses. All participants will wear the device at the high (506 lux lm/m 2 and 230 μW/cm 2) setting. They will be instructed to wear the eyeglasses for 30 minutes 3 hours after their calculated mid sleep time daily for 3 weeks. They will also be instructed to wear blue light blocking glasses outside after 4pm on intervention days prevent blue wavelength ambient light (460–480 nm range) from suppressing melatonin onset. They will receive daily phone calls from a trained research assistant to obtain information about adherence,

difficulties with use and tolerability of the device. Specifically, adherence will be measured by examining the number of days participants utilized the intervention. Participants will rate ease of use from very easy to very difficult (4-point scale; acceptability). They will rate feasibility (5-point scale, strongly disagree to strongly agree) on whether or not they felt the device fit their routine, was comfortable, and whether they would continue to wear the device if they owned one.

Assessments

Health Assessment: Participants will complete a questionnaire with information about their medical history, family history and lifestyle. Information about participants' physical activity will be gleaned from a questionnaire validated for use in older adults [42]. Fatigue will be assessed with the Fatigue Severity Index. Gait speed will be assessed using the National Institutes of Health (NIH) toolbox 2 Minute Walk Endurance Test. All questionnaires will be administered via REDCap a HIPAA compliant data repository that allows for secure sharing of survey forms [43].

Sleep Quality Assessment: Participants will complete the Pittsburgh Sleep Quality Index (PSQI) a self-report questionnaire validated to accurately measure sleep quality in a variety of populations, including older adults [44]. Participants will also be asked to provide sleep diary data the week prior to the intervention, throughout the intervention as well as 6 months post intervention. In addition, participants will provide objective evidence of sleep quality using actigraphs that will be worn on their wrists at night. Actigraphy data will be downloaded at study visit.

Neuropsychological Evaluation: Participants will undergo a comprehensive neuropsychological evaluation pre and post intervention and after 6 months with emphasis on measures of memory, executive function and processing speed. These domains were selected based on documented relationships with measures of sleep quality [4, 22]. Attention will be measured with the digit span test from the Repeatable Battery for Assessment of Neuropsychological Status (RBANS). Executive function will be measured with select tasks from the NIH toolbox (Flanker Inhibitory Control and Attention Test, List Sorting Working Memory, Dimensional Change Card Sort Test) as well as select tasks from the Wechsler Adult Intelligence Scale, 4th edition or Wechsler Abbreviated Scale of Intelligence, 2nd edition at post testing (WAIS-IV Matrix Reasoning, WAIS-IV Similarities, WASI-II Matrix Reasoning, WASI-II Similarities). Processing Speed will also be assessed with select tests from the NIH toolbox (Pattern Comparison Processing Speed Test). Memory will be assessed using the California Verbal Learning Test, Third Edition (CVLT-3) and the RBANS story memory test.

Quality of Life: Participants' quality of life will be examined using the PROMIS Health Quality of Life measure, which is part of the NIH toolbox. In addition, participants will be screened for depression using the Beck Depression Inventory, 2nd edition (BDI-II).

Data analysis

Data analysis will be carried out with the assistance of the University of Miami Clinical and Translational Science Institute Biostatistics core.

Hypothesis testing

Aim 1: To examine the feasibility and tolerability of a timed bright light intervention therapy in the oldest old with circadian rhythm disruption (i.e. intermediate or delayed sleep timing). Information about adherence, feasibility and tolerability will be reported as percentages and analyzed qualitatively.

Aim 2: We will collect effect sizes for post-intervention changes in measures of memory and executive function after 3 weeks of intervention and after 6 months. Paired sample t tests will be used to examine changes in memory and executive function pre and post intervention and after 6 months.

Aim 3: As an exploratory aim, we will examine if participants report improved subjective fatigue and gait speed after 3 weeks of intervention and after 6 months. Paired sample t tests will be used to examine changes in fatigue and gait speed pre and post intervention and after 6 months.

Exploratory follow-up analyses: Effect sizes measuring our primary hypotheses will be calculated for a larger grant proposal. In addition, the contribution of baseline differences in characteristics between participants as well as cardiovascular risk factors (i.e. presence of hypertension, diabetes and high cholesterol) will be assessed in exploratory follow-up analyses by including these factors as covariates in linear mixed models.

Interpretation of alternative findings: We have hypothesized that bright light therapy enhances cognitive performance and reduces fatigue and gait speed in the oldest old. While total negative findings would require complete rethinking of the role of sleep in brain function, a less unlikely scenario is a positive finding in some analyses and negative findings in others. For example, changes in fatigue and gait speed without changes in cognition or improvement in measures of subjective sleep quality but not on actigraphy. These would be potentially interesting results as they would suggest specific mechanisms through which bright light therapy exerts its modulation of brain function.

MCKNIGHT CROSS-SITE COLLABORATION

Participants will be recruited from the well characterized multi-site MBAR study, with each study site recruiting 10 participants. Our team is well placed to conduct the planned studies towards our integrated aims. Our group brings together a unique skill set on experimental aging research (Kaur), and sleep and circadian science (Gamble). Dr. Gamble is an expert in circadian function and the use of circadian rhythm interventions in a wide variety of populations. We will collect necessary preliminary data and determine effect sizes for uncovering the efficacy of bright light therapy in ameliorating cognitive decline. These data will directly relate to a future NIH proposal in which we will study the mechanisms behind this relationship. We expect to complete the proposed aims in the two-year time period (see table 1). Monthly Zoom calls, along with 1-2 in person meetings will coordinate research across sites and ensure a coherent approach to the joint NIH proposal. Cognitive, demographic and sleep data will be shared between the collection sites using REDCap, a web based repository that allows biomedical researchers to securely store and share data [73].

TIMELINE AND FUTURE DIRECTIONS

The proposed study timeline is presented in Table 1. It is hoped that this study will inform larger NIH grants on the mechanisms through which bright light therapy modulates cognitive function in older adults. In particular, we would like to conduct follow-up studies examining the effects of bright light therapy on brain networks. Additional follow-up studies include the long term effects of bright light therapy on amyloid and tau.

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87. Douw, L., et al., *Cognition is related to resting-state small-world network topology: an magnetoencephalographic study.* Neuroscience, 2011. **175**: p. 169-177.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Kaur, Sonya

eRA COMMONS USER NAME (credential, e.g., agency login): SSKAUR1

POSITION TITLE: Instructor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Monash University, Melbourne, Victoria	BA	02/2009	Psychology
University of Texas at Austin, Austin, Texas	PHD	05/2017	Clinical Psychology
Henry Ford Health System, Detroit, Michigan	Resident	07/2017	Internship in Clinical Neuropsychology
University of Miami , Miami, Florida	Postdoctoral Fellow	10/2019	Postdoctoral fellow in Neuropsychology

A. Personal Statement

I am a neuropsychologist with a strong research interest in the area of sleep health disparities and cognitive aging. My prior work examined the impact of obesity and the metabolic syndrome (known sequelae of poor sleep) on cognition and neuroimaging markers of Alzheimers Disease and Related Dementias in a diverse sample of middle aged adults. Over the last 3-4 years, I have been heavily involved in research projects examining the interplay between sleep, metabolic risk, frailty and cognition in diverse Hispanic middle aged to older adults. I hope to build on this background by examining the effects of sleep interventions in slowing down or preventing Alzheimer's disease in vulnerable populations.

1. Kaur SS, Tarraf W, Wu B, Gonzalez KA, Daviglus M, Shah N, Sotres-Alvarez D, Gallo LC, Wohlgemuth W, Redline S, Gonzalez HM, Ramos AR. Modifying pathways by age and sex for the association between combined sleep disordered breathing and long sleep duration with neurocognitive decline in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Alzheimers Dement. 2021 Dec;17(12):1950-1965. PubMed PMID: 34032354.
2. Kaur S, Banerjee N, Miranda M, Slugh M, Sun-Suslow N, McInerney KF, Sun X, Ramos AR, Rundek T, Sacco RL, Levin BE. Sleep quality mediates the relationship between frailty and cognitive dysfunction in non-demented middle aged to older adults. Int Psychogeriatr. 2019 Jun;31(6):779-788. PubMed PMID: 31006402.
3. Haley AP, Oleson S, Pasha E, Birdsill A, Kaur S, Thompson J, Tanaka H. Phenotypic heterogeneity of obesity-related brain vulnerability: one-size interventions will not fit all. Ann N Y Acad Sci. 2018 Sep;1428(1):89-102. PubMed PMID: 29741211.
4. Kaur S, Gonzales MM, Strasser B, Pasha E, McNeely J, Tanaka H, Haley AP. Central Adiposity and Cortical Thickness in Midlife. Psychosom Med. 2015 Jul-Aug;77(6):671-8. PubMed PMID: 26098178.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2019 -	Instructor, University of Miami
2018 - 2019	Ad-hoc reviewer, Journal of the International Neuropsychological Society
2018 - 2019	Ad-hoc reviewer, Neurobiology of Aging
2017 - 2019	Post Doctoral Fellow, University of Miami Miller School of Medicine

2016 - 2017	Neuropsychology Intern, Henry Ford Health System
2010 - 2016	Teaching Assistant, University of Texas at Austin
2008 - 2009	Research Psychologist, National University Health System, Singapore

Honors

2020 - 2021	Sleep Research Program for Advancing Careers (SOAR) fellowship, American Academy for Sleep Medicine Foundation
2019	Young Investigators Research Forum, American Academy of Sleep Medicine Foundation
2016	Lee Willerman Award for Research Excellence, University of Texas at Austin
2016	Graduate student travel award, University of Texas at Austin
2010	Ira and Lousie Ischoe Fellowship, University of Texas at Austin

C. Contribution to Science

1. Incorporating the use of multi-modal neuroimaging with the goal of elucidating neurobiological changes has been an important area of my research. To that end, I have demonstrated that obesity (a known sequela of poor sleep) impinges upon central nervous system functioning prior to the development of cognitive decline through changes in concentrations of cerebral metabolites, cortical thickness, functional neuroimaging response and white matter microstructure.

    a. Birdsill AC, Oleson S, Kaur S, Pasha E, Ireton A, Tanaka H, Haley A. Abdominal obesity and white matter microstructure in midlife. Hum Brain Mapp. 2017 Jul;38(7):3337-3344. PubMed Central PMCID: PMC5632566.

    b. Kaur S, Birdsill AC, Steward K, Pasha E, Kruzliak P, Tanaka H, Haley AP. Higher visceral fat is associated with lower cerebral N-acetyl-aspartate ratios in middle-aged adults. Metab Brain Dis. 2017 Jun;32(3):727-733. PubMed Central PMCID: PMC6802935.

    c. Kaur S, Gonzales MM, Strasser B, Pasha E, McNeely J, Tanaka H, Haley AP. Central Adiposity and Cortical Thickness in Midlife. Psychosom Med. 2015 Jul-Aug;77(6):671-8. PubMed PMID: 26098178.

    d. Gonzales MM, Kaur S, Eagan DE, Goudarzi K, Pasha E, Doan DC, Tanaka H, Haley AP. Central adiposity and the functional magnetic resonance imaging response to cognitive challenge. Int J Obes (Lond). 2014 Sep;38(9):1193-9. PubMed Central PMCID: PMC4097967.

2. Given my clinical background, I have pursued research with regards to neurobiological markers of cognition in diverse samples of middle aged and older adults. In particular, I have explored the effects of neurotrophins, pro-inflammatory cytokines and vascular risk in cognitively healthy middle aged adults. In highlighting the mediating effect of these peripheral markers on cognition, I have added to the literature on the significant effect of vascular risk on cognitive outcomes.

    a. Gourley D, Pasha EP, Kaur SS, Haley AP, Tanaka H. Association of Dementia and Vascular Risk Scores With Cortical Thickness and Cognition in Low-risk Middle-aged Adults. Alzheimer Dis Assoc Disord. 2020 Oct-Dec;34(4):313-317. PubMed PMID: 32467426.

    b. Kaur S, Gonzales MM, Tarumi T, Villalpando A, Alkatan M, Pyron M, Tanaka H, Haley AP. Serum Brain-Derived Neurotrophic Factor Mediates the Relationship between Abdominal Adiposity and Executive Function in Middle Age. J Int Neuropsychol Soc. 2016 May;22(5):493-500. PubMed PMID: 27026196.

    c. Kaur SS, Gonzales MM, Eagan DE, Goudarzi K, Tanaka H, Haley AP. Inflammation as a mediator of the relationship between cortical thickness and metabolic syndrome. Brain Imaging Behav. 2015 Dec;9(4):737-43. PubMed Central PMCID: PMC4424190.

3. Given the underrepresentation of minorities in clinical research, I have made conducting research that includes diverse samples an important priority. To that end, I have contributed to publications that have highlighted important differences in arterial stiffness, cortical thinning and cognitive dysfunction among non-demented participants who identify as Hispanic/Latino.

a. Kaur SS, Tarraf W, Wu B, Gonzalez KA, Daviglus M, Shah N, Sotres-Alvarez D, Gallo LC, Wohlgemuth W, Redline S, Gonzalez HM, Ramos AR. Modifying pathways by age and sex for the association between combined sleep disordered breathing and long sleep duration with neurocognitive decline in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Alzheimers Dement. 2021 Dec;17(12):1950-1965. PubMed PMID: 34032354.

b. Agudelo C, Tarraf W, Wu B, Wallace DM, Patel SR, Redline S, Kaur S, Daviglus M, Zee PC, Simonelli G, Mossavar-Rahmani Y, Sotres-Alvarez D, Zeng D, Gallo LC, González HM, Ramos AR. Actigraphic sleep patterns and cognitive decline in the Hispanic Community Health Study/Study of Latinos. Alzheimers Dement. 2021 Jun;17(6):959-968. PubMed Central PMCID: PMC8312581.

c. Gourley D, Pasha EP, Kaur SS, Haley AP, Tanaka H. Association of Dementia and Vascular Risk Scores With Cortical Thickness and Cognition in Low-risk Middle-aged Adults. Alzheimer Dis Assoc Disord. 2020 Oct-Dec;34(4):313-317. PubMed PMID: 32467426.

d. Pasha EP, Kaur SS, Gonzales MM, Machin DR, Kasischke K, Tanaka H, Haley AP. Vascular function, cerebral cortical thickness, and cognitive performance in middle-aged Hispanic and non-Hispanic Caucasian adults. J Clin Hypertens (Greenwich). 2015 Apr;17(4):306-12. PubMed Central PMCID: PMC4390456.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Karen L. Gamble

eRA COMMONS USER NAME (credential, e.g., agency login): KLGAMBLE

POSITION TITLE: Professor of Psychiatry and Behavioral Neurobiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
King College, Bristol, TN	B.A.	1993-1996	Psychology
Georgia State University, Atlanta, GA	M.A.	1999-2001	Neuropsychology
Georgia State University, Atlanta, GA	Ph.D.	2001-2004	Neuropsychology

A. Personal Statement

The overall goal of my research program is to investigate environmental modulation of circadian clock function in mammalian systems and the contribution of clock disruption to pathological disease. I have diverse experience in circadian rhythm and sleep disorders at the bench in animal models as well as at the clinical level, publishing extensively in the chronobiology and sleep fields. My research program has continually received federal NIH funding for circadian rhythms projects. At UAB, I currently lead the Circadian Clocks group, which is a group of > 40 investigators at UAB with common interests in sleep and/or circadian physiology. Through this very inter-disciplinary group, numerous collaborations have been established. My basic science laboratory has recently discovered day-night differences in neuronal excitability is an early marker of disease in pathological conditions such as Alzheimer's disease and Parkinson's Disease (currently funded by NIA and NINDS). In our clinical projects, we have published showing the sleep, cognitive, and cardiometabolic consequences of shift work as well as the potential therapeutic benefit of light therapy for adults with ADHD. We are currently investigating sleep and circadian regulation of craving and withdrawal in smokers. For the proposed project, I will provide mentoring in chronobiology as well as lend my expertise in tailored light therapy using our published methods. Ongoing projects that I would like to highlight include:

R01 DA046096
Cropsey, Gamble (MPI)
07/15/20-03/31/25
Circadian and sleep mechanisms among racial groups for nicotine dependence, craving, and withdrawal

R01 NS082413
Gamble (PI)
03/15/13 – 03/31/23
Circadian Dysfunction and Neurodegenerative Disease

R01 NS108713
Gamble, Cowell (MPI)
07/15/18 - 06/30/23
The Nigral Molecular Clock and Vulnerability to Neurodegeneration

R01 AG061785
Roberson, Gamble (MPI)
09/15/21 – 05/31/26
Circadian Changes in Network Excitability and Alzheimer Disease Pathogenesis

Citations:

1. Fusilier AR, Davis JA, Paul JR, Yates SD, McMeekin LJ, Goode LK, Mokashi MV, Remiszewski N, van Groen T, Cowell RM, McMahon LL, Roberson ED, **Gamble KL** (2021). Dysregulated clock gene expression and abnormal diurnal regulation of hippocampal inhibitory transmission and spatial memory in amyloid precursor protein transgenic mice. Neurobiol Dis,158: 105454. PMCID: PMC8477442.
2. Davis JA, Paul JR, Yates SD, Cutts EJ, McMahon LL, Pollock JS, Pollock DM, Bailey SM, **Gamble KL** (2021). Time-restricted feeding rescues high-fat-diet-induced hippocampal impairment. iScience, 24(6):102532. PMCID: PMC8188491.
3. Fargason, R.E., Fobian, A.D., Hablitz, L.M., Paul, J.R., White, B.A., Cropsey, K.L., and **Gamble, K.L.** (2017). Correcting delayed circadian phase with bright light therapy predicts improvement in ADHD symptoms: A pilot study. J Psych Res, 91, 105-110. NIH Public Access Compliance: N/A.
4. 79. Hylton E Molzof, S. Justin Thomas, Courtney M Peterson, Gabrielle F Gloston, Russell L Johnson and Karen L. Gamble (2022). Nightshift Work and Nighttime Eating are Associated with Higher Insulin and Leptin Levels in Hospital Nurses. Front Endocrinol, 13:876752. PMCID: PMC9124849.

B. Positions and Honors

Positions and Employment

1994-1996	Undergraduate Assistant, Dept of Psychology, King College
1999–2004	Graduate Research Assistant, Dept of Psychology, Georgia State University
2004–2009	Postdoctoral Research Associate, Dept of Biological Sciences, Vanderbilt University
2009-2015	Assistant Professor, Dept of Psychiatry, University of Alabama at Birmingham
2016-	Tate Jordan Thomas Professorship in Psychiatric Medicine
2015-2020	Associate Professor, Dept of Psychiatry, University of Alabama at Birmingham
2000-	Society for Neuroscience, member
2000-	Society for Research in Biological Rhythms (SRBR), member
2011-	Society for Light Treatment and Biological Rhythms, member
2013-	International Working Time Society, member
2013-2016	SRBR 2014 and 2016, Professional Development Chair
2015	SRBR Rep. to the Drowsy Driving Consensus Workgroup, National Sleep Foundation
2015-	Co-Director, UAB Graduate Biomedical Sciences (GBS) Neuroscience Theme
2020-	SRBR Co-Chair, Government Affairs Committee
2020-	Professor, Dept of Psychiatry, University of Alabama at Birmingham
2020-2021	Interim Director, Behavioral Neurobiology Division, Department of Psychiatry
2020-	Chair, Society for Neuroscience, Sleep and Circadian DataBlitz Committee
2021-present	Vice Chair of Basic Research, Department of Psychiatry

HONORS:

1996	Bachelor of Arts Degree, Summa Cum Laude, King College
2003	Bailey M. Wade Award, Georgia State University
2004	Richard Morrell Outstanding Graduate Student Fellowship Award, Georgia State University
2004	Postdoctoral Research Fellowship, Vanderbilt Kennedy Ctr for Res on Human Development
2005	Postdoctoral Neurogenomics Fellowship, Vanderbilt University, NIH T32 MH065215
2006	Society for Research in Biological Rhythms Travel Award
2009	Gordon Research Conference on Chronobiology Hot Topics Selected Speaker
2010	*Assembling a Multi-Cellular Circadian Pacemaker,* Lorentz Centre Workshop, Leiden, Netherlands
2011	National Science Foundation Modulation Panel, Panelist
2012	Society for Research in Biological Rhythms (SRBR) Meeting Workshop Leader
2013	NIH NIA, FOA "Molecular Mechanisms of Circadian Clocks in Aging Tissues," SEP Member
2013	NIH NIAAA, "Alcohol Abuse, Sleep Disorders and Circadian Rhythms (R21)," Ad hoc member
2013	International Scientific Group of Circadian Rhythm Experts (INSPIRE) Meeting, Italy
2013	International Chronobiology School, Instructor
2013	Young Investigator, William C. Dement Sleep and Chronobiology Apprenticeship, Brown University
2013	Invited speaker, 21st International Symposium on Shiftwork and Working Time 2013, Sauipe, Brazil
2014	CDC NIOSH, "Safety and Occupational Health Study Section," Ad hoc member
2014	UAB Department of Psychiatry, Innovative Teaching Award
2015	CDC NIOSH, "Safety and Occupational Health Study Section," Ad hoc member
2015	NIH CSR, "Neuroendocrinology, Neuroimmunology, Rhythms, and Sleep (NNRS)," Ad hoc member

2015 Invited speaker, Latin American Society for Chronobiology 2015, Sao Paolo, Brazil
2019 NIH CSR, "Behavioral Neuroendocrinology, Neuroimmunology, Rhythms, and Sleep (BNRS)," member

C. Contribution to Science

80 publications; current h-index = 35, i10-index = 63, and Google Scholar citations 4236 (Jun 2022).
http://www.ncbi.nlm.nih.gov/sites/myncbi/karen.gamble.1/bibliography/40897530/public/?sort=date&direction=ascending

1. **Neurochemistry of circadian clock synchronization.** During my graduate training at Georgia State University and post-doctoral training at Vanderbilt University, my research investigated how environmental signals are communicated with the neuronal network to produce a shift in circadian timing. The results of these studies defined the effects of photic signaling molecules VIP and GRP and the nonphotic neurotransmitter NPY and their effects on SCN neuronal synchronization and phase resetting properties within the primary clock in the suprachiasmatic nucleus (SCN) of the hypothalamus. By using GRP as a proxy for light, we also showed that upregulation of the circadian clock gene *Per1* is necessary for increased excitability associated with the early phase resetting period. Collectively, these studies have demonstrated the importance of excitatory and inhibitory neurotransmitter interactions as well as how these neurotransmitters (especially VIP) impact the intrinsic clock in individual neurons as well as the neuronal clock network (interneuronal synchronization).
   a. **Gamble KL**, Paul KN, Karom MC, Tosini G, Albers HE. (2006). Paradoxical effects of NPY in the suprachiasmatic nucleus. Eur J Neurosci 23(9):2488-94. Public Access Policy N/A
   b. **Gamble KL**, Allen GC, Zhou T, McMahon DG. (2007). Gastrin-releasing peptide mediates light-like resetting of the suprachiasmatic nucleus circadian pacemaker through cAMP response element-binding protein and *Per1* activation. J Neurosci 27(44):12078-87. Public Access Policy N/A
   c. Ciarleglio CM, **Gamble KL**, Axley JC, Strauss BR, Cohen JY, Colwell CS, McMahon DG. (2009). Population encoding by circadian clock neurons organizes circadian behavior. J Neurosci 29(6):1670-6. PMCID: PMC2670758.
   d. Ciarleglio CM1, Axley JC, Strauss BR, **Gamble KL**, McMahon DG. Perinatal photoperiod imprints the circadian clock (2011). Nat Neurosci 14(1):25-7. PMCID: PMC3058292.
2. **Circadian regulation of neuronal excitability.** Beginning with my post-doctoral training under Dr. Doug McMahon at Vanderbilt University, I sought to extend my research on interactions of neurotransmitters in the circadian clock from gene expression and behavior to neurophysiological output. Specifically, my research program has sought to address how the intrinsic cellular clock in neurons directs both endogenous and environmentally-induced changes in neurophysiological properties and intrinsic excitability. For example, we defined the effects of photic signaling molecules VIP and GRP and the nonphotic neurotransmitter NPY and their effects on SCN neuronal membrane properties. More recently, my laboratory reported a novel discovery that G-protein coupled, inwardly rectifying potassium (GIRK) channel proteins and channel function (key channels implicated in addiction, epilepsy, and neurodevelopmental disease) are regulated in a time-of-day-dependent manner as well as in response to NPY. Collectively, these studies have demonstrated the importance of excitatory and inhibitory neurotransmitter interactions as well as how these neurotransmitters impact the intrinsic membrane properties and excitability.
   a. Hablitz, L.M., Molzof, H.M., Abrahamsson, K.E., Cooper, J.M., Prosser, R.A. and **Gamble, K.L.** (2015). GIRK channels mediate the nonphotic effects of exogenous melatonin. J Neurosci, 35(45):14957-65. PMCID: PMC4642232.
   b. Hablitz, L.M., Molzof, H.E., Paul, J.R, Johnson, R.L. and **Gamble, K.L.** (2014). Suprachiasmatic nucleus function and circadian entrainment are modulated by G protein-coupled inwardly-rectifying (GIRK) channels. J Physiol, 592(Pt 22):5079-92. PMCID: PMC4259544
   c. Kudo T, Tahara Y, **Gamble KL**, McMahon DG, Block GD, Colwell CS. (2013). Vasoactive intestinal peptide produces long-lasting changes in neural activity in the suprachiasmatic nucleus. J Neurophysiol 110(5):1097-106. PMCID: PMC4073931.
   d. Besing, R.C., Hablitz, L.M., Paul, J.R., Johnson, R.L., Prosser, R.A., & **Gamble, K.L.** (2011). NPY-induced phase shifts of PER2::LUC rhythms are mediated by long-term suppression of neuronal excitability in a phase-specific manner. Chronobiol Int 29(2), 91-102. PMCID: PMC3568491
3. **GSK3 phosphorylation state regulation of neuronal excitability and behavior.** A key question in the circadian field is how the intrinsic molecular clock is linked to daily changes in membrane properties and excitability. We recently discovered that a ubiquitous kinase, GSK3, is regulated by the circadian clock and in turn, regulates neuronal excitability in a time-of-day-dependent manner. This finding is critically important

to overall brain health because GSK3 is found throughout the brain in other areas expressing a molecular clock. Moreover, GSK3 is altered during aging and is implicated in neurodegenerative disease such as Alzheimer's disease as well as in regulation of mood and neuropsychiatric disease such as depression. My laboratory is currently funded to examine circadian rhythms in GSK3 in extra-SCN brain regions in the normal physiological condition as well as in aging and neurodegenerative disease. We also have experience with and ongoing projects in examining the role of GSK3 and the circadian clock in regulating neuropsychiatric disease such depression and bipolar disorder.

a. Besing, R.C., Rogers, C.O., Paul J.R., Hablitz, L.M., Johnson, R.L., McMahon, L.L. and **Gamble, K.L.** (2017). Glycogen kinase synthase 3 regulates the hippocampal molecular clock and day-night differences in plasticity. Hippocampus, 17(8): 890-898. PMCID: PMC5511075.
b. Paul JR, McKeown AS, Davis JA, Totsch SK, Mintz EM, Kraft TW, Cowell RM, **Gamble KL**. (2017). Glycogen synthase kinase 3 regulates photic signaling in the suprachiasmatic nucleus. Eur J Neurosci, 45(8):1102-1110. PMCID: PMC5395359.
c. Besing, R.C., Paul J.R., Hablitz, L.M., Johnson, R.L., Young, M.E. and **Gamble, K.L.** (2015). Molecular clock gene regulation by glycogen synthase kinase 3 (GSK3) in the suprachiasmatic nucleus. J Biol Rhythms, 30(2):155-60. PMCID: PMC4586074
d. Paul, J.R., Johnson, R.L., Jope, R.S., and **Gamble, K.L.** (2012). Disruption of circadian rhythmicity and suprachiasmatic action potential frequency in a mouse model with constitutive activation of glycogen synthase kinase-3. Neuroscience, 226, 1-9. PMCID: PMC3490018.

4. **Circadian rhythms and sleep timing in humans.** In addition to basic chronobiology research, research in my laboratory has also addressed the question of whether the timing of sleep (and not just sleep quantity/quality) is an important moderator of shift work adaptation as well as inattention and hyper-activity in adults with ADHD diagnosis. Specifically, we have discovered that delayed sleep timing significantly predicts inattention and hyper-active/impulsive symptoms in adults with ADHD. Furthermore, we have defined novel sleep strategies utilized by permanent night shift workers (hospital nurses) to switch back and forth from diurnal sleep (on work days) to nocturnal sleep (on days off). Sleep strategies that utilize daily naps or sleep deprivation are significantly associated with greater disruptions of sleep, poor adjustment to shift work, and more frequent reports of cardiovascular problems.
   a. Fargason, R.E., Fobian, A.D., Hablitz, L.M., Paul, J.R., White, B.A., Cropsey, K.L., and **Gamble, K.L.** (2017). Correcting delayed circadian phase with bright light therapy predicts improvement in ADHD symptoms: A pilot study. J Psych Res, 91, 105-110. NIH Public Access Compliance: N/A.
   b. Molzof HE, Wirth MD, Burch JB, Shivappa N, Hebert JR, Johnson RL, **Gamble KL**. The impact of meal timing on cardiometabolic syndrome indicators in shift workers. Chronobiol Int (2017) 34(3): 337-348. PMID: 28107043. PMCID: PMC5527274.
   c. Petrov, M.E., Clark, C.B., Molzof, H.E., Johnson, R.L. Jr., Cropsey, K.L., **Gamble, K.L.** (2014). Sleep Strategies of Night-Shift Nurses on Days Off: Which Ones are Most Adaptive? Front Neurol 5:277. PMCID: PMC4271573
   d. **Gamble, K.L.,** May, R.S., Besing, R.C., Tankersly, A.P., and Fargason, R.E. (2012). Delayed Sleep Timing and Symptoms in Adults with Attention-Deficit/Hyperactivity Disorder: A Controlled Actigraphy Study. Chronobiol Int, 30(4):598-606. Public Access Policy N/A

5. **Circadian regulation of cardiometabolic disease.** Although classically trained as a behavioral neuroscientist, I have recently begun work in the metabolism field, specifically as it relates to circadian clock control. To this end, we have established vibrant collaborations among the Bailey, Young, and Gamble laboratories that have produced numerous peer-reviewed articles in the past few years. The majority of our collaborative work has focused on circadian regulation of metabolic mechanisms and interactions with time-of-day restricted feeding or ethanol consumption. Findings in these areas have demonstrated the importance of the cardiomyocyte circadian clock for cardiovascular health and susceptibility to metabolic disease.
   a. Zhang D, Colson JC, Jin C, Becker BK, Rhoads MK, Pati P, Neder TH, King MA, Valcin JA, Tao B, Kasztan M, Paul JR, Bailey SM, Pollock JS, **Gamble KL**, Pollock DM. (2021). Timing of Food Intake Drives the Circadian Rhythm of Blood Pressure. Function (Oxf). 2(1):zqaa034. PMCID: PMC7772288.
   b. Valcin JA, Udoh US, Swain TM, Andringa KK, Patel CR, Al Diffalha S, Baker PRS, **Gamble KL**, and Bailey SM. (2020) Alcohol and liver clock disruption increase small droplet macrosteatosis, alter liver metabolism and clock gene mRNA rhythms, and remodel the triglyceride lipidome in mouse liver. Front Physiol. 11:1048. PMCID: PMC7504911.
   c. Speed JS, Hyndman KA, Roth K, Heimlich JB, Kasztan M, Fox BM, Johnston JG, Becker BK, Jin C, **Gamble KL**, Young ME, Pollock JS, Pollock DM (2018). High dietary sodium causes dyssynchrony of

the renal molecular clock in rats. Am J Physiol Renal Physiol (2018) Jan 1; 314(1): F89-F98. PMCID: PMC5866350.

d. Udoh US, Swain TM, Filiano AN, **Gamble KL**, Young ME, Bailey SM (2015). Chronic ethanol consumption disrupts diurnal rhythms of hepatic glycogen metabolism in mice. Am J Physiol Gastrointest Liver Physiol, 308(11):G964-74. PMCID: PMC4451320

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Bonnie E. Levin, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): bonnie_levin

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Georgetown University	BS (cum laude)	1974	Psychology
Temple University	Ph.D.	1983	Psychology

A. Personal Statement

I have broad expertise in cognitive, socio-emotional and behavioral change over the life course. My primary focus has been on the intersection between normative aging and early neurodegenerative disease. A major interest has been on identifying the cognitive, social-emotional, and physical changes signaling the beginning of a decline and developing interventions to change the downward trajectory. I founded the Division of Neuropsychology and Cognitive Neuroscience in the Department of Neurology at the University of Miami Miller School of Medicine, a bilingual clinical service that evaluates over 800 patients a year. At this time, I hold the Bernard and Alexandria Schoninger Professorship in Neurology. In this capacity, I direct the Schoninger Neuropsychology Teaching Program in which my role is to direct and implement all cognitive and behavioral assessments carried out in the Division of Neuropsychology and Cognitive Neuroscience and supervise the activities of eight practicum graduate students, four post doctoral fellows and oversee six clinical neuropsychology faculty. I supervise all research activities within the Division and mentor advanced PhD students and fellows to become clinician-scientists. I work collaboratively with research teams in Neurology, Neurosurgery, Bascom Palmer Eye Institute, Radiology and Otolaryngology on multiple projects examining cognitive, behavioral, and neural changes associated with normal aging and neurodegenerative disease. I am a Co-I on the NIH-funded population based Northern Manhattan Study (NOMAS), in which I am a member of the dementia adjudication consensus panel. Other projects where I serve as a Co-I include: a project investigating the role of gut microbiota on brain metabolism, inflammation, and cognition in Alzheimer's disease. I am currently the UM site PI of the cognitive core on the Mcknight Brain Research Institute study of the oldest old funded, working in close collaboration with three other institutions. I also direct the UM McKnight Frailty Project, a study that examines frailty as a marker of physical vulnerability and risk factor for cognitive decline. I am a co-I on a funded NIH/NIA U19 examining precision medicine' concepts to predict individual brain health risks and discover personalized solutions to maximize cognitive healthspan. At this time, I am the PI of a funded FLDOH Moore pilot study and Co-I on a consortium (co-I) that seeks to translate a novel tool of scam susceptibility based on real life scams for use in Hispanic/Latinx individuals with mild cognitive impairment/Alzheimer's disease and develop training exercises to reduce exploitation risk in patients and their caregivers.

I believe that my strong research expertise in cognitive, behavioral, and socioemotional aging neuroscience over the adult lifespan and in the detection of early biomarkers of behavioral and cognitive decline in neurodegenerative disease and a history of working closely with the team at University of Miami, combined with experience as the director of a large clinical neuroscience lab, puts me in an excellent serve puts me in an

excellent position to collaborate with Dr. Kaur on a study that focuses on circadian rhythm and mild cognitive impairment. I will serve as her primary mentor in the area of cognitive aging.

Ongoing and recently completed projects that I would like to highlight include:

R01AG068110 (PI: Pahwa) 09/30/20-04/30/25 $761,028
NIH/NIA
Tfh dysfunction in HIV and Aging
This study addresses the immune deficiency in virally suppressed *HIV* infected young and older individuals that can lead to failure of an effective response to influenza vaccination. It also provides insight into the functioning of a specialized peripheral blood CD4 T cell subset (pTfh for peripheral T follicular helper cell) that can be of critical importance in facilitating Ab responses to influenza and other vaccines. Understanding the underlying defects in pTfh and other cells that impair the antibody secretion by B cells in the context of aging and *HIV* infection may lead to development of scientific strategies to optimize vaccine responses to improve the immune responses in *HIV* infected elderly population. Role: Co-Investigator

Scythian Bioscience (PI: Hotz) 7/25/16-1/30/22 $7,478,710
The Effects of Cannabinoids on TBI
This study will examine the inflammatory properties of cannabinoids and determine whether they can be used as a therapeutic intervention in traumatic brain injury.
Role: Co-Investigator, Director of Clinical Trials

21A16 (Levin) 4/7/21-2/28/23 $100,000
Ed and Ethel Moore Alzheimer's Disease Research Program (FDOH)
Detection and reduction of scam susceptibility among Hispanic/Latinx and non-Hispanic/Latinx individuals with mild cognitive impairment and Alzheimer's disease
Translate from English to Spanish a novel and ecologically valid screening instrument to assess susceptibility to scamming based on real life scams. This measure is administered to susceptibility among Hispanic/Latinx and non-Hispanic/Latinx individuals with MCI and early AD and compare with caregiver ratings. It also develops a tailored educational intervention to promote knowledge of scam awareness and decrease susceptibility to deception. Role: PI

R56NS029993-28A1 (PI: Sacco) NIH/NINDS 02/01/03-08/31/22 $537,250
Stroke Incidence and Risk Factors in a Tri-Ethnic Region
The goals of this project are to determine the effects of risk factors for stroke, MI, and vascular death, as well as evaluate predictors of cognitive impairment and the importance of subclinical MRI findings in a prospective cohort study of 3300 persons from 3 race-ethnic groups from Northern Manhattan. Role: Co-Investigator

1U19AG056169-01A1 (PI, Barnes, U Arizona) 09/01/2021-8/31/2026 $12,472,457
NIH/NIA
Precision Aging Network: Closing the Gap Between Cognitive Healthspan and Human Lifespan
The strategic goal of the Precision Aging Network (PAN) is to develop the essential scientific knowledge and appropriate technologies for the application of 'precision medicine' concepts to predict individual brain health risks and discover personalized solutions to maximize cognitive healthspan. Role: Co-Investigator, Project 2

B. Positions, Scientific Appointments, and Honors

1979-1980	Fellow in Psychology, Department of Psychiatry, Harvard Medical School, Boston, MA
1979-1980	Intern, Clinical Pediatric Neuropsychology, Children's Hospital Center, Boston, MA.
1980	Extern, Boston Veteran's Administration Hospital, Boston, MA
1981-1982	Instructor, Department of Neurology, University of Miami

1981	Director, Division of Neuropsychology, Department of Neurology, University of Miami
1986-1992	Assistant Professor, Department of Neurology, University of Miami
1992-2011	Associate Professor (with tenure), Department of Neurology, University of Miami Miller School of Medicine
2011-	Professor of Neurology, Department of Neurology, University of Miami Miller School of Medicine

Honors

Cum Laude, Georgetown University; Psi Chi Honor Society1974

Fellow, Mahoney Residential College

International Neuropsychology Society (INS) Program Chair-1997

INS Board of Governors 1998-2001

NINDS Study Section Member NSD-K, 2001-2005

NINDS AD hoc Reviewer-NSD-A 2001, 2002

NINDS Special Emphasis Panels 7/1998, 8/1999, 12/1999, 5/2000, 8/2000, 10/2000, 12/2001, 6/2001, 10/2001, 8/2002, 12/2002, 1/2004, 8/2004, 12/2004, 2/2005, 1/2006, 10/2006, 11/2006, 11/2006, 6/2007, (6/24 & 6/29) 3/2008, 4/2008.

NINDS Ad hoc reviewer NSD-K Study Section, 2006 - 2008

Alzheimer Association Medical and Scientific Council Reviewer, 1999, 2002

Consultant: University of Miami Brain Endowment Bank, Department of Neurology; Clinical Neuroscience Unit, UM Department of Neurology

Member, National Acute Brain Injury Study: Hypothermia II: Data Safety of Monitoring Board

Pediatrics; UM Sleep Center, Department of Neurology.

Professional Advisory Board: Epilepsy Foundation of South Florida

Editorial Boards: Neuropsychology, Journal of International Neuropsychology Society, Neuropsychology Review, Aging, Neuropsychology and Cognition

Alexandria and Bernard Schoninger Endowed Professorship in Neurology, 2009

C. Contributions to Science

C.1. Over the past 30 years, my research has focused on cognitive and behavioral changes over the adult life span. My research projects are largely in the field of aging, examining age-related cognitive decline and early biomarkers of sensory, behavioral, and cognitive decline in normal aging and neurodegenerative disease. As the Schoninger Professor of Neurology, I oversee the Division of Neuropsychology and Cognitive Neuroscience, a major training and research site that evaluates over 300 patients a year examining age related cognitive change as well as pathological behavioral alterations associated with degenerative disease. I have published extensively on cognitive change across the adult lifespan.

1. Hoffer ME, **Levin BE**, Snapp H, Buskirk J, Balaban C. Acute Findings in an Acquired NeurosensoryDysfunction. Laryngoscope Investig Otolaryngol. 2018 Dec 12;4(1):124-131. doi: 10.1002/lio2.231. eCollection 2019 Feb.
2. Rundek T, Gardener H, Dias Saporta AS, Loewenstein DA, Duara R, Wright CB, Dong C, **Levin B,** Elkind MSV, Sacco RL. Global Vascular Risk Score and CAIDE Dementia Risk Score Predict Cognitive Function in the Northern Manhattan Study. J Alzheimers Dis. 2020;73(3):1221-1231
3. Kaur, S, Banerjee, N, Miranda, M, Slugh, M, Sun-Suslow, N, McInerney, K.F, Sun, X, Ramos, A.R., Rundek, T., Sacco, R.L., **Levin, B.E**. Sleep quality mediates the relationship between frailty and cognitive dysfunction in non-demented middle aged to older adults, International Psychogeriatrics 2019 Jun;31(6):779-788.
4. Airen S, Shi C, Liu Z, **Levin BE**, Signorile JF, Wang J, Jiang H. Focal alteration of the intraretinal layers in neurodegenerative disorders. Ann Eye Sci 2020;5:8.

C.2. Our group was among the earliest investigators to document and describe non-motor changes in Parkinson's disease. I examined how gait and other lateralized motor changes are linked to cognitive and

behavioral symptoms and Parkinson's disease progression. These studies reflect my longstanding interest in gait, movement, and cognition.

1. **Levin, BE**, Llabre, MM, Weiner, WJ: Cognitive impairments associated with early Parkinson's disease. Neurology, 1989, 39:557-561.
2. **Levin, BE**, Llabre, MM, Weiner, WJ, Brown, MC: Visuospatial decline in Parkinson's disease. Neurology, 1991; 41:365-369.
3. Tomer, R, **Levin, BE**, Weiner, WJ: Side of motor onset influences cognition in Parkinson's disease. Annals of Neurology, 1993; 34:579-584.
4. Katzen, H, **Levin, BE**, Llabre, M: Age of onset influences cognition in Parkinson's disease. Journal of International Neuropsychological Society, 1998, 4, 285-290.

C.3. I am am involved in several studies examining the relationship between proton magnetic resonance spectroscopy (MRS) metabolites and other imaging changes associated with normative aging, TBI, ALS and Parkinson's disease. These studies utilize a unique whole-brain analysis that permits the study of a large fraction of the brain volume, including the cortical mantle. My role as the neuropsychologist on these projects is to identify sensitive outcome measures and to work with my collaborators linking the behavioral presentation associated with traumatic injury or neurologic illness with distributions of white matter changes, cortical brain volume, and proton MRS observed metabolites throughout the whole brain.

1. **Levin BE**, Katzen, HL, Maudsley, A, Post, J, Myerson, C, Govind, G, Nahab, F, Scanlon, B, Mittel. A Whole-brain proton MR spectroscopic imaging in Parkinson's disease. Journal of Neuroimaging, 2014, 24, 39-44
2. Maudsley, A, Govind, V, **Levin, BE**, Saigal, G, Harris, L, Sheriff, S Distributions of MR Diffusion and Spectroscopy Measures with Traumatic Brain Injury. J. Neurotrauma. 2015; 32 (14): 1056-1063
3. Widerstrom-Noga, E, Govind, VB, Adcock, J**, Levin, BE**, Maudsley, A Subacute Pain after TBI is associated with lower insular N-acetyl-aspartate concentrations. J Neurotrauma, 2016; 33(14):1380-9.
4. Headley, A., De Leon-Benedetti, A., Dong, C., **Levin, B.,** Loewenstein, D., Camargo C., Rundek, T., Zetterberg, H., Blennow, K., Wright, C., Sun, X. and AD Neuroimaging Initiative. Neurogranin as a Predictor of Memory and Eecutive Function Decline in MCI patients, 2018, *Neurology*, *90*(10), e887–e895. doi:10.1212/WNL.0000000000005057

Complete List of Published Work at NCBI:
http://www.ncbi.nlm.nih.gov/pubmed/?term=(%22levin%2C%20bonnie%22%5BAll%20Fields%5D)&cmd=DetailsSearch

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: Feasibility of a timed bright light exposure therapy to improve circadian function

Principal Investigator(s): Kaur, Sonya, Sarjit

Institutions: U. Miami; U. Alabama

OVERALL IMPACT

Please provide your assessment of the strengths and weaknesses of the application using brief bullet points to reflect the project's likelihood to exert a sustained, powerful impact on the research field(s) involved, using the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact. Please score the application's potential using the following 1 (Highest Impact) to 9 (Lowest Impact) rating scale for each review criteria section:

Impact	High	Medium	Low
Score: 5	1 2 3	4 5 6	7 8 9

Overall Impact *Write a brief paragraph summarizing the factors that informed your Overall Impact score.*

One of the proposal's strengths is the emphasis on improving sleep in the oldest old, which potentially can have a measurable improvement in cognitive functioning. The PI has considerable experience in neuropsychology and has studied the role of lifestyle factors like sleep on cognition. The mentoring team is quite strong and the research infrastructure at the two participating institutions is impressive. The application of bright light exposure therapy to the oldest old is a reasonable extension of the existing literature. There were a few aspects of the application, however, that potentially limit the proposal's impact. One of the study goals is to assess tolerability and feasibility but these are not well defined in the application. The absence of a control group also limits the ability to estimate effect sizes for a larger study. A significant methodological gap is not addressing whether the light intervention improves sleep or circadian rhythm; without this step, looking for changes in cognition is less meaningful. The proposed neuropsychological battery is also excessive, with no operational definitions of key constructs and ways of addressing practice effect.

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance 5

Strengths

- This project targets sleep, a critical element in cognitive aging
- Establishing that bright light therapy is feasible and tolerable in the oldest old will lead to additional, well-powered studies

Weaknesses

- Presumably, bright light therapy enhances cognition by improving sleep. Unfortunately, measurement of whether sleep improves after treatment is left out, making it difficult to draw any inferences about post-intervention changes in cognition

- Aims 2 and 3 are designed to collect effect sizes but the absence of any control group makes this less likely to be successful
- The lack of clear criteria for what feasible and tolerable are limits the potential significance of Aim 1
- The impact of this study on our understanding of cognition in the oldest old will be modest

2. Investigator(s) 3

Strengths

- The PI is an instructor at the U of Miami and has a strong background in neuropsychology
- The PI plans to submit a career development award
- Although the PI's research background appears to be mostly related to obesity, there are recent publications related to sleep, reflecting some expertise in this area
- While it was difficult to guage the PI's research productivity in the application (or PubMed), she appears to have been productive enough to justify submitting a K
- Dr. Gamble has impressive expertise in studying sleep and is a very suitable mentor
- Dr. Levin is an exceptional mentor for the neuropsychology component

Weaknesses

- None noted

3. Innovation 3

Strengths

- Using bright light exposure therapy in the oldest old is novel, although just an extension of an existing paradigm to an older cohort

Weaknesses

- None noted

4. Approach 6

Strengths

- The MBAR is an excellent cohort
- Sleep measures include actigraphy, self-report, and diary data
- Clear methods for the sleep intervention
- Intervention can be carried out in the subject's home

Weaknesses

- Sample size was 20 seems quite small for Aims 2 and 3
- The neuropsychological testing is excessive for subjects 85 and older. There are multiple measures of the same construct without any data reduction plan. There was also no discussion of alternate forms needed to test at three separate time points

- The approach does not address whether the light intervention improves sleep.
- Per the protocol, having to wear the glasses 3-hours after the subject's mid-sleep time might result in some very early morning interventions

5. Environment 2

Strengths

- Both the University of Miami and University of Alabama have impressive research infrastructures

Weaknesses

- It was not clear if there were other MBAR resources that could be leveraged to help support the study

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes:

Strengths

- There is a high degree of collaboration between U. of Florida and U. of Alabama

Weaknesses

-

2. Potential for clinical translational impact of the intervention on cognitive aging and memory

Strengths

- Sleep is an important behavior with specific age-assocated problems and risks for cognitive impairmemt

Weaknesses

- The impact of light therapy on sleep and secondarily of cognition is likely to be small

3. Potential for future NIH funding of the research

- Modest. The results of this pilot work would have to be very compelling

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: Feasibility of a timed bright light exposure therapy to improve circadian function

Principal Investigator(s): Sonya Kaur, PhD, Karen Gamble, PhD

Institutions: UMiami (Contact), UAB

OVERALL IMPACT

Please provide your assessment of the strengths and weaknesses of the application using brief bullet points to reflect the project's likelihood to exert a sustained, powerful impact on the research field(s) involved, using the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact. Please score the application's potential using the following 1 (Highest Impact) to 9 (Lowest Impact) rating scale for each review criteria section:

Impact	High	Medium	Low
Score	1 2 3	4 5 6	7 8 9

Overall Impact: 5

Write a brief paragraph summarizing the factors that informed your Overall Impact score.

The proposed application by a junior neuropsychologist investigator seeks to determine the feasibility and tolerability of a wearable device for light exposure to enhance circadian function surrounding sleep in the oldest old. The potential significance of this intervention is that better sleep will improve cognition in a cohort where sleep disorders are increasingly common, with known consequences on cognition. UMiami and UAB are the proposed collaborating McKnight institutions, with the UAB co-PI a renowned expert in sleep. The use of the MBAR cohort is a strength. Unfortunately, there are a number of limitations that significantly reduce enthusiasm for this project. A failure to demonstrate feasibility and tolerability, themselves not defined, will preclude any demonstration of early efficacy on cognition or interpretability regarding subjective fatigue and gait speed. There is a very weak analysis plan and no criteria for justifying a future, larger application. The MBAR group, given their excellent aging, is not likely to have the numbers of individuals with sleep problems needed to address study questions. Thus, the likelihood of establishing effect sizes is small since there will be little variability. Moreover, there will be a ceiling effect with respect to their cognition. Although an intriquing intervention, the preliminary data on this method, especially in older individuals, may not yet justify is application in this setting. The nature and methods of data transfer and integrity were lacking.

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance score: 5

Strengths

- There is a high prevalence of sleep disorders among those ≥65 years old, and poor sleep quality in older adults is socciated with cognitive decline and dementia. An intervention that improves sleep in this population and thereby reduce the incidence of these side effects would have significant benefit.
- There does not appear to be adverse effects associated with the Re-Timer glasses used for the proposed intervention.

Weaknesses

- The study outcomes are poorly described analytically with the criteria that would justify a larger application are not stated.
- The goal is to recruit 10 participants each from the Miami and UAB sites from the MBAR cohort, who are successful agers ≥85 years old. Though unpublished, these are high functioning individuals who are unlikely to have prevalent sleep disorders and alterations in cognition. The generalizability of their findings to those with significant sleep problems and cognitive decline is not persuasive.
- Poor sleep quality is also associated with anxiety and stress, and pain from arthritis, which are not addressed as confounding factors.

2. Investigator(s): 3

Strengths

- The PI is a junior investigator is a junior investigator with publications in cognition and in sleep disorders. The UAB PI is a senior, well funded investigator in sleep.

Weaknesses

- Neither the Miami or UAB PI's have experience with the intervention

3. Innovation: 3

Strengths

- The application of light therapy to the proposed age group is novel.

Weaknesses

-

4. Approach: 6

Strengths

- The use of the MBAR participants who have been well characterized is a strength.
- Studies which use remote assessments hold promise for higher enrollment and retention.

Weaknesses

- The specific aims are such that a failure to demonstrate feasibility and tolerability (SA1) would render the ability to address SA2 and SA3 unanswerable.
- Although justification of sample size is not always possible in a pilot study, what the proposed N=20 will allow them to infer is not clear. There does not have to be a control group in a pilot study, but there has to be some basis for concluding that a change has taken place as a result of intervention that cannot be attributed to random variation, regression to the mean in the setting of baseline impairment, practice effects, etc. The analysis of the proposed covariates does not seem feasible. Indeed, the analysis plan is only one sentence. For example, how will the outcomes of the neuropsychological tests be analyzed.
- This reviewer was unable to find preliminary data regarding the effectiveness of the light intervention in older populations. Unfortunately, the references in the text did not

correspond to the bibliography. In fact, there are many assertions with references to justify them. Along a similar line, what was the justification for the timing and duration of the intervention? Is it realistic to have them wear the glasses for 30 minutes 3 hours after mid-sleep, which seems to be 6am?

- The PI states that it is unlikely to have contradictory findings. Contrary to this assertion, the multiple endpoints make contradictory findings more likely and difficult to interpret.
- What is the evidence that daily phone calls are a valid measure of adherence in this population?

5. Environment: 2

Strengths

- The environments are well suited for this project

Weaknesses

-

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes:

Strengths

- The collaborating sites are UMiami and UAB. There will be monthly Zoom calls and 1-2 in-person meetings to coordinate this project and ensure a coherent approach.

Weaknesses

- There no description of the logistics between the institutions. Where will the data be stored? Who will do the analysis? How will they ensure that transfer of PHI is HIPAA compliant. Who will train and credential the UAB coordinator in cognitive assessments.

2. Potential for clinical translational impact of the intervention on cognitive aging and memory:

Strengths

- The light intervention is an extremely promising method to improve sleep quality, which holds the potential for a non-invasive technique to mitigate cognitive aging and memory decline.

Weaknesses

-

3. Potential for future NIH funding of the research:

- There is high potential for use of this technique, but this specific project will not likely produce the preliminary data needed for an NIH application.

THE UNIVERSITY OF
ALABAMA AT BIRMINGHAM
Department of Neurobiology

June 30, 2022

The MBRF Cognitive Aging and Memory Intervention Core
Inter-Institutional Pilot 2023-2024 Program

Dear Committee Members:

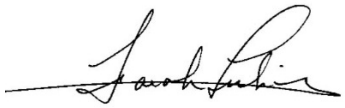
Please find attached our Inter-Institutional Pilot proposal, entitled, “Ketogenic Diet Improvement of Age-Related Memory Impairments, Nominates Cell-type Specific O-GlcNAc Deficiencies in the Aged Hippocampus.” The collaborating MBI institutions are the University of Alabama at Birmingham and the University of Arizona. Our application is targeted toward gaining a greater understanding of the underlying metabolic mechanisms involved in the benefit of Ketogenic diet therapy on improvement of memory impairments associated with age.

Potential reviewers from within the Memory in Aging research community who are not from the two collaborating institutions:

1. Jennifer Bizon, PhD, Univ of FL
2. Tom Foster, PhD, Univ of FL
3. Sarah Burke, PhD, Univ of FL

Thank you for your consideration of our proposal.

Sincerely,



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[i]**Date:** July 1, 2022

Title: Ketogenic Diet Improvement of Age-Related Memory Impairments, Nominates Cell-type Specific O-GlcNAc Deficiencies in the Aged Hippocampus.

Principle Investigator:

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RESEARCH PLAN
A. SUMMARY

We propose to investigate the contribution of metabolic O-linked N-acetylglucosamine (O-GlcNAc) signaling in response to ketogenic Diet (KD) therapy and cell-type specific transcription profiles associated with the intervention therapy involved in enhancing memory resiliency with age.

Interventions to enhance memory resilience within the aging population are possible. However, research studies that inform resiliency in this area are still lacking. Within the aging hippocampus, it is now clear that abnormal control of gene transcription mechanisms contributes to memory deficits. This proposal targets aging where most patients exhibit decreases in cognitive decline. The proposed pilot studies will begin to determine if *O*-GlcNAc signaling is a metabolic target of the ketogenic diet (KD) that regulates glucose metabolism. Few studies have explored the research idea that restoring proper *O*-GlcNAc homeostasis in the aging brain could lead to normalization of the aberrant energy metabolism that leads to restoration of memory dysfunction with age. The ***long-term*** goal of this proposal is to identify and characterize the ability of the KD therapy to restore *O*-GlcNAc signaling in association with memory improvements with age. Additional experiments outlined for a future NIH proposal will investigate the molecular and cellular mechanisms through which *O*-GlcNAc signaling might be involved in the age-related memory modifying effects of KD therapy. Collectively, these proposed pilot studies include combinations of experiments to gain a complete understanding of the *O*-GlcNAc signaling mechanisms involved in metabolic control of cell-type specific gene transcription profiles in memory deficits associated with aging. Notably, proposed experiments will uncover fundamental mechanisms involved in the neuropathology of aging. Unfortunately, use of KD therapy has been hampered by strict compliance on a challenging and potentially unpalatable diet as well as concerns of other health effects[1-6]. Therefore, we propose that identification of the underlying metabolic mechanisms triggered by KD therapy will lead to novel, more palatable, age-preventing therapeutic interventions for memory deficits.

B. SPECIFIC AIMS

O-GlcNAc is a newly identified post-translational modification that is regulated by two enzymes, O-GlcNAc transferase (OGT) which catalyzes the transfer of the GlcNAc moiety onto serine and threonine residues of proteins, and O-GlcNAcase (OGA) which removes the GlcNAc moiety from proteins[7]. To date, O-GlcNAc is the only post-translational modification other than phosphorylation that modifies serine and threonine residues of proteins[8]. This dynamic post-translational modification has been shown to be most abundant in the brain, and specifically in the hippocampus[9]. Uridine diphosphate-GlcNAc (UDP-GlcNAc) is the donor of O-GlcNAc and is synthesized via the hexosamine biosynthetic pathway (HBP) which, in turn, is dependent on the levels of glucose available[10] (**Figure 1**). Hence, O-GlcNAc is an attractive target that involves brain metabolism with the subsequent downstream differential gene regulation by O-GlcNAcylation. O-GlcNAc is necessary for neuronal survival and synaptic function. The genetic deletion of either OGT or OGA leads to genetic lethality[10]. Moreover, several proteins that are essential for neuronal functioning such as cyclic adenosine monophosphate (AMP)-response element-binding protein (CREB) and calcium/calmodulin-dependent kinases II (CaMKII) are modified by O-GlcNAcylation. Research articles in the field have established a global decrease in O-GlcNAcylation and OGT expression levels in the aged hippocampus compared to young adults[11]. These findings propose that O-GlcNAc signaling may play a critical role in synaptic and plasticity related molecular dysfunctions impacted with age[11]. Although there is sufficient evidence linking aging and aged related disorders to O-GlcNAc deficiency, the exact role of this modification remains unclear. The ***consequences*** of O-GlcNAc deficiencies are significant and include major disruptions in epigenetic control of gene expression necessary for overall cognitive health. Indeed, catalytic deficiency of OGT leads to hyperexcitability, seizures, and memory impairments through epigenetic mechanisms[12,13].

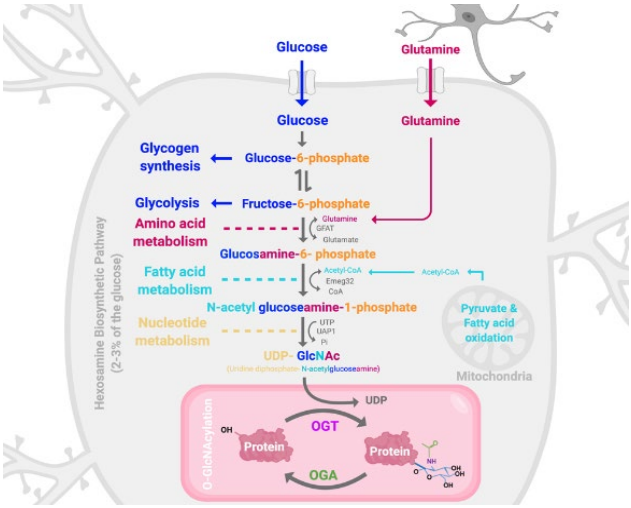

Figure 1. *Hexosamine Biosynthetic Pathway*

Knowing that O-GlcNAc modification is glucose dependent, and KD therapy engages O-GlcNAc signaling through the hexosamine biosynthetic pathway, we propose that KD might restore O-GlcNAcylation levels in the aged hippocampus. Interestingly, KD has been associated with the differential expression of OGT and OGA, the enzymes that regulate O-GlcNAc modification[14]. Further studies suggest that decreases in O-GlcNAcylation levels may be cell-type specific, as glial fibrillary acidic protein (GFAP), a marker of reactive astrocytes, was significantly increased after OGT knockout specifically in astrocytes[15]. Given the importance of astrocytes in ameliorating cognitive impairments in aging[16], the role of cell-type specific deficits in O-GlcNAc signaling should be thoroughly investigated in the context of aging. Therefore, our ***overarching hypothesis*** is that O-GlcNAc signaling deficiencies in the aged hippocampus occur in specific sensitive cell-types, resulting in cognitive impairment, which can be rescued by KD therapy. We propose the following two aims.

Aim1: **To identify the specific cell-types demonstrating O-GlcNAc deficiencies in the aged hippocampus**. Because hippocampal neurons are extremely heterogeneous, anatomically, physiologically, neurochemically, and in their transcriptional profiles, we hypothesize that specific cell-types within the hippocampus will express decreases in components of the O-GlcNAc signaling pathway in association with differential gene expression profiles. We will use single nuclei RNA-sequencing to systematically characterize gene transcription in cells from the hippocampus of young and aged mice.

Aim2: **To determine if Ketogenic diet intervention will restore age-related O-GlcNAc deficiencies in association with an improvement in memory.** Based on prior research studies, we know that the KD increases bulk O-GlcNAcylation levels in the hippocampus. Therefore, we hypothesize that KD improves memory impairments in aged adults via restoration of O-GlcNAc signaling in the hippocampus.

C. RESEARCH STRATEGY

C.1. Significance:

Scientific Premise: With the increasing aging population, it is crucial to understand the biological processes impacted with age that contribute to the development of neurological disorders including memory impairments. It is well established that the KD is a metabolic therapy option to improve memory performance with age[14,17]. Unfortunately, use of KD therapy has been hampered by strict compliance on a challenging and potentially unpalatable diet as well as concerns of other health effects[1-6]. Therefore, we propose that identification of the underlying metabolic mechanisms triggered by KD therapy will lead to novel, more palatable, aging-preventing therapeutic interventions for associated cognitive decline. Additionally, the study of how the KD therapy triggers key cellular and molecular mechanisms involved in memory restoration with age may help to identify novel targets for prevention or mitigation of these aging effects.

Project Goals. *This project aims to understand cell-type O-GlcNAc deficits in the aged hippocampus and proposes that memory impairment rescue by KD therapy involves O-GlcNAcylation dysregulation in cell-types that are sensitive to age.*

C.2. Innovation:

1)The study of cell-type specific O-GlcNAcylation in the hippocampus of aged mice in conceptually novel.

- Studies have also demonstrated microglial and astrocytic dysfunction in the hippocampus with age [18].
- Interestingly, in the medial prefrontal cortex, astrocyte dysfunction has been associated with abnormal glucose metabolism and irregular O-GlcNAcylation levels that were associated with differential expression of downstream genes [15].
- These studies highlight the importance of studying O-GlcNAcylation in cell types that lose normal functionality and become sensitive to age.

2)We will be the first to address age associated deficiencies in O-GlcNAc signaling that may be rescuable by KD therapy.

- O-GlcNAcylation and OGT expression in the hippocampus decreases with age, which correlates with cognitive impairment [11].
- KD has been shown to alter expression levels of proteins that are modified by O-GlcNAc [19].
- KD improvement of memory deficits [17]. In this project, KD will be used as an intervention to rescue age associated memory impairment.
- We will determine whether the rescue effect of KD on age-related memory impairments is mediated via differential O-GlcNAcylation regulation in sensitive cell-types in the aged hippocampus.

C.3. Rigor and reproducibility:

Our experimental design and methods will achieve robust and un-biased results. This is achieved by a clear and approachable scientific premise, clear justification of power analyses in quantifications of the results and a plan to address the biological variable of sex in a sex-linked disorder.

***Authentication of key resources**:* All animals in the study and take duplicate samples to ensure that there are no problems with our breeding colony and that the animals are properly identified. We will use the same background strain for all our proposed experiments. All immunohistochemistry analyses will be performed with commercially obtained antibodies.

Considerations of Data Rigor and Relevant Biological Variables: Experiments described in this proposal were designed in consultation with a biostatistician using guidelines and recommendations provided by the NIH. Experiments will use randomization and blinding procedures to ensure unbiased data collection and handling. All animals excluded from an experiment will be reported along with explanation for exclusion. Sex-comparisons are justified based on the NIH policy that preclinical experimental designs consider possible differences between males and females. This is important to consider because there is a well-established body of literature discussing sex differences in hippocampal function and memory[20-23]. Lastly, experiments and tissue isolation will be performed at the same time-of-day, because there is a large and emerging literature about diurnal time being an important biological variable to consider in rodents[24].

Table 1. Example power calculation for sample size based on preliminary experiments. (Aim 2) Power =0.80, Alpha =0.05. SD – Standard Deviation

	Difference detected				
SD	1.0	1.5	2.0	2.5	3.0
.6	6	3	1	1	1
.8	10	4	2	2	1
1.0	16	7	4	3	2
1.2	23	10	6	4	3
1.4	31	14	8	5	3

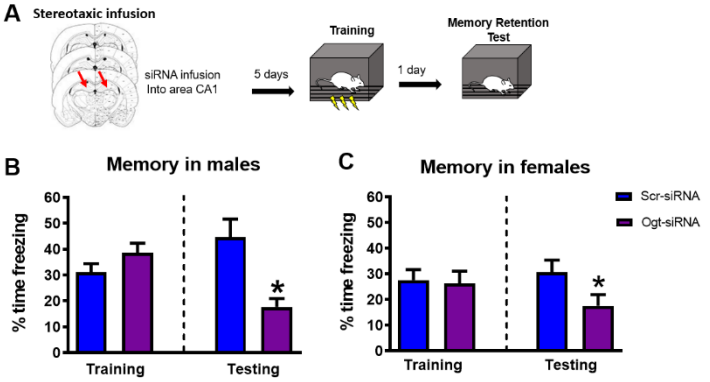

Figure 2. OGT *Knockdown in CA1 impairs memory in male and female rodent animals.* **A.** Diagram of experimental design. Male and female adult animals experienced learning in the training chamber and 24hrs later, long-term memory retention test was performed. **B.** OGT knockdown in CA1 significantly interfered with memory retention in males. **C.** Females demonstrated similar deficits in memory retention with OGT knockdown. Student's t-test, *p<0.05, Error bars represent the SEM, (n=7-8/group).

Statistical Design and Power Analysis: Sample sizes for each experiment have been determined by power analysis based on published or preliminary data using the formula $\sigma_p=(\pi(1-\pi)/N)$ *(1/2) where power = 0.96.The proposed experiment will be conducted with a predicted 30% loss of aged animals. All primary comparisons will be made using 2-sided tests with stringent control of the family-wise error rate at 0.025. Unless otherwise specified, Holm-Bonferroni procedure will be used to adjust for multiplicity.

C.4. Approach:

Specific Aim1: To identify cell-type specific O-GlcNAcylation dysregulation in the aged hippocampus.

Rationale: Our pilot studies demonstrate that OGT siRNA knockdown is necessary for proper long-term memory formation in both female and male rodents (**Figure 2**). We also found that OGT knockdown resulted in the inhibition of memory-permissive genes such as Camk4, Gria1, Grin1 (**Figure 3**). Overall, these studies support the research idea that O-GlcNAc signaling pathways are altered in the hippocampus to contribute to memory deficits with aging. Interestingly, studies have shown cell type specific dysfunctions in the hippocampus with age[18]. For example, disruptions in astrocytic function and increased astrocytic reactivity have been correlated with abnormal glucose metabolism and abnormal O-GlcNAcylation levels in the medial prefrontal cortex. Importantly, this has

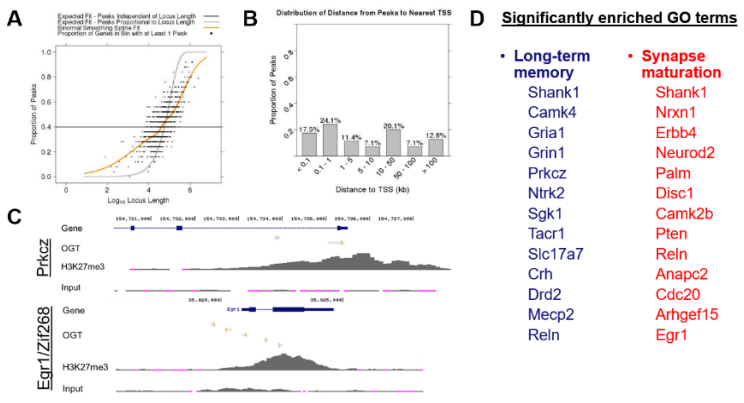

Figure 3. *Chromatin Immunoprecipitation sequencing analysis (ChIP-seq*). **A.** Curve showing the distribution of peaks vs locus length (i.e. distance to TSS). Approximately forty percent of all peaks are within 5kb of a TSS. Each gene has the same probability of a peak (dark grey horizontal line). Each probability is proportional to locus length (light grey curve.) **B.** Distribution of Distance from Peaks to Nearest transcription start site (TSS); note that there is some enrichment for regions near TSS. **C.** ChIP-seq and Gene Ontology (GO) term analysis reveals that OGT and H3K27me3 peaks co-localize around Transcription start sites of genes associated with the memory process (PKCζ) and genes necessary for synapse maturation, n=3.

been linked to differential gene expression profiles during the process of long-term memory formation[15]. Because of the heterogeneity of cells within the hippocampus, specific cell types differ in sensitivities and responses to the aging process. Thus, we hypothesize that O-GlcNAcylation and components of the O-GlcNAc signaling pathway will be decreased in specific cell types within the hippocampus, and that would be correlated with differential gene expression profiles. To test this hypothesis, we will be using single nuclei RNA-sequencing (snRNAseq) to illustrate gene expression in the different cell types of aged mice hippocampi versus young mice.

Animals: 10 aged female and male C57BL/6 mice (n=20, 18-22 months), 10 young female and male C57BL/6mice (n=20, 4-5 months) will be habituated to behavior facilities and handled by the experimenter for 2 weeks before tissue collection.

Study Design: In collaboration with Genomics and bioinformatics specialist, Dr. Huentelman at the Univ. of Arizona (see Biosketch), the hippocampus will be dissected out from young and aged mice and the dorsal CA1 of the hippocampus will be subdissected out and nuclei isolated using commercially available Nuclei EZ Prep (Sigma). The isolated nuclei will be filtered and stained with DAPI (ThermoFisher Scientific) before enrichment and elimination of debris using fluorescent-activated cell sorting. Individual cells will be captured and barcoded using the 10X Genomics Chromium system followed by library construction using the Chromium Single Cell 3' Library & Gel Bead Kit v2 (10x Genomics) according to manufacturer's instructions. Sequencing will be performed at the UA Genomics Core on a NextSeq 500 platform (Illumina) and analysis of the resulting data will be done using the CellRanger software (10x Genomics). For quality control, cells falling outside the 5th and 95th percentile with respect to gene number detected, and those with an abnormally high ratio of mitochondrial RNA to endogenous RNA, will be discarded. Cell type identification will be performed using the R package BRETIGEA.[25] *We predict that decreasing O-GlcNAc signaling in aged animals will result in changes in gene expression profiles different from that found in young animals.*

<u>Specific Aim2:</u> To determine if KD intervention will rescue O-GlcNAc deficiency in association with memory improvement.

Rationale: We chose KD as an intervention to rescue memory deficits because of its clear link to glucose metabolism and memory amelioration. KD has been shown to improve memory in aged mice. In a preliminary rodent study, we were able to show an increase in O-GlcNAcylation levels as a result of treatment by ketogenic diet for 4 weeks (**Figure 4**). However, the mechanisms involved in KD participation in improvements in memory deficits remains unclear. Because UDP-GlcNAc is synthesized from glucose via the HBP (**Figure 1**), we <u>*hypothesize*</u> that KD, as a metabolic therapy, will engage the O-GlcNAc signaling pathway in the aged hippocampus leading to improved memory impairments. This highlights the importance of determining whether the rescue effect of KD, a metabolic therapy, on age-related memory deficits is mediated through differential O-GlcNAc signaling in the different cell types of the hippocampus whose normal functions are impacted by age.

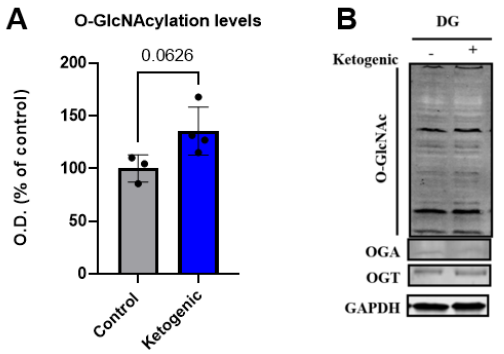

Figure 4*. O-GlcNAcylation levels in the dentate gyrus DG of the hippocampus after 4 weeks of ketogenic diet. Student's t-test, *p=0.0626, Error bars represent the SEM, (n=7-8/group).*

Animals: 24 aged (18-22 months) female mice C57BL/6, 24 aged (18-22 months) male mice C57BL/6, 24 young (4-5 months) female mice C57BL/6, and 24 young (4-5 months) male mice C57BL/6. They will be handled for habituation to the environment for 2 weeks before use. Mice groups will be divided as follows; 12 aged females fed control diet, 12 aged females fed KD, 12 aged males fed control diet, 12 aged males fed KD, 12 young females fed control diet, 12 young females fed KD, 12 young males fed control diet, 12 young males fed KD.

Study Design: The mice will undergo baseline assessment of OGT, O-GlcNAc, and OGA expression in the hippocampus of young versus aged adults. To test the impact of 4-week KD therapy on the memory we will include the hippocampus-dependent Object location memory test and Barnes Maze. After one full month on the KD or diet regimen, mice will undergo another testing to determine the effect of the diet on learning and memory in aged mice compared to young. *Open field*: Mice will be placed in a clear plastic open field to

explore and a computerized tracking system will record latency to enter the center square. Time spend in each quadrant and total distance traveled will also be recorded. *Two-trial Y maze:* According to previously published protocols[26], mice will be allowed to explore the maze with one arm blocked. Twenty-four hours later the mice will be returned to the Y maze for testing and allowed to explore with all three arms open. A Noldus system will be used to record the percent duration spent in the novel arm. *Morris Water Maze:* According to previously published protocols[27] mice will be placed in a maze pool and trained to locate a platform submerged slightly below the water and spatial cues will be placed outside of the maze and around the walls. To evaluate memory, track path length, escape latency and time spent in each quadrant will be recorded. *Context Fear Conditioning***:** Mice will then be trained according to a standard contextual fear conditioning training paradigm as previously described[28,29]. The "freezing" behavior will be scored via Med Associates software. Once the effect is established, another batch of mice will be obtained and will undergo the same paradigm for tissue collection. Again, the hippocampi will be collected and will undergo single cell RNA-sequencing to determine differential O-GlcNAc signaling. Data from the behavioral experiments will be collected using the Noldus EthoVision XT program and will be analyzed using GraphPad Prism.

D. MULTI-SITE MBI Collaboration

This project involves the help of two Evelyn F. McKnight Brain Institutes: The University of Alabama at Birmingham (UAB) and Arizona University (AU). Our Aims will be accomplished with the combined efforts and strengths of the UAB Flow Cytometry and Single Cell Services Core and The Translational Genomics Research Institute at UA in collaboration with Dr. Huentelman. Data will be shared between both institutes using an encrypted and secure platform. UAB has expertise in KD therapy, epigenetics, and in memory, with the resources of the UA Genetics “-omics” facilities in obtaining single nuclei RNA from brain cells and in the analysis of in the NIH-funded laboratory of Dr. Huentelman. Drs. Lubin and Huentelman have known each other through the MBI community for more than a decade and have finally initiated collaboration on a genomic and transcriptomics project. SnRNAseq Data will be stored in a secured REDCap database at UAB, and data transmission from UA to UAB will take placed on an encrypted platform already developed for world-wide clinical trials, such as CREST-2.

E. Timeline and Future Directions

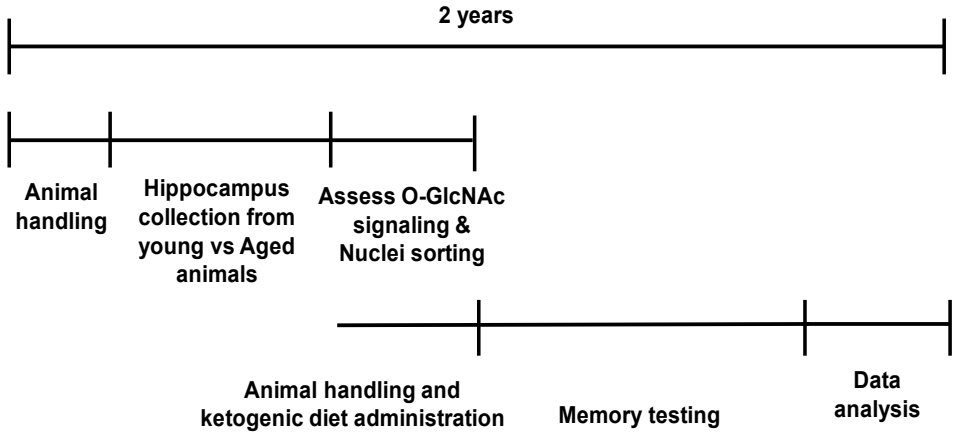

Figure 5. Proposed timeline

Future Direction: The proposed study will provide critical information to guide future studies. 1) The KD therapy intervention will inform us regarding the role of O-GlcNAcylation in reversing age associated memory deficits and cognitive dysfunction in adults with hypertension. Such information will serve as preliminary data for determining future study doses and intensity of exercise for which the recent report of the National Academies indicates there is little guidance. Thus, we fully realize that these experiments, while testing important predictions of the hypothesis of a role for O-GlcNAc signaling in the control of key gene targets involved in the therapeutic benefits of kD therapy on aging, will not test the idea that dysregulation of O-GlcNAc signaling is the only metabolic mechanism to effect memory with aging. Rather, these experiments will mark a beginning for testing the viability of the idea that metabolic dysfunction has the capacity to negatively affect cellular mechanisms underlying aging related memory and cognitive deficts. If these experiments are successful, they will provide a strong foundation for potential future studies and drug development in humans.

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28. Morse, S.J., Butler, A.A., Davis, R.L., Soller, I.J. & Lubin, F.D. Environmental enrichment reverses histone methylation changes in the aged hippocampus and restores age-related memory deficits. *Biology (Basel)* **4**, 298-313 (2015).
29. Butler, A.A., Johnston, D.R., Kaur, S. & Lubin, F.D. Long noncoding RNA NEAT1 mediates neuronal histone methylation and age-related memory impairment. *Science signaling* **12**(2019).

Lubin (UAB), PI
Huentelman (UA), Co-I

BUDGET

A. Detailed Budget

Yr1							
UAB							
PERSONNEL YEAR 1	**06/1/2023-05/31/2024**			**Fringe**	**Total**	**Total**	**Year 1**
NAME	**ROLE IN PROJECT**	**Effort**	**Base Salary**	**%**	**Salary**	**FB**	**TOTALS**
UAB							
	06/1/2023-05/31/2024			**Fringe**	**Total**	**Total**	**Year 1**
NAME	**ROLE IN PROJECT**	**Effort**	**Base Salary**	**%**	**Salary**	**FB**	**TOTALS**
Farah D. Lubin	Principal Investigator	1%	$180,697	32.9%	$1,861	$612	$2,474
Joelle Saad	Graduate Student Assistant	100%	$32,960	0.0%	$32,960	0%	$32,960
			Total Yr 1 UAB Personnel				**$35,434**
Non-Personnel Costs			**Total**				
General Chemicals			$ 2,750				
Chemicals used to prepare buffers and solutions for basic experiments							
Centrifuge tubes, pipet tips, gloves, etc.							
Animal cost			$ 6,250				
Biochemical Supplies			$ 7,000				
Molecular Biology Supplies							
				Total Non-Personnel Costs	**16,000**		
Univ of Arizona				**Total Yr 1 UAB**			**$53,434**
PERSONNEL YEAR 1	**06/2023-05/31/2024**						
NAME	**ROLE IN PROJECT**	**Effort**	**Base Salary**	**Fringe**	**Total**	**Total**	**Year 1**
Matt Heuntelman	Principal Investigator	1%	$203,700	**%**	**Salary**	**FB**	**TOTALS**
				32.9%	$2,037	$670	$2,707
			Total Yr 1 Univ. of Arizona Personnel				
						2,707	
				Project Yr 1 Total			
						57,141	
Yr2							
UAB							
	06/1/2024-05/31/2025			**Fringe**	**Total**		
NAME	**ROLE IN PROJECT**	**Effort**	**Base Salary**	**%**	**Salary**	**Total**	**Year 1**
Farah D. Lubin	Principal Investigator	1%	$180,697	32.9%	$1,861	**FB**	**TOTALS**
Joelle Saad	Graduate Student Assistant	100%	$32,960	0.0%	$32,960	$612	$2,474
						0%	$32,960
			Total Yr 2 UAB Personnel		**$35,434**		
Non-Personnel Costs							
Non-Personnel Costs			**Total**				
Animal cost			$ 3,250				
				Total Non-Personnel Costs	**$3,250**		

Univ of Arizona							
	06/1/2024-05/31/2025	**Effort**					
NAME	**ROLE IN PROJECT**	**%**	**Base Salary**				
Matt Huetelman	Site Principal Investigator	1.00%	$203,700	**Fringe**	**Total**		
				%		**Salary**	
			Yr 2 UA Personnel cost	32.9%	$2,037	**FB**	**TOTALS**
						$670	$2,707
Single Nuclei RNA sequencing for 24 animals Reagents Sequencing	40 samples						
							$23,000
				Project Yr 2 Total		**$64,391**	
				Total Project Costs		**$115, 825**	

Budget Justification

The budget provided represents the actual cost of performing and completing the experiments. Personnel will contribute by implementing their knowledge on the topic and their experience in various molecular and biochemical experiments, behavioral experiments with rodents, and their analyzing skills. All the reagents, supplies, and materials are necessary for the completion of the experiments and will enable us to start this new project in the lab.

Personnel:

University of Alabama at Birmingham

Farah D. Lubin, PhD
Dr. Lubin is an associate professor in the Neurobiology Department at the University of Alabama at Birmingham (UAB). She is also the Director of the Graduate Neuroscience Roadmap Scholar Program. Her research focuses on epigenetic mechanisms involved in regulating gene expression in learning and memory formation. She studies memory impairments associated with age in addition to impairments associated with temporal lobe epilepsy. Because of her background knowledge and astounding research, Dr. Lubin is currently a PI for the UAB Neuroscience Roadmap Scholars Program (2R25 NS089463-06), Epigenetic Effects of Exercise on Epilepsy (R21 NS116937), and Long Non-coding RNA Regulation in Astrocytes within the Aging Brain (R01 AG071785). She is also a Co-I for The Mentored Experiences in Research, Instruction, and Teaching (MERIT) program a funded Institutional Development Award from the Division of Minority Opportunities in Research (K12 GM088010-09) and Molecular and Cellular Basis of Neurodevelopmental Disorders (R01 MH113948). In this project, Dr. Lubin will serve as the PI. She will supervise Ms. Joelle Saad regarding the scientific method and experiments. She will oversee the budget and manage different aspects of the work. She will also work closely with Dr. Huentelman at The University of Arizona to ensure timely completion of experiments and statistical analysis. We are requesting 1% effort.

Joelle Saad, MSc
Ms. Joelle Saad is a graduate student at UAB. She completed her MSc degree in Biological Sciences with emphasis on epigenetics in neuroscience. Her previous research focused on epigenetic mechanisms involved in learning and memory formation with exercise or specific diets. She also worked on identifying epigenetic mechanisms involved in anxiety and depression. She has a significant knowledge working with animals. She has performed several behavioral tests such as the Morris Water Maze, Open Field, Elevated Plus Maze, Social interaction, etc. She also has experience in molecular biology for she has performed several biochemical techniques in the lab such as PCRs, Western Blots, IHCs and FISH. Ms. Joelle Saad will be performing the molecular experiments for this project. She will also be the one to work with the animals

and perform the behavioral experiments. In addition, she will be analyzing the data under the supervision of Dr. Farah Lubin. We are requesting 100% effort.

University of Arizona

Matthew Huentelman, PhD
Dr. Huentelman is a professor at the University of Arizona (UA). His research focuses on identifying biomarkers linked to neurodegenerative diseases such as Alzheimer's Disease. He also studies and identifies genetic basis of neurological disorders. He has expertise in live cell imaging and molecular dissection of cells of the central nervous system. His lab has been part of several discoveries including Fluid Biomarker Discovery and the Discovery of Genetic Basis of Rare Diseases in Children. Dr. Huentelman will perform the single nuclei RNA-sequencing for this project. He will also be in charge of analyzing the data for the single nuclei RNA-sequencing. We will benefit from Dr. Huentelman's expertise in molecular genetic "-omics". We are requesting 1% effort.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Lubin, Farah Dominique**

eRA COMMONS USER NAME (credential, e.g., agency login): **FLUBIN**

POSITION TITLE: **Associate Professor of Neurobiology**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Alabama State University, Montgomery, AL	BS	05/1996	Biology/Chemistry
Binghamton University (SUNY), Binghamton, NY	Ph.D.	08/2001	Cellular and Molecular Biology/Immunology
Baylor College of Medicine, Houston, TX (Anne Anderson)	Postdoctoral	08/2005	Neuroscience
Baylor College of Medicine, Houston, TX (J. David Sweatt)	Postdoctoral	05/2008	Neuroscience

A. Personal Statement

I am an Associate Professor in Neurobiology at UAB. For the past 13 years, my laboratory has focused on studying the epigenetic basis for transcriptional regulation of genes that integrate and encode information in the brain. Epigenetics is the study of both heritable and non-heritable regulation of gene expression that occurs without any alteration in the DNA sequence. We and others have observed that neurons have “hijacked” epigenetic processes such as DNA methylation and posttranslational histone modifications to coordinate gene transcription changes in the hippocampus, thus revealing an unexpected role for chromatin structure regulation in mature, non-dividing neurons during memory formation. My laboratory uses interdisciplinary methods ranging from systems to molecular genetics neuroscience to understand the cellular, molecular, and genetic basis of memory and its disorders. Specifically, we use innovative tools such as CRISPR/dCas9 for gene reprograming, Electrophoretic Mobility Shift assays, Laser-capture microdissections, neurophysiology, Genomic analyses, high-throughput sequencing and bioinformatics tools to understand how neuronal activity alters the epigenome to direct gene expression patterns. My work has provided insights into epigenetic mechanisms that participate in the regulation of gene expression during memory encoding, allocation, storage and recall in hopes of unraveling the causes of cognitive deficits like those associated with normal aging and to develop treatment options. Results from these studies have provided fundamental information concerning epigenetics in mature neurons with clear relevance in neurological disorders and related-memory deficits.

An additional strength of training at UAB is the university-wide commitment to whole-genome sequencing and bioinformatics. UAB has made a considerable investment in these areas via the recent development of the UAB/Hudson Alpha Center for Genomic Medicine, which allows direct access to one of the world leaders in genome sequencing. The Hudson Alpha Institute for Biotechnology houses a world-class complement of Illumina sequencing technology, including two MiSeq, one NextSeq 500, seven HiSeq 2000, five HiSeq2500, and one HiSeq X10 sequencers. The Lubin Lab has an ongoing relationship with researchers at UAB/Hudson Alpha and has performed RNA-seq and ChIP-seq with hundreds of biological samples. The focus on metabolic regulation of epigenetic modifiers in the central nervous system uniquely positions us at an interface between basic and translational research and allows us to directly translate basic research findings into novel

therapeutic approaches. My background in epigenetics will be an asset for the development of molecular genetic strategies to investigate molecular mechanisms of normal aging and associated memory dysfunction.

Since the establishment of my independent lab at UAB in January 2009, I have served on numerous committees and established programs to enhance diversity and inclusion in the Neuroscience workforce including serving as Director of the NIH/NINDS Neuroscience Roadmap Scholar graduate program at UAB. I also contribute to training outside the lab as a lecturer in several courses and as a co-director of the IRACDA-MERIT postdoctoral program and serving on the advisory board of the Medical Scientist Training (MSTP) Program. I have served on the Neuroscience Theme Admissions committee and have spent much effort over the years in teaching and mentoring undergraduate and graduate students and postdoctoral fellows, and have found my interactions with them to be a significant source of personal satisfaction in my academic mission; 3 of my lab trainees have established their own independent scientific careers in the US. Two of my current graduate students have received individual NIH training fellowships.

In sum, I have served on over 40 PhD student thesis committees and I have previously mentored 7 postdoctoral fellows, graduated 6 PhD students, 1 MD/PhD, 1 Master's degree student, over 40 undergraduates and 10 postbachelor students. I currently mentor 5 graduate students and 4 undergraduate students performing their honor thesis work in my lab. I am involved in hands-on training of individuals in my lab and assist them with challenging experiments, learning new techniques, and troubleshooting. As a testament to my commitment to training and mentorship, I received the UAB Graduate Dean's Award for Excellence in Mentorship in 2017, and the 2022 Commission on the Status of Women Padma Award, in the category of Becky Trigg Outstanding UAB Faculty Member for my dedication to Diversity, Equity, and Inclusion.

Ongoing and recent projects that I would like to highlight include:

R01 AG071785
Lubin (PI)
04/15/21-03/31/26
Long Non-coding RNA Regulation in Astrocytes within the Aging Brain

R21 NS116937
Lubin (PI)
09/30/20-08/31/22
Epigenetic Effects of Exercise on Epilepsy

R01 MH113948
Powell (PI), Role: co-investigator
03/10/20-01/31/25
Molecular and Cellular Basis of Neurodevelopmental Disorders

5R25 NS089463-07
Lubin (PI)
08/01/20-07/31/25
UAB Neuroscience Roadmap Scholars Program

K12 GM088010-13
Schwiebert (PI), Role: co-investigator
09/01/19-08/31/24
The Mentored Experiences in Research, Instruction, and Teaching (MERIT) Program

Citations (Examples of publications demonstrating the role of epigenetic mechanisms in memory and aging):

1. Butler A.A., Johnston D.R., Kaur S., and **Lubin F.D.** lncRNA Neat1 mediates neuronal histone methylation and age-related memory impairment. Science Signaling. 2019;12(588). PMCID: PMC7219525.

2. Butler A.A., Jarome T., Sanchez R.G., Webb W.M., and **Lubin F.D.** O-GlcNAc signaling and EZH2-mediated epigenetic regulation of gene expression during consolidation of fear memories. Learning and Memory. 2019;26(9):373-379. PMCID: PMC6699408.
3. Morse S., Butler A., Davis R.L., Soller I., and **Lubin FD**. Environmental enrichment reverses histone methylation changes in the aged hippocampus and restores age-related memory deficits . Biology. 2015;4(2):298-313. PMCID: PMC4498301.
4. Gupta-Agarwal S, Franklin AV, Deramus T, Wheelock M, Davis RL, McMahon LL, **Lubin FD**. G9a/GLP histone lysine dimethyltransferase complex activity in the hippocampus and the entorhinal cortex is required for gene activation and silencing during memory consolidation. J Neurosci. 2012;32(16):5440-53. PMCID: PMC3332335.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020-Present Co-Chair, Black/African American Faculty Association, UAB School of Medicine
2020-Present Faculty Advisor, Black Postdoctoral Association, UAB
2020-Present Administrator/Faculty Advisor of Project Sunshine, UAB
2017-Present Co-Director of Research, NIH/NIGMS IRACDA-Mentored Experiences in Research, Instruction, and Teaching (MERIT) Program, UAB
2015-Present Associate Professor with Tenure, Dept. of Neurobiology, Dept. of Cell, Developmental and Integrative Biology, and Genetics Dept., University of Alabama at Birmingham (UAB), Birmingham, AL
2015-Present Director, Comprehensive Neuroscience Center EEG core, UAB
2014-Present Associate Professor, Center for Glial Bio in Med, UAB
2014-Present Associate Professor, Center for Neurodegeneration & Exp Ther (CNET), UAB
2014-Present Associate Professor, Integrative Center for Aging Research
2014-Present Scientist, UAB Global Center for Craniofacial, Oral and Dental Disorders
2014-Present Director, NIH/NINDS Neuroscience Roadmap Scholar Program, UAB
2011-2015 Assistant Professor, Genetics Dept., UAB
2011-2014 Principal Investigator, GS-13/1, Veteran Affairs at UAB
2009-Present Investigator, McKnight Brain Institute, UAB
2009-Present Associate Scientist, Alzheimer's Disease Center, UAB
2009-Present Associate Scientist, Civitan International Research Center, UAB
2009-Present Associate Scientist, General Clinical Research Center, UAB
2009-Present Member, Comprehensive Neuroscience Center, UAB
2009-2015 Assistant Professor, Department of Neurobiology, UAB
2009-2015 Assistant Professor, Dept. of Cell Biology, UAB

Honors

Faculty

2022 Commission on the Status of Women Padma Award, in the category of Becky Trigg Outstanding UAB Faculty Member
2022 Chair, American Epilepsy Society Board of Directors appointed, Diversity, Equity and Inclusion Committee
2021 Society for Neuroscience *Global Connectome Plenary speaker*
2021 Nominated for UAB School of Medicine Dean’s Excellent Award for Mentorship
2020 UAB School of Medicine Dean’s Excellent Award for Diversity Enhancement
2020 President’s Diversity Champion Award-UAB
2018 *Merritt-Putnam Symposium Plenary speaker*, American Epilepsy Society meeting
2018 50 Under 50 - Alabama State University Distinguished Alumni Award
2018 Mentor training on cultural awareness - National Research Mentoring Network
2017 UAB Dean's Award for Excellence in Mentorship
2013-2014 Excellence in Editing/Reviewing- Neurobiology of Learning and Memory Journal
2013-2016 American Epilepsy Society Basic Sciences Committee
2012-2014 UAB Health Services Foundation Award
2010-2011 McNulty Civitan International Scientist Award

2010-2012 American Epilepsy Society Official Fellows Host-Chair
2009-2012 Cell Science Journal Review Board

Postdoctoral Fellow

2008-2011 NIMH/NIH Pathway to independence Award (K99/R00 MH082106)
2008 FASEB Postdoctoral Professional Development and Enrichment Award
2005-2007 NINDS/NIH Research Award (F32NS48811)
2004-2005 NINDS/NIH Microarrays Supplemental Research Award (R01NS39942)
2004-2005 AES/Milken Epilepsy Foundation Award
2002-2005 METPAC SFN Travel Fellowship Grant Award
2002 Gordon Conference Travel Award (Synaptic Transmission)
2002 UNCF-Merck Post-doctoral Science Research Fellowship (alternate)
2002-2003 NINDS Post-doctoral Supplemental Research Award (R01NS39942)

Graduate Student

2000 Robert L. Szymanski III memorial Travel Award
1998 Clifford D. Clark Fellowship Research Award
1996-2001 Clifford D. Clark Fellowship Academic Award
1994-1996 Minority Access to Research Careers Award (MARC; 5T35HL007801)
1993-1994 Minority Biomedical Research Services Award (MBRS; 2T34GM008167)

Society Memberships

2009-Present Epigenetics Society
2008-Present American Physiological Society
2005-Present Molecular and Cellular Cognition Society
2002-Present Society for Neuroscience
2002-Present American Epilepsy Society
2002-Present Women in Neuroscience

C. Contributions to Science

1. **A role for epigenetic mechanisms in activity-dependent gene transcription during memory formation.**
   Epigenetic mechanisms were once thought to occur only during development in order to establish the cellular phenotype and remain static thereafter. Yet the research idea that epigenetics mechanisms and chromatin remodeling persist in adult hippocampal neuronal cells of mammals has generated considerable enthusiasm for understanding how post-mitotic neurons have "hijacked" the epigenetic process such as DNA methylation and posttranslational histone modifications to coordinate gene transcription changes in the hippocampus. As a postdoctoral fellow with David Sweatt, we identified an unexpected role for chromatin structure regulation in mature, non-dividing neurons during memory formation. Since that time, I've continued to study epigenetic mechanisms in the non-heritable regulation of gene expression that occurs without any alteration in the DNA sequence.

   a. **Lubin FD**, Sweatt JD. The IkappaB kinase regulates chromatin structure during reconsolidation of conditioned fear memories. Neuron. 2007;55(6):942-57. PMCID: PMC2587178.
   b. Jarome T.J., Butler A.A., Nichols J.N., Pacheco N.L., and **Lubin F.D**. NF-kappaB mediates Gadd45beta expression and DNA demethylation in the hippocampus during fear memory formation. Frontiers in Molecular Neuroscience. 2015;8:54. PMCID: PMC4584956.
   c. **Lubin FD**, Roth TL, Sweatt JD. Epigenetic regulation of BDNF gene transcription in the consolidation of fear memory. J Neurosci. 2008;28(42):10576-86. PMCID: PMC3312036. *F1000 recommended

2. **Histone Methylation in the central nervous system.**
   My lab has provided experimental verification that Histone lysine methylation mechanisms is an ideal candidate to study in the context of both active gene transcription and gene silencing. Histone lysine methylation is unique because depending on the histone protein modified and degree of lysine methylation this can lead to gene activation or gene silencing. My lab provided further experimental verification to elucidate how epigenetic mechanisms, such as histone lysine methylation regulation of genes, influence long-term changes in behavior. Our follow-on studies implicated histone lysine

methylation in the molecular cross-talk between histone acetylation and DNA methylation, and demonstrated a role for NMDA and ERK signaling pathways in these processes. Additionally, my work continues to demonstrate that transcription factors like NF-κB are coupled to epigenetic mechanisms, such as posttranslational modification of histones, namely histone acetylation and phosphorylation and DNA demethylation to mediate activity-dependent gene transcription during memory formation.

a. Gupta S, Kim SY, Artis S, Molfese DL, Schumacher A, Sweatt JD, Paylor RE, **Lubin FD**. Histone methylation regulates memory formation. J Neurosci. 2010;30(10):3589-99. PMCID: PMC2859898.
b. Gupta-Agarwal S, Franklin AV, Deramus T, Wheelock M, Davis RL, McMahon LL, **Lubin FD**. G9a/GLP histone lysine dimethyltransferase complex activity in the hippocampus and the entorhinal cortex is required for gene activation and silencing during memory consolidation. J Neurosci. 2012;32(16):5440-53. PMCID: PMC3332335. *F1000 recommended
c. Jarome T.J., Perez G.A., Hauser R.M., Hatch K.M., and **Lubin FD**. EZH2 Methyltransferase Activity Controls Pten Expression and mTOR Signaling During Fear Memory Reconsolidation. J. Neurosci. 2018;38(35):7635-7648. PMCID: PMC6113900.
d. Webb W.M., Irwin A.B., Pepin M.E., Henderson B.W., Huang V., Butler A.A., Herskowitz J.H., Wende A.R., Cash A.E., and **Lubin F.D.** The SETD6 Methyltransferase Plays an Essential Role in Hippocampus-Dependent Memory Formation. Biol. Psychiatry. 2020;87(6):577-587. PMCID: PMC6906268.

3. **Epigenetic mechanisms in memory disorders associated with epilepsy and aging.**
Moreover, we found that manipulating epigenetic mechanisms has potential for therapeutic treatment of memory dysfunction associated with neurological disorders such as epilepsy and aging-related dementia. Currently, there is no cure for memory deficits associated with these disorders. We are among a few investigators that have recognized the need for insights into this research area. I have published seminal papers showing that epileptic rats have aberrant regulation of DNA methylation in the hippocampus and that these changes were involved in epileptogenesis. In addition, subsequent publications from my lab demonstrate the potential of manipulating these epigenetic mechanisms to reduce the progression of epilepsy. What is exciting is that this is the first time we have been able to delay epilepsy progression through a better understanding of DNA methylation. In addition, subsequent publications from my lab demonstrate the potential of manipulating these epigenetic mechanisms to reduce cognitive dysfunction in epilepsy and aging-related dementia.

a. Parrish R.R., Albertson A., Buckingham S., Hablitz J., Mascia K.L., Haselden W., and **Lubin F.D**. Status epilepticus triggers early and late alterations in brain-derived neurotrophic factor and NMDA glutamate receptor GRIN2B DNA methylation levels in the hippocampus. Neuroscience. 2013;248:602-19. PMCID: PMC3830613.
b. Parrish R.R., Buckingham S., Mascia K.L., Johnson J.J., Matyjasik M.M., Lockhart R.M., and **Lubin F.D**. Methionine increases BDNF DNA methylation and improves memory in epilepsy. Annals of Clinical and Translational Neurology. 2015;2(4):401-16. PMCID: PMC44002085.
c. Sánchez R.G., Parrish R.R., Rich M., Webb W.M., Lockhart R.M., Nakao K., Ianov L., Buckingham S.C., Broadwater D.R., Jenkins A., de Lanerolle N.C., Cunningham M., Eid T., Riley K., and **Lubin F.D**. Human and rodent Temporal Lobe Epilepsy is characterized by changes in O-GlcNAc homeostasis that can be reversed to dampen epileptiform activity. Neurobiology of Disease. 2019;124:531-543. PMCID: PMC6379093.
d. Butler A.A., Johnston D.R., Kaur S., and **Lubin F.D**. lncRNA Neat1 mediates neuronal histone methylation and age-related memory impairment. Science Signaling. 2019;12(588). PMCID: PMC7219525.

Complete List of Published Work in MyBibliography:
https://scholar.google.com/citations?user=DCq1n38AAAAJ&hl=en

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Huentelman, Matthew John

eRA COMMONS USER NAME (credential, e.g., agency login): MHUENTELMAN

POSITION TITLE: Professor of Neurogenomics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Ohio University – Athens, OH	B.S.	06/1998	Biochemistry
University of Florida – Gainesville, FL	Ph.D.	08/2003	Physiology & Genomics
University of Florida – Gainesville, FL	Fellow	06/2004	Physiology & Genomics
Translational Genomics Res. Inst. – Phoenix, AZ	Fellow	07/2006	Neuroscience & Genomics

A. Personal Statement

I have researched traits and diseases of the central nervous system for over twenty years, and I have extensive training in the physiology, live cell imaging, and molecular dissection of neuronal and glial cells. During the past eighteen years I have focused on the application of molecular genetic "-omics" technologies in the study of the basic characteristics of the brain as well as rare childhood and adult diseases, aging, and Alzheimer's disease. The focus of my lab is on the molecular association and biomarker discoveries linked to neurodegenerative and neurobehavioral diseases as well as cognitive performance in healthy individuals.

My laboratory is located on the city-owned Phoenix Biomedical Campus at the non-profit academic research institute, TGen, in downtown Phoenix, Arizona. During my time at TGen, my lab has grown significant experience in the wet laboratory generation and bioinformatics assessment of next generation DNA and RNA sequencing data. My laboratory is split approximately 75:25 between wet laboratory (11 full-time employees; 2 postdoctoral fellows, 2 Masters-level lab technicians, and 7 Bachelors-level lab technicians totaling over 25 years of experience on my laboratory team) and bioinformatics (4 full-time employees; 1 Research Assitant Professor, 1 Masters-level, and 2 Bachelors-level totaling over 16 years of experience on my lab team) personnel and I have a demonstrable publication track record in both general areas of research.

In regards to Dr. Lubin's MBRF Pilot grant, I will provide my expertise in molecular genetic "-omics" and will be responsible for single nuclei RNA sequencing protocol development, nuclei isolation, and sequencing. In addition, I will be responsible for nuclei integraty, RNA quality and assessment and outcome analyses.

Dr. Huentelman's recent publication record

2021: 29 publications, 2020: 21 publications, 2019: 28 publications, 2018: 20 publications

B. Positions, Scientific Appointment, and Honors

Positions and Scientific Appointments

02/16-present **Professor**, Translational Genomics Research Institute, Phoenix, AZ
07/14-present **Research Associate Professor**, Dept of Basic Medical Sciences, Univ. of AZ, Phoenix, AZ
10/13-present **Scientific Director**, Center for Rare Childhood Disorders, TGen, Phoenix, Arizona
08/11-present **Adjunct Faculty Member**, Arizona State University SoLS, Tempe, Arizona
06/10-present **Affiliate**, Evelyn F. McKnight Brain Institute at the University of Arizona, Tucson, Arizona
12/08-02/16 **Associate Professor**, Translational Genomics Research Institute, Phoenix, AZ
08/06-12/08 **Assistant Professor**, Translational Genomics Research Institute, Phoenix, Arizona
07/04-08/06 **Postdoctoral Research Fellow**, Translational Genomics Research Institute, Phoenix, AZ
11/03-06/04 **Postdoctoral Research Fellow**, University of Florida, Gainesville, FL

08/03-11/03 **Visiting Postdoctoral Research Fellow**, University of Bristol, Bristol, United Kingdom
06/98-08/98 **Visiting Researcher**, MV Lomonosov Moscow State University, Moscow, Russia

Honors

2014-2016 **Board Member**, Alzheimer's Association / Desert Southwest Chapter
2013 **40 Under 40 Awardee**, Phoenix Business Journal
2009 **Award for Research Excellence (nominee)**, Arizona Bioindustry Association
2008 **Young Investigator Award**, The Arizona Alzheimer's Consortium, Phoenix, Arizona
2001 **Proctor and Gamble Professional Opportunity Award**, American Physiological Society
2000-2002 **American Heart Association Predoctoral Fellowship**, Florida/Puerto Rico Affiliate
1998 **Jeanette Grasseli-Brown Undergraduate Research Award**, Ohio University, Athens, Ohio
1998 **Hamilton Community Foundation Award**, Hamilton, Ohio
1994 **Hiram and Florence Wilson Scholarship**, Dept. of Chemistry, Ohio University, Athens, Ohio
1994 **Richard Eddy Service Award, Dept. of Chemistry**, Ohio University, Athens, Ohio

C. Contributions to Science

1. Identification of the Genetic Basis of Human Disease – Rare Diseases in Children and Alzheimer's Disease: During the last eighteen years my laboratory has focused on the use of multi-omics approaches [DNA, RNA, and protein analyses] to identify the genetic basis of rare and common human neurological diseases. Typically these studies involve either a long-distance collaboration with other clinics and sequencing laboratories or large multi-laboratory collaborative efforts (this is especially true for our Alzheimer's disease work). In the last ten years, we have reported on the identification of a new genetic basis for over eight different neurological disorders.

   In TGen's Center for Rare Childhood Disorders (C4RCD) clinic we have sequenced over 2,000 DNA samples in our attempts to identify the basis of disease in pediatric patients with neurological symptoms. Due to our focused efforts and extremely close collaboration with each treating neurologist we have identified the genetic cause in ~40% of our families. A particular focus of our Center is in the study of underserved individuals including over 60% of our families who are on Arizona's medical public assistance program (called AHCCCS) and a partnership with a medical clinic in Hermosillo, Mexico in the cross-border Arizona-neighboring state of Sonora.

   For Alzheimer's disease, we collaborative openly with the national and international efforts focused on the disease including the ADGC, ADSP, ADNI, and IGAP. We were one of the first groups to openly share the genetic data resulting from our neuropathologically characterized AD cohort (an autopsy-based case/control series collected by Dr. John Hardy when he was at the National Institute on Aging at the NIH, known by the AD field as "TGen II"). These efforts have helped to greatly expand our collaborative network and we have been honored to play a role in the collective better understanding of AD genetic risk and protection.

   Listed below are some of our published works related to rare neurological disease. Not shown are the several dozen publications with the Alzheimer's community at large that include work with ADNI, ADGC, IGAP, and others.

   a. Balak C, Belnap N, Ramsey K, Joss S, Devriendt K, Naymik M, Jepsen W, Siniard AL, Szelinger S, Parker ME, Richholt R, Izatt T, LaFleur M, Terraf P, Llaci L, De Both M, Piras IS, Rangasamy S, Schrauwen I, Craig DW, **Huentelman M**, Narayanan V. A novel FBXO28 frameshift mutation in a child with developmental delay, dysmorphic features, and intractable epilepsy: A second gene that may contribute to the 1q41-q42 deletion phenotype. Am J Med Genet A. 2018 Jul;176(7):1549-1558. doi: 10.1002/ajmg.a.38712. PMID: 30160831.

   b. Lessel D, Schob C, Küry S, Reijnders MRF, Harel T, Eldomery MK, Coban-Akdemir Z, Denecke J, Edvardson S, Colin E, Stegmann APA, Gerkes EH, Tessarech M, Bonneau D, Barth M, Besnard T, Cogné B, Revah-Politi A, Strom TM, Rosenfeld JA, Yang Y, Posey JE, Immken L, Oundjian N, Helbig KL, Meeks N, Zegar K, Morton J, The Ddd Study, Schieving JH, Claasen A, **Huentelman M**, Narayanan V, Ramsey K; C4RCD Research Group, Brunner HG, Elpeleg O, Mercier S, Bézieau S, Kubisch C, Kleefstra T, Kindler S, Lupski JR, Kreienkamp HJ. De Novo Missense Mutations in DHX30 Impair Global Translation and Cause a Neurodevelopmental Disorder. Am J Hum Genet. 2018 Jan 4;102(1):196. doi: 10.1016/j.ajhg.2017.12.016. PMC5777981.

c. Schrauwen I, Szelinger S, Siniard AL, Kurdoglu A, Corneveaux JJ, Malenica I, Richholt R, Van Camp G, De Both M, Swaminathan S, Turk M, Ramsey K, Craig DW, Narayanan V, **Huentelman MJ**. A Frame-Shift Mutation in CAV1 Is Associated with a Severe Neonatal Progeroid and Lipodystrophy Syndrome. PLoS One. 2015 Jul 15;10(7):e0131797. doi: 10.1371/journal.pone.0131797. eCollection 2015. PMC4503302.

d. Szelinger S, Malenica I, Corneveaux JJ, Siniard AL, Kurdoglu AA, Ramsey KM, Schrauwen I, Trent JM, Narayanan V, **Huentelman MJ**, Craig DW. Characterization of X chromosome inactivation using integrated analysis of whole-exome and mRNA sequencing. PLoS One. 2014 Dec 12;9(12):e113036. doi: 10.1371/journal.pone.0113036. eCollection 2014. PMC4264736.

2. Technology Development – Lentiviral Vectors | SNP Genotyping | Bioinformatics: During my career I have demonstrated a significant impact on technology development in the fields I work in. This initiated during the early days of my graduate studies. I was working in the newly emerging field of lentiviral vector development (late 1998). At the time the field was struggling to make high quality viral vector in high concentrations. I co-developed a standardized transfection and purification approach that yielded industry leading titers approaching 1 X 10^{10} infectious units / ml on a routine basis. This was an important advance for the field because high titer stocks of virus are critical for brain injections of the vector where small injection volumes are necessary and therefore high titer virus is paramount. Innovation in tech development has continued throughout my post PhD career including the development of an improved SNP genotyping calling algorithm which generated additional usable data from some of the early human microarrays, the development of a pooled genotyping approach on the microarray which permitted rapid screening of samples for “low hanging fruit” associated with disease, the reduction to practice of bar-coded next generation sequencing on the Illumina equipment which ushered in the beginning of our ability to optimize sequencing design and depth per sample, and the demonstration that iPSC can be generated from autopsy donor-derived fibroblasts thereby allowing one to make these important model cells from donors with accompanying autopsy data which is critical for neurological disease. In short, I have demonstrated an ability to innovate as necessary to both advance my specific scientific goals as well as others in the field.

   a. Craig DW, Pearson JV, Szelinger S, Sekar A, Redman M, Corneveaux JJ, Pawlowski TL, Laub T, Nunn G, Stephan DA, Homer N, **Huentelman MJ**. Identification of genetic variants using bar-coded multiplexed sequencing. Nat Methods. 2008 Oct;5(10):887-93. PMID: 18794863

   b. Pearson JV, **Huentelman MJ**, Halperin RF, Tembe WD, Melquist S, Homer N, Brun M, Szelinger S, Coon KD, Zismann VL, Webster JA, Beach T, Sando SB, Aasly JO, Heun R, Jessen F, Kolsch H, Tsolaki M, Daniilidou M, Reiman EM, Papassotiropoulos A, Hutton ML, Stephan DA, Craig DW. Identification of the genetic basis for complex disorders by use of pooling-based genomewide single-nucleotide-polymorphism association studies. Am J Hum Genet. 2007 Jan;80(1):126-39. PMC1785308.

   c. Hua J, Craig DW, Brun M, Webster J, Zismann V, Tembe W, Joshipura K, **Huentelman MJ**, Dougherty ER, Stephan DA. SNiPer-HD: improved genotype calling accuracy by an expectation-maximization algorithm for high-density SNP arrays. Bioinformatics. 2007 Jan 1;23(1):57-63. PMID: 17062589.

   d. Coleman JE, **Huentelman MJ**, Kasparov S, Metcalfe BL, Paton JF, Katovich MJ, Semple-Rowland SL, Raizada MK. Efficient large-scale production and concentration of HIV-1-based lentiviral vectors for use in vivo. Physiol Genomics. 2003 Feb 6;12(3):221-8. PMID: 12488511.

3. Fluid Biomarker Discovery: Since 2010 my laboratory has investigated biomarkers for human disease in fluid biological samples including blood, urine, saliva, and CSF. Our major area of focus has been on cell-free molecular investigations (biomarkers in exosomes and other freely circulating microvesicles) of RNA species and their use as biomarkers (“exRNA”). We were funded as part of NIH’s innagural extracellular RNA communication consortium (ERCC) to further this work. Our expertise includes both the development of wet laboratory methods and informatics approaches for biomarker discovery and characterization.

   a. Quinn JF, Patel T, Wong D, Das S, Freedman JE, Laurent LC, Carter BS, Hochberg F, Van Keuren-Jensen K, **Huentelman M**, Spetzler R, Kalani MY, Arango J, Adelson PD, Weiner HL, Gandhi R, Goilav B, Putterman C, Saugstad JA. Extracellular RNAs: development as biomarkers of human disease. J Extracell Vesicles. 2015 Aug 28;4:27495. PMC4553262.

   b. Laurent LC, Abdel-Mageed AB, Adelson PD, Arango J, Balaj L, Breakefield X, Carlson E, Carter BS, Majem B, Chen CC, Cocucci E, Danielson K, Courtright A, Das S, Abd Elmageed ZY, Enderle D, Ezrin

A, Ferrer M, Freedman J, Galas D, Gandhi R, **Huentelman MJ**, Van Keuren-Jensen K, Kalani Y, Kim Y, Krichevsky AM, Lai C, Lal-Nag M, Laurent CD, Leonardo T, Li F, Malenica I, Mondal D, Nejad P, Patel T, Raffai RL, Rubio R, Skog J, Spetzler R, Sun J, Tanriverdi K, Vickers K, Wang L, Wang Y, Wei Z, Weiner HL, Wong D, Yan IK, Yeri A, Gould S. Meeting report: discussions and preliminary findings on extracellular RNA measurement methods from laboratories in the NIH Extracellular RNA Communication Consortium. J Extracell Vesicles. 2015 Aug 28;4:26533. PMC4553263.

c. Napolioni V, Ober-Reynolds B, Szelinger S, Corneveaux JJ, Pawlowski T, Ober-Reynolds S, Kirwan J, Persico AM, Melmed RD, Craig DW, Smith CJ, **Huentelman MJ**. Plasma cytokine profiling in sibling pairs discordant for autism spectrum disorder. J Neuroinflammation. 2013 Mar 14;10:38. PMC3616926.

d. Kim S, Swaminathan S, Shen L, Risacher SL, Nho K, Foroud T, Shaw LM, Trojanowski JQ, Potkin SG, **Huentelman MJ**, Craig DW, DeChairo BM, Aisen PS, Petersen RC, Weiner MW, Saykin AJ; Alzheimer's Disease Neuroimaging Initiative. Genome-wide association study of CSF biomarkers Abeta1-42, t-tau, and p-tau181p in the ADNI cohort. Neurology. 2011 Jan 4;76(1):69-79. PMC3030225.

Complete List of Published Work in NCBI's MyBibliography (260 total publications since 1998):

https://www.ncbi.nlm.nih.gov/myncbi/1nmZZMm8R79/bibliography/public/

*Name of Individual: Farah D. Lubin
Commons ID: FLUBIN

Other Support – Project/Proposal

*Title: "Long Non-coding RNA Regulation in Astrocytes within the Aging Brain"

*Major Goals: We anticipate that these experiments will identify long-lasting epigenetic mechanisms involved in memorydecline with age, and help devise targeted therapies to rescue cognition or promote resilience in aging individuals, including those with Alzheimer's disease.

*Status of Support: Active

Project Number: R01 AG071785

Name of PD/PI: Farah Lubin

*Source of Support: NIH/NIA

*Primary Place of Performance: UAB

Project/Proposal Start and End Date: 04/01/2021 – 03/31/2026:

* Total Award Amount (including Indirect Costs): $371,250

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##. ##)
1. 2021-2022	3.0
2. [enter year 2]	
3. [enter year 3]	
4. [enter year 4]	
5. [enter year 5]	

*Title: "Molecular and Cellular Basis of Neurodevelopmental Disorders"

*Major Goals: The major goals of this grant are to characterize novel models for neurodevelopmental disorders using Kctd13 knockout and Cul3 knockout and conditional knockout mice and neuronal cultures from same. There is no scientific or budgetary overlap.

*Status of Support: Active

Project Number: R01 MH113948

Name of PD/PI: Craig Powell

*Source of Support: NIMH/NIH/DHHS

*Primary Place of Performance: UAB

Project/Proposal Start and End Date: (04/01/2020-01/31/2025):

* Total Award Amount (including Indirect Costs): $1,341,459

* Person Months (Calendar/Academic/Summer) per budget period.

Name of Individual: Farah D. Lubin
Commons ID: FLUBIN

Year (YYYY)	Person Months (##. ##)
1. 2020-2021	0.6
2. 2021-2022	0.6
3. [enter year 3]	
4. [enter year 4]	
5. [enter year 5]	

*Title: “Hippocampal Internal Architecture in Human Temporal Lobe Epilepsy”

*Major Goals: This proposal seeks to understand the contribution of epigenetic mechanisms to temporal lobe epilepsy and hippocampal architecture.

*Status of Support: Active

Project Number: R01 NS094743

Name of PD/PI: Ver Hoef

*Source of Support: NIH/NINDS

*Primary Place of Performance: UAB

Project/Proposal Start and End Date: 08/01/2016 – 06/30/2022

* Total Award Amount (including Indirect Costs): $422,416

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##. ##)
1. 2018	1.44
2. 2019	1.44
3. 2020	1.44
4. 2021	1.44
5. 2022	1.44

*Title: “Epigenetic Effects of Exercise on Epilepsy”

*Major Goals: The goal of this proposal is to interrogate the research idea that chronic exercise is linked to epigenetic control of gene transcription in the epileptic brain and that these modifications can be manipulated using pharmacological drugs, CRISPR/dCas9 or siRNA approaches to normalize abnormal gene transcription in TLE and improve memory retention.

*Status of Support: Active

Project Number: R21 NS116937

Name of PD/PI: Farah Lubin

*Source of Support: NIH/NINDS

*Primary Place of Performance: UAB

Name of Individual: Farah D. Lubin
Commons ID: FLUBIN

Project/Proposal Start and End Date: 09/30/2020 – 08/31/2022

* Total Award Amount (including Indirect Costs): $408,375

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2020-2021	3,0
2. 2021-2022	3.0
3. [enter year 3]	
4. [enter year 4]	
5. [enter year 5]	

*Title: “Neuroscience Roadmap Scholars Program

*Major Goals: The Neuroscience Roadmap Scholars Program competing renewal will continue to target the obstacles impeding success with the goal of attracting an increased number of diversity trainees to neuroscience research and providing them with the necessary tools and skills early in their PhD careers which are essential to making this a life-long career choice

*Status of Support: Active

Project Number: R25 NS089463 -06

Name of PD/PI: Lubin

*Source of Support: NIH/NINDS

*Primary Place of Performance: UAB

Project/Proposal Start and End Date: 08/01/2020 – 07/31/2025

* Total Award Amount (including Indirect Costs): $270,000

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
1. 2020-2021	2.4
2. 2021-2022	2.4
3. [enter year 3]	
4. [enter year 4]	
5. [enter year 5]	

*Title: “Experiences in Research, Instruction, and Teaching (MERIT) program

*Major Goals: The MERIT program is a funded Institutional Development Award from the Division of Minority Opportunities in Research at the NIGMS

*Status of Support: Active

Name of Individual: Farah D. Lubin
Commons ID: FLUBIN

Project Number: K12GM088010-09

Name of PD/PI: Schwiebert; Co PI: Lubin

*Source of Support: NIH/NIGMS

*Primary Place of Performance: UAB

Project/Proposal Start and End Date: 09/01/2018 – 08/31/2023

* Total Award Amount (including Indirect Costs): $250,000

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##. ##)
1. 2018-2019	.3
2. 2019-2020	.3
3. 2020-2021	.3
4. 2021-2022	.3
5. [enter year 5]	

Name of Individual: Farah D. Lubin
Commons ID: FLUBIN

IN-KIND

*Summary of In-Kind Contribution: UAB IMPACT FUND

*Status of Support: Active

*Primary Place of Performance: UAB

Project/Proposal Start and End Date 10/01/2017 – 09/31/2022

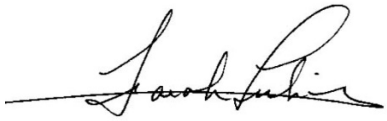
*Person Months (Calendar/Academic/Summer) per budget period

Year (YYYY)	Person Months (##. ##)
1. 2018	0.6
2. 2019	0.6
3. 2020	0.6
4. 2021	0.6
5. 2022	0.6

*Estimated Dollar Value of In-Kind Information: $350,000

***Overlap** (summarized for each individual):
There is no scientific overlap.

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.



*Signature: _____

Date: July 01, 2022

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title:

Principal Investigator(s):

Institutions:

OVERALL IMPACT

Please provide your assessment of the strengths and weaknesses of the application using brief bullet points to reflect the project's likelihood to exert a sustained, powerful impact on the research field(s) involved, using the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact. Please score the application's potential using the following 1 (Highest Impact) to 9 (Lowest Impact) rating scale for each review criteria section:

Impact	High	Medium	Low
Score: 2	1 2 3	4 5 6	7 8 9

Overall Impact *Write a brief paragraph summarizing the factors that informed your Overall Impact score.*

Recent work indicates that O-GlcNAc levels decrease in the adult brain during both normal aging and neurodegenerative disease. Neuronal O-GlcNAc transferase (OGT) expression and O-GlcNAcylation ameliorates cognitive impairments in aged mice. The proposed studies will attempt to positively modify this process through diet. The results of the current proposal could address the reasons for successful/unsuccessful KD treatment. Very impressive is the innovation including the hypothesis, and cells specific transcription in region CA1. The preliminary data for Aim2, demonstrating an increase in O-GlcNAcylation levels as a result of treatment by ketogenic diet is exciting, required for the proposed studies, and suggests studies will be successful. The researchers are outstanding and complement each other. Precieved weaknesses were minor.

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance

Strengths

- It is crucial to understand the biological processes impacted with age that contribute to the development of neurological disorders including memory impairments.
- It is well established that diet (caloric restriction) influences longevity. However, dietary restrictions are hard to implement in humans.
- An understanding of mechanisms could lead to novel and more palatable treatments.

Weaknesses

- Most studies support beneficial effects of KD on cognition during aging and neurodegenerative disease. However, there are a few exceptions. This minor weakness could be off-set by the results of the current proposal that could address the reasons for successful treatment.

2. Investigator(s)

Strengths

- The principal investigators are leaders in the field of cognitive aging and molecular mechanisms for memory and hippocampal function in aging.
- Their individual expertise complement each other, greatly increasing the impact of the proposed studies.

Weaknesses

-

3. Innovation

Strengths

- The focus on O-GlcNAc and modification by a KD as a mechanism/treatment of age-related memory decline.
- Cells specific transcription in region CA1.
- Levels decrease in the adult brain during both normal aging and neurodegenerative disease.
- O-GlcNAc transferase (OGT) expression and O-GlcNAcylation ameliorates cognitive impairments in aged mice.

Weaknesses

-

4. Approach

Strengths

- Studies will include male and females.
- Preliminary data indicate a role for O-GlcNAc in memory and that memory deficits are associated with decreased expression of memory and synaptic genes.
- The preliminary data for Aim2, demonstrating an increase in O-GlcNAcylation levels as a result of treatment by ketogenic diet is exciting, required for the proposed studies, and suggests studies will be successful.
- Aim 1 is straight forward, although technically innovative, and will examine cell specific changes in gene expression with age, focusing on “O-GlcNAc signaling”.
- Aim 2 will also examine cell specific changes in genes associated with differences in behavior and after modifying O-GlcNAcylation levels.

Weaknesses

- A perceived weakness is that , since O-GlcNAc is involved in many processes, including transcription, and memory, it is unclear how the researchers will specify genes that represent “decreasing O-GlcNAc signaling”. This could be a few as 16 genes in the GlcNAc metabolic process GO:0006044, to the large list of proteins from the O-

GlcNAcome. Since the same transcriptional studies are performed in Aim2 after modifying O-GlcNAcylation levels, it is likely that the differences in transcript on between Aim1 and Aim2 will provide genes that are differentially expressed due to differences in O-GlcNAc signaling. Thus, this is a minor weakness.

-

5. Environment

Strengths Execellent

-

Weaknesses

-

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes:

Strengths

- Data will be shared between both institutes using an encrypted and secure platform.
- Each researcher/Institute provides unique expertise that can be synergized across labs.
- UAB has expertise in KD therapy, epigenetics, and behavior and can obtaining single nuclei RNA from brain cells. Dr. Huentelman has expertise to use this RNA in transcriptomics.

Weaknesses

-

2. Potential for clinical translational impact of the intervention on cognitive aging and memory

Strengths

- The potential for translation is two fold. First, is a dietary intervention. As noted above, most studies support beneficial effects of KD on cognition during aging and neurodegenerative disease. However, there are a few exceptions. This minor weakness could be off-set by the results of the current proposal that could address the reasons for successful treatment. Thus, the second potential is an understanding of a novel target signaling pathway.

Weaknesses

-

3. Potential for future NIH funding of the research

- There is a strong potential for NIH support due to the novelty including the novel signling pathway - metabolic O-linked N-acetylglucosamine (O-GlcNAc) signaling and

technological innovation examining cell-type specific transcription profiles. In addition, there is scientific and public interest in the role of diet in aging including the ketogenic diet.

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: Ketogenic Diet Improvement of Age-Related Memory Impairments, Nominates Cell-type Specific OGlcNAc Deficiencies in the Aged Hippocampus.

Principal Investigator(s): Farah D. Lubin and Matthew Huentelman

Institutions: University of Alabama at Birmingham

McKnight Brain Research Foundation at the University of Arizona, Translational Genomics Research Institute

OVERALL IMPACT

Please provide your assessment of the strengths and weaknesses of the application using brief bullet points to reflect the project's likelihood to exert a sustained, powerful impact on the research field(s) involved, using the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact. Please score the application's potential using the following 1 (Highest Impact) to 9 (Lowest Impact) rating scale for each review criteria section:

Impact	High	Medium	Low
Score: 4	1 2 3	4 5 6	7 8 9

Overall Impact *Write a brief paragraph summarizing the factors that informed your Overall Impact score.*

Several proteins that are essential for neuronal functioning such as cyclic adenosine monophosphate (AMP)-response element binding protein (CREB) and calcium/calmodulin-dependent kinases II (CaMKII) are modified by O-GlcNAcylation. An earlier study has demonstrated a global decrease in O-GlcNAcylation and OGT (the enzyme that catalyzes the transfer of the GlcNAc moiety onto serine) expression levels in the aged hippocampus compared to the young hippocampus. Considering these the proposal will test the hypothesis that O-GlcNAc signaling deficiencies in the aged hippocampus occur in specific sensitive cell types, resulting in cognitive impairment, which can be rescued by ketogenic diet therapy. The hypothesis will be tested in two specific aims. The first aim will identify the specific cell types demonstrating O-GlcNAc deficiencies in the aged hippocampus. The second aim will determine if ketogenic diet intervention restores age-related O-GlcNAc deficiencies in association with an improvement in memory. Innovation, preliminary data supporting the feasibility of the proposed experiments, an experienced investigative team with complementary expertise, rigorous experimental design, use of animals of both sexes, and environments at respective institutes are strengths of the proposal. However, a weak scientific premise, a moderate weakness in approach, and a lack of details of future NIH proposals are weaknesses for this otherwise strong proposal.

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance

Strengths

- Understanding the biological processes that contribute to age-related memory impairments is of high clinical significance.
- Although the ketogenic diet improves memory performance with age, it is also associated with compliance issues and other health effects. Thus, identifying the underlying metabolic mechanisms triggered by ketogenic diet therapy may help design novel therapeutic interventions for age-associated cognitive decline.

Weaknesses

- The scientific premise is weak as the ketogenic diet had a marginal (non-significant) effect on O-GlcNAc levels.

2. Investigator(s)

Strengths

- The PI, Dr. Lubin, is an associate professor in the Neurobiology Department at the University of Alabama at Birmingham (UAB). She has experience working on epigenetic mechanisms involved in regulating gene expression in learning and memory formation and memory impairments associated with age in addition to impairments associated with temporal lobe epilepsy. Her research is currently supported by R01, R21, and R25 grants. She has published over 80 manuscripts. Overall, she appears well-qualified to lead the project.
- The co-I, Dr. Huentelman, is a professor at the University of Arizona. He will help with proposed single nuclei RNA-sequencing studies. He also appears well-qualified to carry out his proposed role.

Weaknesses

-

3. Innovation

Strengths

- Understanding cell-type specific O-GlcNAc deficits in the aged hippocampus to use those findings in future studies to lower age-related memory impairment is novel.

Weaknesses

-

4. Approach

Strengths

- The first aim will identify cell-type specific O-GlcNAcylation dysregulation in the aged hippocampus.
- The second aim will determine if ketogenic diet intervention will rescue O-GlcNAc deficiency in association with memory improvement.
- A robust and unbiased experimental design will be employed.
- Animals belonging to both sexes will be included.
- Sample size estimates are based on power analysis.
- Preliminary data provided demonstrate the ability of the investigative team to perform proposed experiments.
- Multiple behavior tests will be used for experiments proposed in aim 2.

Weaknesses

- Preliminary data presented in Figure 4A-B demonstrates marginal non-significant effect of a 4-week ketogenic diet feeding on O-GlcNAcylation. However, the proposed experiments will use the same diet paradigm. It is not clear why the duration of the therapy will not be titrated to identify the best duration that shows a significant effect on O-GlcNAcylation.

5. Environment

Strengths

- The environments at the University of Alabama at Birmingham, McKnight Brain Research Foundation at the University of Arizona, and Translational Genomics Research Institute are outstanding for the proposed experiments.

Weaknesses

-

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes:

Strengths

- The project is designed in such a way that complementary expertise of both the PI and co-I will be used. Both institutes will have significant involvement in the project.

Weaknesses

-

2. Potential for clinical translational impact of the intervention on cognitive aging and memory

Strengths

- This is a basic science study that explores potential mechanisms which may ultimately help design novel therapies to prevent age-related memory impairments.

Weaknesses

- It may take years and a significant amount of funding before the idea presented in this proposal can be translated into the clinic.

3. Potential for future NIH funding of the research

- Although a paragraph is provided describing how results generated from this project will support the future grant application. However, more details would have clarified what would be proposed in future applications. Also, it is not clear if the results generated from the proposed studies would be sufficient to support the NIH R01 level grant proposal.

UF UNIVERSITY of FLORIDA

College of Liberal Arts and Sciences
Department of Psychology

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PO Box 112250
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Phone: 678-467-1297
Email: dpehlivanoglu@ufl.edu

June 30, 2022

The McKnight Research Foundation (MBRF) Cognitive Aging and Memory Intervention Core Inter-Institutional Pilot Program

Dear Review Committee:

Attached please find submission of our grant proposal entitled *A Neural Network and Guided Eye-Tracking Approach for Characterizing and Combating Fake News Detection in Aging* in response to the call for proposal from the MBRF Cognitive Aging and Memory Intervention Core Inter-Institutional Pilot Program.

The proposed research will (i) characterize the neurocognitive mechanisms to fake news detection using artificial intelligence; (ii) develop a brief fake news detection paradigm for integration into large-scale data collection from a nationally representative, diverse adult lifespan sample; (iii) determine behavioral benefits of an eye-tracking guided "nudging" intervention for fake news detection in older adults. Our team members, who are all affiliated with the McKnight Brain Institute, span across the University of Florida and the University of Arizona and bring together a diverse set of skills on experimental and cognitive aging research, deception and aging, and modeling of decision making. To enhance clinical impact of this work, our collaboration with Dr. Huentelman from the TGen Institute will provide us with a unique opportunity to characterize fake news detection ability among a nationally representative sample of individuals from diverse backgrounds, including those with particular risk for Alzheimer's disease, recruited through the MindCrowd cohort. Knowledge gained through this project has the potential to inform recommendations for mechanistic research on fake news detection in aging; as well as the design of real-life decision-supportive interventions that adopt an age-targeted approach towards the long-term goal of financial risk reduction in older individuals.

We recommend the following potential reviewers: 1) Emily Rogalski, PhD (e-rogalski@northwestern.edu); 2) Eric Porges (eporges@phhp.ufl.edu); 3) Sarah Barber (sbarber10@gsu.edu). Biosketches for all members of the research team and letter of support by Dr. Matt Huentelman, Co-Founder of the Mindcrowd Platform at TGen Institute, are included in the application. Please contact us if you have any questions or if we can provide additional information. Thank you for your consideration. We look forward to hearing from you!

Sincerely,

Dr. Didem Pehlivanoglu (PI)
on behalf of Drs. Caroline Phelps (Co-PI), Natalie Ebner (Co-Investigator/Mentor), Robert Wilson (Co-Investigator/Mentor), and Matt Huentelman (Collaborative team member)

The MBRF Cognitive Aging and Memory Intervention Core
Inter-institutional Pilot Program Application Face Page

Title of Project

A Neural Network and Guided Eye-Tracking Approach for Characterizing and Combating Fake News Detection in Aging

Senior/Key Personnel

Didem Pehlivanoglu, PhD, Principal Investigator

Caroline Phelps, PhD, Co-Principal Investigator

Natalie Ebner, PhD, Co-Investigator/Mentor

Robert Wilson, PhD, Co-Investigator/Mentor

Project/Performance Sites

University of Florida

University of Arizona

Contact PI: Didem Pehlivanoglu, PhD

Address: Department of Psychology, University of Florida, 945 Center Dr., Gainesville, FL, 32611

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PROJECT SUMMARY

Fabricated information mimicking news media, referred to as 'fake news', is an epidemic deception technique constantly manipulating public opinion. Older adults are particularly vulnerable to deception via fake news, especially those with lower cognitive functioning [1-3]. Currently only technical solutions exist (e.g., fact checking), but fake news continues to break through, leaving human decision making as the last line of defense. In this context, the goal of **Aim 1** is to develop a neural network model to identify the features in the news headline and the cognitive characteristics of the individual that influence fake news detection. Informed by this modeling approach, the goal of **Aim 2** is to use the fake news headlines that contain the features deemed as important by the neural networks to examine fake news detection ability in a large nationally representative sample recruited through the MindCrowd platform. Optimizing detection of fake news via artificial intelligence is highly promising. Human decision making, which is crucial for effectiveness of a reliable detection prevention solution, however, is not flawless, particularly in aging. Focusing on this potentially vulnerable group, the goal of **Aim 3** is to develop and validate an eye-tracking guided "nudging" intervention that draws attention to these features to improve fake news detection among older adults. **Knowledge gained through this project has the potential to inform recommendations for mechanistic research on fake news detection in aging; as well as the design of real-life decision-supportive interventions that adopt an age-targeted approach towards the long-term goal of financial risk reduction in older individuals.**

SPECIFIC AIMS

Aim 1. Characterize the neurocognitive mechanisms to fake news detection using artificial intelligence. Our previous work shows that older age is associated with reduced ability to detect fake news, with this age-related decline more pronounced with lower cognitive functioning [1,2]. Using a neural network modeling approach, we will identify features in news headlines and cognitive characteristics of individuals that enhance fake news detection in an adult lifespan sample.

Aim 2. Develop a brief fake news detection paradigm for integration into large-scale data collection from a nationally representative, diverse adult lifespan sample. Informed by the neural network modeling results under Aim 1, we will select the most and least deceptive fake news headlines for integration into a short fake news paradigm, which will be implemented on the MindCrowd platform to facilitate large-scale data collection from a nationally representative, wide age range sample of individuals with diverse backgrounds, including those with particular risk for Alzheimer's disease. Under this aim, we will also determine the extent to which age and level of cognitive functioning will moderate the ability to detect fake news.

Aim 3: Determine behavioral benefits of an eye-tracking guided "nudging" intervention for fake news detection in older adults. Our pilot data and the literature [3-5] show that age-related deficits in deception detection are associated with greater reliance on superficial features (i.e., reputation of news sources) than central features (i.e., news content). We will test the extent to which eye-tracking guided attention to *both news headlines and news sources* in the intervention condition, will enhance fake news detection, over the control condition, and particularly in older adults with low cognitive functioning.

SIGNIFICANCE

In a digitally connected world, manipulation of public opinion via fake news has reached epidemic proportions, constituting an emerging societal problem that requires surveillance and intervention. Older adults may be particularly vulnerable to deception via fake news, and perhaps especially so in an online context, as they must navigate the complexities and ambiguity of internet decision making while dealing with age-related cognitive changes [1,4,6-7]. Recent statistics show that older adults are the age group that shared the most fake news during the 2016 U.S. election on social media platforms [8-9]. In pioneering work, we show that older adults, and particularly the oldest-old individuals, experience difficulties with fake news detection [1]; with fake news detection deficits particularly pronounced among individuals with low memory and analytical reasoning abilities [2-3].

Traditional solutions to mitigate fake news are limited and rely primarily on technical solutions, such as fact-checking (e.g., FactCheck.org), blacklists, and the blocking of fake news websites. Despite some success of these approaches, fake news gets through filters, and human decision making is the last line of defense against them. **Artificial intelligence based neural network models can inform both message features as well as human characteristics that underlie fake news detection; thus providing a combined machine-human defense solution to deception.** Neural networks can filter malicious content via automatic fake news detection [10-11]; but they can also predict individual susceptibility to any given deceptive content. While this approach has not yet been applied to fake news, it has long been used to power recommendation systems in industry. In essence, these systems try to predict how a particular person will rate a particular product given how they rated

other products, in much the same way as we would like to predict how effective a particular text is at deceiving a particular person given how easily they have been deceived by other texts. One of the most famous examples in the machine learning literature comes from Netflix which, in 2006, ran a competition to predict user ratings of movies given their ratings of other movies [12]. Neural networks do an excellent job in this case [13-15]. In the simplest of these architectures, the network learns to embed both the movies and the subjects into a (relatively) low-dimensional space such that each movie and each person can be thought of as a vector in that space. The rating of a given movie by a given person is then computed by taking the dot product of these vectors. In this model, each dimension of the low-dimensional space can be thought of as a different *feature* of the movie, with a movie's score on each dimension quantifying how strongly that feature is present in that movie and a subject's score on each dimension quantifying how strongly their rating is influenced by that feature. Thus, **the goal of Aim 1 is to develop such a neural network model to identify the features in the news headline and the cognitive characteristics of the individual that influence fake news detection. Aim 2 will use the fake news headlines that contain the features deemed as the most and least deceptive by the neural networks to investigate fake news detection ability in a nationally representative and diverse sample of individuals.**

Optimizing detection of fake news via artificial intelligence is highly promising and reliable. Human decision making, which is crucial for effectiveness of a reliable detection prevention solution, however, is not flawless, especially when attentional capacities are limited. Age-related reduction in the ability to focus attention increases distractibility, thus interfering with decision making processes in aging [16-17]. Focusing on this potentially at-risk population, **the goal of Aim 3 is to develop an intervention training for "nudging" attention to enhance fake news detection in aging.** Simply tagging fake news as false may not be sufficient, and may in fact even be non-beneficial, as a defense solution in aging [5]. Our **preliminary data** collected from 124 older adults (aged 61-81) show that the oldest-old individuals were less accurate in fake news detection when the news stories were paired with credible (e.g., NY Times) compared to non-credible (e.g., True Pundit) news sources ($\chi^2_{(1)} = 6.29$, $p = 0.01$) (**Figure 1**). This finding suggests that age-related decline in fake news detection may be due to increased reliance on superficial (e.g., source reputation) over central (e.g., coherency of the news story) features in the deceptive messages; processing differences that can be directly implemented in eye tracking guided nudging interventions to enhance fake news detection in aging.

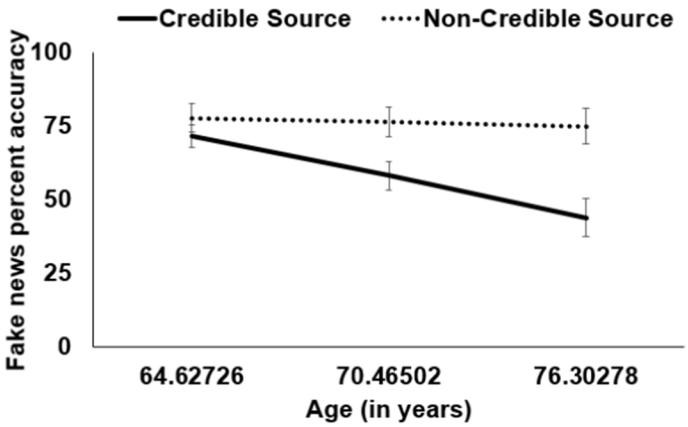

Figure 1. Greater age was associated with reduced accuracy in detecting fake news from credible sources.

INNOVATION

This interdisciplinary project from a strong research team with relevant, non-overlapping expertise in experimental aging, computational modeling, and decision making, leverages recent advances in neural network modeling and eye-tracking guided attentional nudging to address the significant real-life risk of fake news deception. Conceptually, methodologically, and translationally extending previous work, this project will for the first time: (i) **identify discrete features that promote fake news detection** in older adults with varying levels of cognitive functioning as part of a novel neural network model; (ii) **make available to the scientific community a brief fake news detection paradigm** suitable and efficient for large data collection in individuals from diverse backgrounds; (iii) **design and test a novel intervention approach to enhance fake news detection**.

APPROACH

Aim 1 /Study 1. We will **generate a large dataset to train and test the neural network.**

Participants. 600 participants will be recruited through Prolific for an adult lifespan sample with a wide age range (18-100 years; approximately equal numbers of participants per decade and gender). Our sample size was determined based on previous studies, which trained the neural networks using ratings/reviews collected from a large sample of individuals [18-19]. ***Inclusion/Exclusion.*** All participants must be able to understand and give informed consent, speak English fluently to ensure compliance with the study protocol, and must be living in the US to reduce potential differences in perception of study material (e.g., news headlines) by cultural background. All participants will be screened for cognitive impairment.

Stimuli/Procedure. Training the neural network requires a large dataset, not only in the number of participants, but also in the number of fake news headlines. We will develop a large stimulus pool of news headlines (1,000 real, 1,000 fake). Real news headlines will be compiled from a wide variety of reliable mainstream sources (e.g., The New York Times, The Wall Street Journal). Fake news headlines will be compiled from fact-checking websites (e.g., Snopes.com) or websites that routinely publish fake news stories (e.g., World Daily News Report). ***Fake News Task.*** Participants will be presented with 200 news headlines. 50 headlines will be identical for all participants, while the remaining 150 will be different for each participant and randomly selected from our set of 2,000 news headlines. For each news headline, participants will answer: 1) "To the best of your knowledge, how accurate is the claim in the above headline?" (options: not at all accurate/not very accurate/somewhat accurate/very accurate), 2) "Have you seen or heard about this story before?" (options: no/unsure/yes). ***Additional measures:*** brief demographics; short cognitive task battery involving measures of analytical reasoning [20], processing speed [21], and memory functioning [22]. Total study duration will be about 90 mins.

Neural Network Model. Behavioral data from the fake news task will be modeled with two separate neural networks, which both have the same architecture, differing only in the data they are trained on. As depicted in **Figure 2**, each network is split into two processing streams: (i) stream processing the text in the fake news headline; (ii)stream processing the participant information (such as age and level of cognitive functioning). In the text processing stream, the fake news headline is first converted to a numerical vector in a high-dimensional space using a state-of-the-art, off-the-shelf, large language model such as GPT-3 [23-24]. Next, this high-dimensional vector is passed to a compressing layer, which learns a low-dimensional embedding of the text that best predicts the participant's response. In the participant processing stream, age and level of cognitive functioning are fed into the model as input. These factors are then combined and compressed in a feedforward network to provide a low-dimensional embedding of the participant. The output of the two streams are combined in the combination layer, which computes the dot product of the text and participant embeddings. Finally, this dot product is compared with the actual rating that this particular participant gave for this particular text to determine the error. In the learning phase, this error is used to update weights in the neural network via back-propagation. In the testing phase, this error is averaged across the test set to compute average performance.

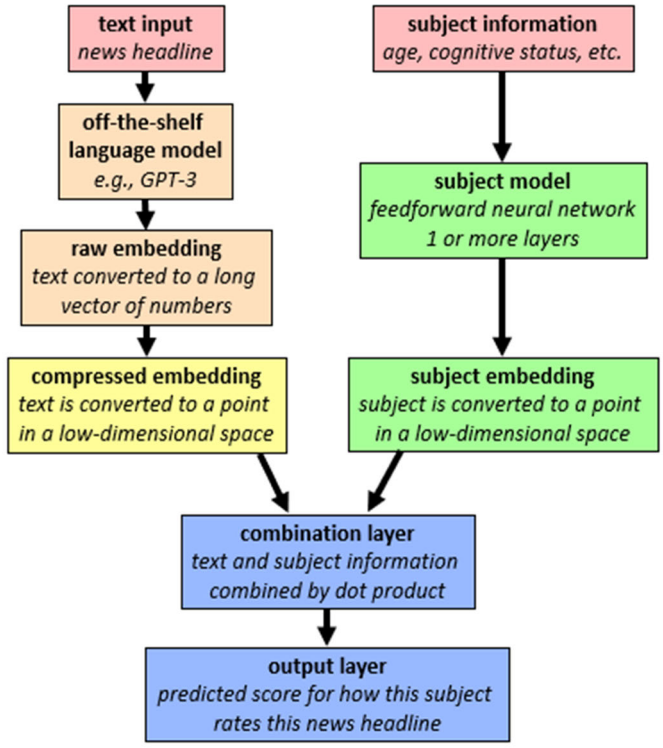

Figure 2. Schematic of neural network model.

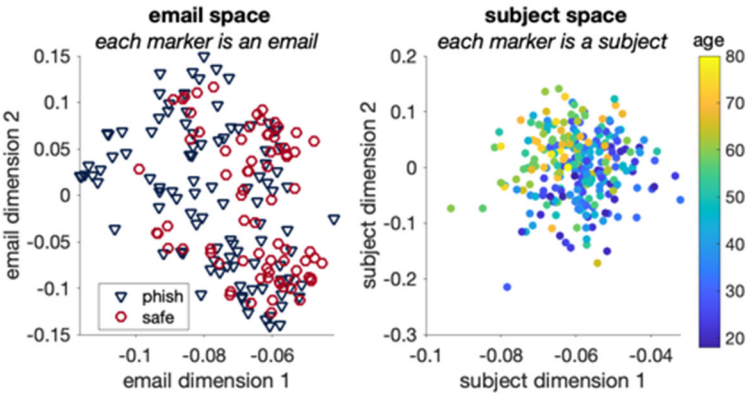

Figure 3. Example of neural network embeddings found by the network for emails and subjects.

Preliminary Data. We trained a simple version of the network on data from 279 subjects classifying 180 phishing emails. In **Figure 3,** we plot the first two dimensions of the email and subject embeddings. Note how the embeddings appear to encode the type of deceptive message (phish vs. safe) and the subject's age, despite the fact that this simple network was not trained on these. In addition, we quantified the ability of this network to predict the label that people would assign to each email (i.e., safe or phishing). On the held-out test set, which includes emails the model has never seen before, we find an accuracy over 75%, suggesting that this approach can predict an individual's deception (phishing email) detection.

Aim 2 /Study 2: We will **develop a *short fake news paradigm* for data collection in a large nationally representative, diverse sample.**

Participants. 600 participants (18-100 years) will be recruited through the MindCrowd platform. To date, the MindCrowd cohort comprises over 200,000 individuals, with approximately 50,000 consented to be re-contacted for future research. Thus, recruitment is low-cost, efficient, and fast-paced, including individuals who are typically hard to reach (e.g., across the US, in rural areas). Currently, in the cohort there is a known 15% APOE4 allele frequency, 20% of individuals are known to have a first-degree family history of Alzheimer's disease, which constitutes another risk factor for progression to Alzheimer's disease [25-26]. Our sample size was determined based on published effect size for age effects on fake news detection [1] and will result in a power of >98% at $p < .05$. ***Inclusion/Exclusion.*** The same criteria as described under Aim 1 will apply.

Stimuli/Procedure. Based on the literature [27-28] and leveraging preliminary findings from the neural network modeling under Aim 1, we will select the 10 most and 10 least deceptive fake news headlines as well as 20 real news headlines to develop a *short fake news paradigm.* Task details of this short version are identical to the ones described under Aim 1. This short task version will be integrated into a newly developed dashboard on the MindCrowd's website for any MindCrowd user to participate in. Participants will also complete a measure for analytical reasoning [20]. Study duration will be 15-20 mins.

Analysis. We will use multilevel modeling to investigate the extent to which the ability to detect fake news changes as a function of deceptiveness level (most vs. least deceptive fake news), age, and level of cognitive functioning (analytical reasoning ability). We will also explore moderation of demographics (race/ethnicity, rural/city, gender) and genetic risk for Alzheimer's disease on fake news detection.

Aim 3 /Study 3 We will **develop an attentional nudging intervention and test its effect on enhancing fake news detection among older adults with varying levels of cognitive functioning.**

Participants. We will recruit 120 older adults (60-90 years) via recruitment procedures established in our lab. With the proposed sample size and at $p = .05$, our power will be 80% to detect a small to medium effect (Cohen's $f = 0.15$) for the training intervention effect and to detect a small to medium effect (Cohen's $f = 0.17$) for the interaction between training intervention and cognitive functioning. ***Inclusion/Exclusion.*** The same criteria as described under Aim 1 will apply.

Stimuli/Procedure. We will sample two sets of 40 news headlines (20 real, 20 fake news headlines in each set) from our newly created stimulus pool under Aim 1.

Figure 4. Example fake news headlines paired with credible (left) and non-credible (right) source.

Real and fake news articles will be systematically paired with either credible (e.g., The Washington Post) or non-credible (e.g., True Pundit) news sources, resulting in 10 news headlines per category in each set (**Figure 4**). Text length in each news headline will be similar so timing for training probes will be equal across headlines and participants. ***Eye-tracking Guided Training Intervention Procedure.*** After informed consent, participants will provide demographic information and complete a short cognitive test battery, including measures of reasoning ability [20], processing speed [21], attentional efficiency [29], working memory capacity [30], and memory performance [22]. Then, participants will undergo the nudging intervention. In the **pre-intervention** phase, participants will be presented with the first set of 40 news headlines. Each news headline will be presented one at a time for 60 seconds. Then, the news headline will disappear, and participants will be asked to evaluate its accuracy: "To the best of your knowledge, how accurate is the claim in the headline you just saw?" (options: not at all accurate/not very accurate/somewhat accurate/very accurate). In the **intervention** phase, participants will be randomly assigned to either intervention (N=60) or control (N=60) condition. In the ***intervention* condition**, participants, while processing the news headline, will be guided via the eye tracker to view two probes (frames), presented one at a time on news source and headline. The eye tracker will record viewing times online on a pre-defined area of interest determined for each of the probes (5 secs for the news source, 15 secs for the news headline) and only if the pre-defined viewing duration is achieved will the color of the probe turn from black to green, and the probe will disappear. After viewing the probes, the news headline will disappear, and participants will be asked to evaluate its accuracy (using the same question/response format as in the pre-intervention phase). The ***control condition*** will be identical to the intervention condition with the exception that there will be no probes. The **post-intervention** phase will use the first set of 40 news headlines and the procedure will be identical to the pre-intervention phase. The total study duration will be about 2.5 hours.

Analysis. We will use multilevel modeling. The model will consider the main effects of news headline type (real, fake; within-subjects), intervention condition (both headline and source, only source, free viewing; between-subjects), timepoint (pre, post; within-subjects), and their interactions to test the effect of the nudging intervention on accuracy as well as interaction term with cognitive functioning.

MULTISITE MBI COLLABORATIONS

Our team members, who are all affiliated with the McKnight Brain Institute, span across the University of Florida and the University of Arizona and bring together a diverse set of skills on experimental and cognitive aging research (Pehlivanoglu, Ebner), deception and aging (Pehlivanoglu, Ebner, Wilson), and modeling of decision making including artificial intelligence methods (Phelps, Wilson) for comprehensive data collection and analysis. To enhance clinical impact of this work, our collaboration with Dr. Huentelman from the TGen Institute will provide us with a unique opportunity to characterize fake news detection ability among a nationally representative sample of individuals from diverse backgrounds, including those with particular risk for Alzheimer's disease, recruited through the McKnight Brain Institute associated MindCrowd cohort. Over the past years, our team has demonstrated effective collaboration in research on deception in aging [31-32]. The momentum behind this collaboration is reflected in two joint manuscripts in preparation for submission [33-34]. Thus, the proposed work reflects a rapidly emerging teamwork among highly productive researchers. Crucially, if funded, preliminary data collected from this MBRF pilot grant will prepare and train Drs. Pehlivanoglu and Phelps, who are both early career scientists, towards submission of joint extramural grant applications on interventional cognitive aging research.

PROJECT TIMELINE

The proposed project is designed to be completed in two years (Table 1). Biweekly zoom calls among the entire study team, along with one in-person meeting, will allow for close coordination of the different aspects of the project across the MBI sites and will ensure project success and extramural grant submissions.

Table 1. **Research plan, task lead, and schedule**

Task	Lead	Other	Year 1	Year 2
Aim 1: Characterize neurocognitive mechanisms of fake news detection				
Develop stimuli; implement online study	*Pehlivanoglu, Phelps*	*Ebner, Wilson*	*X*	
Collect data from 600 participants	*Pehlivanoglu, Phelps*	*Ebner, Wilson*	*X*	*X*
Data preprocessing and analysis	*Pehlivanoglu, Phelps*	*Ebner, Wilson*	*X*	*X*
Build, refine, and test neural network model	*Phelps, Pehlivanoglu*	*Wilson, Ebner*	*X*	*X*
Apply neural network model	*Phelps, Pehlivanoglu*	*Wilson, Ebner*	*X*	*X*
Aim 2: Integration of short fake news paradigm into MindCrowd				
Develop short fake news task	*Pehlivanoglu, Phelps*	*Ebner, Wilson*	*X*	
Task integration into MindCrowd platform	*Pehlivanoglu*	*Phelps, Ebner, Huentelman*	*X*	
Data collection from 600 participants	*Pehlivanoglu*	*Phelps, Ebner, Huentelman*	*X*	*X*
Data preprocessing and analysis	*Pehlivanoglu, Phelps*	*Ebner, Wilson, Huentelman*		
Aim 3: Determine behavioral benefits of an attentional nudging intervention				
Implement nudging intervention study	*Pehlivanoglu, Phelps*	*Ebner, Wilson*	*X*	
Collect data from 120 participants	*Pehlivanoglu, Phelps*	*Ebner, Wilson*	*X*	*X*
Data preprocessing and analysis	*Pehlivanoglu, Phelps*	*Ebner, Wilson*	*X*	*X*

FUTURE DIRECTIONS

This project will demonstrate feasibility and will result in crucial pilot data to generate effect sizes for extramural grant submissions. Throughout the project timeline, we plan to disseminate our findings via conference presentations and publications (1-2 per aim). The following grant submissions (both in response to *PAR-18-538: Basic and Translation Research on Decision Making in Aging and Alzheimer's Disease)* are planned: An R21 led by Drs. Pehlivanoglu and Phelps to (i) develop a novel pool containing highly-deceptive and low-deceptive fake news by leveraging findings from the neural network model; (ii) develop two eye-tracker guided training interventions: one with high-deceptive fake news, the other with low-deceptive fake news; and (iii) test their effectiveness. An R01 led by Drs. Ebner and Wilson on extending application of the neural network model in investigation of different forms of deception (e.g., deepfakes, financial exploitation) among diverse sample of adults varying in levels of cognitive and socioemotional functioning.

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Budget Name	A Neural Network and Guided Eye-Tracking Approach
Budget Type	Project
Responsible Person	Didem Pehlivanoglu
Responsible Department	LS-PSYCHOLOGY-GENERAL

Sponsor Grand Totals	Period 1	Period 2	Cumulative
Personnel:	**$24,595.00**	**$16,681.00**	**$41,276.00**
Salaries:	$22,809.00	$15,423.00	$38,232.00
Fringe:	$1,786.00	$1,258.00	$3,044.00
General:	**$13,480.00**	**$13,580.00**	**$27,060.00**
Equipment	$0.00	$0.00	$0.00
Travel - Domestic	$1,880.00	$1,980.00	$3,860.00
Travel - Foreign	$0.00	$0.00	$0.00
Participant Support	$0.00	$0.00	$0.00
Material and Supplies	$2,000.00	$2,000.00	$4,000.00
Publication Costs	$0.00	$0.00	$0.00
Consultant Services	$0.00	$0.00	$0.00
Computer Services	$0.00	$0.00	$0.00
Rental/User Fees - Equipment or Facility	$0.00	$0.00	$0.00
Alterations and Renovations	$0.00	$0.00	$0.00
Other			
Tuition	$0.00	$0.00	$0.00
Animal	$0.00	$0.00	$0.00
Patient Care	$0.00	$0.00	$0.00
Human Subject Payment	$9,600.00	$9,600.00	$19,200.00
Scholarships and Fellowships	$0.00	$0.00	$0.00
Other	$0.00	$0.00	$0.00
Trainee:	**$0.00**	**$0.00**	**$0.00**
Subaward:	**$21,800.00**	**$27,650.00**	**$49,450.00**
Subaward Direct:	$21,800.00	$27,650.00	$49,450.00
Subaward Indirect:	$0.00	$0.00	$0.00
Total Direct less Subaward Indirect:	**$59,875.00**	**$57,911.00**	**$117,786.00**
Total Direct:	**$59,875.00**	**$57,911.00**	**$117,786.00**
Total Indirect:	**$0.00**	**$0.00**	**$0.00**
Project Total:	**$59,875.00**	**$57,911.00**	**$117,786.00**

Indirect Costs	**Period 1**	**Period 2**	**Cumulative**
Start Date:	9/1/2022	9/1/2023	
End Date:	8/31/2023	8/31/2024	
Indirect Cost Base:	NONE	NONE	
Indirect Cost Rate:	52.50%	52.50%	
Indirect Cost Amount:	$0.00	$0.00	$0.00
Indirect Funds Requested:	$0.00	$0.00	$0.00

PERSONNEL COSTS	Period 1	Period 2	Cumulative
Didem Pehlivanoglu	$3,094.00	$3,188.00	$6,282.00
Salary:	$2,753.00	$2,836.00	$5,589.00
Fringe:	$341.00	$352.00	$693.00
Committed Months:	0.60	0.60	1.20

TBD: Other OPS/Temp Work Study	$11,428.00	$13,493.00	$24,921.00
Salary:	$10,660.00	$12,587.00	$23,247.00
Fringe:	$768.00	$906.00	$1,674.00
Committed Months:	4.10	4.70	8.80

TBD: Other OPS/Temp Work Study	$10,073.00	$0.00	$10,073.00
Salary:	$9,396.00	$0.00	$9,396.00
Fringe:	$677.00	$0.00	$677.00
Committed Months:	1.08	0.00	1.08

GENERAL COSTS	Period 1	Period 2	Cumulative
Materials and Supplies	Period 1	Period 2	Cumulative
Cost	$2,000.00	$2,000.00	$4,000.00

Human Subject Payment	Period 1	Period 2	Cumulative
Cost	$6,000.00	$6,000.00	$12,000.00

Human Subject Payment	Period 1	Period 2	Cumulative
Cost	$3,600.00	$3,600.00	$7,200.00

Travel - Domestic	Period 1	Period 2	Cumulative
Cost	$1,880.00	$1,980.00	$3,860.00

SUBAWARD COSTS	Period 1	Period 2	Cumulative
Total Direct:	$21,800.00	$27,650.00	$49,450.00
Total Indirect:	$0.00	$0.00	$0.00
Total Cost:	$21,800.00	$27,650.00	$49,450.00
Amount in UF Base:	$0.00	$0.00	$0.00
UF Indirect Cost:	$0.00	$0.00	$0.00

BUDGET JUSTIFICATION

SALARIES:

The budget provides the anticipated effort for persons to be involved in this research project, if funded, for the total requested time period. For projected time occurring in future years, the salaries have been adjusted with a 3.0% increase for cost-of-living adjustments.

SENIOR PERSONNEL:

Didem Pehlivanoglu, PhD, Principal Investigator (effort = 0.60 CM/year): Dr. Pehlivanoglu in close communication with Drs. Phelps, Ebner, and Wilson, will provide oversight of all aspects of this research project, including communication with the research team, budget management, development of stimuli, experimental tasks, guided eye-tracking procedure. Dr. Pehlivanoglu will oversee training and mentoring of the research assistant involved in the project, who will help with data collection and day-to-day responsibilities for this project. In close communication with the other members of the team, she will take primary responsibility for data analysis, interpretation of the data, manuscript write-up, dissemination of the results, and preparation of the R21 grant submission. She will also be responsible for transferring de-identified data between project sites for cross-site analysis as well as application of the neutral network model.

OTHER PERSONNEL:

TBD, Research Assistant, (effort = 4.1 CM in year 1; 4.7 CM in year 2): The research assistant under close supervision of Dr. Pehlivanoglu, will be responsible for managing the day-to-day activities of this project, including management of the participant database, scheduling participants for the in-lab and online data collection, collecting the data, IRB revisions, preparing the data for analysis, and will actively participate in report and manuscript write-up.

TBD, Programmer, (effort = 1.08 CM in year 1): The programmer under Dr. Pehlivanoglu's supervision, will be responsible for coding the fake news and phishing task for integration into the MindCrowd platform.

FRINGE BENEFITS:

Fringe benefits, including FICA, State Unemployment, Workers' Compensation, Retirement, Life and Health Insurance, are assessed as a percentage of the respective employee's salary. Fringe benefits are calculated on the requested salary budgeted according to the University of Florida's proposed benefit rates, which have been submitted to the U.S. Department of Health and Human Services for approval. Once approved these rates will become effective July 1, 2022 and will be incorporated into UF's federally negotiated rate agreement. The proposed benefit rates can be found here: https://administrativememo.ufl.edu/2022/04/proposed-2022-2023-fringe-benefit-pool-rates/

TRAVEL:

All travel costs are consistent with the University of Florida's travel policy (located at http://www.fa.ufl.edu/directives-and-procedures/travel).

Domestic:
Total funds in the amount of $3,860 are requested for domestic travel to conferences to disseminate research results (e.g., to the Society of Psychophysiological Research which will be held in New Orleans in 2023 in Year 1; to the Cognitive Aging Conference which will be held in Atlanta in 2024 in Year 2).

Cost estimates based on location are included below:

Flight: $500
Lodging: $175/night x 4 = $700
Meals: $36/day X 5 = $180
Registration: $300
Transportation: $200
Total: $1,880 in Year 1

Flight: $500
Lodging: $200/night x 4 = $800
Meals: $36/day X 5 = $180
Registration: $300
Transportation: $200
Total: $1,980 in Year 2

OTHER DIRECT COSTS:

1. Materials & Supplies:

Supplies requested will be used for launching the project, running experimental sessions, and analyzing and backing up the acquired data throughout the project.

Funds in the amount of $2,000 are requested in Year 1. Laptop ($750; i5 CPU; 16 GB RAM) dedicated to this project will be used for programing, data collection, and keeping record of study logistics. Software license ($750) will be used to host psychological tasks and measures. Eye-tracker related supplies ($500) will be used for collecting eye-tracker data (e.g., chin rest, disinfectant wipes).

Funds in the amount of $2,000 are requested in Year 2 for computing software licenses (e.g., STATA, DataViewer; $1800), which will be used for processing and analysis of the behavioral and eye-tracker data; and for an external hard drive for data storage ($200), which will be used for backing up the data.

2. Subawards:

A subaward to the University of Arizona (UA) is requested in each year of the project. UA will lead the neural network modeling and running of the online behavioral experiments and will oversee coding, and development of the behavioral tasks in Aim 1 as well building computational models to analyze the data as described in the proposal. Please see the separate subaward budget and budget justification included for a detailed breakdown.

3. Human Subject Payments:

For the neural network modeling study (Study 1), participant costs ($20 per participant) will amount to $6,000 for 300 participants in Year 1 and $6,000 for 300 participants in Year 2.

For the intervention study with eye-tracker (Study 3), participant costs ($60 per participant) will amount to $3,600 for 60 participants in Year 1 and $3,600 for 60 participants in Year 2.

TOTAL DIRECT COSTS: $117,786

Budget

University of Arizona

Site	Year 1	Year 2
University of Arizona		
Personnel	$19,800.00	$21,800.00
Supplies	$2,000.00	$1,500.00
Other costs		
Travel		$4,350.00
Subtotal	***$21,800.00***	***$27,650.00***

Budget Justification

UNIVERSITY OF ARIZONA (UA)

Personnel

TBD, Research Engineer (effort=4.8 CM in year 1; 5.28 CM in year 2) will be responsible for developing, programming, and training the complex networks of algorithms under the supervision of Drs Wilson and Phelps. S/He will also help with data collection for Study 1, interpretation of findings resulting from the neural network modeling, and contribute to manuscript write-up.

Fringe Benefits: The University of Arizona defines fringe benefits as direct costs and estimates benefits as a standard percent of salary applied uniformly to all types sponsored activities, and charges benefits to sponsors in accordance with the Federally-negotiated rates in effect at the time salaries are incurred. The rates used in the proposal budget are based on the current Federally-negotiated Rate Agreement rate. The rates are as follows: 31.9% for faculty and full-time staff. Current DHHS-approved rates for faculty, research staff and students can be accessed via this link https://www.fso.arizona.edu/sites/default/files/202204/rate_agreement_2022_4.22_0.pdf

Supplies

Funds in the amount of $2,000 are requested in Year 1 to purchase a laptop and software license (e.g., GPT-3) for developing machine-learning and artificial intelligence modeling algorithms and applying them to the data acquired throughout the project. Funds in the amount of $1,500 are requested in Year 2 to renew the software license for modeling and to purchase an external hard drive for data storage.

Other costs

N/A

Travel

Funds in the amount of $4,350 are requested in Year 2 for traveling of three UA personnel to UF for a collaborative meeting. Cost per person will include flight ($800), accommodation ($400; for 2 nights), meals ($110; for 3 days), ground transportation ($140).

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Pehlivanoglu, Didem

eRA COMMONS USER NAME (credential, e.g., agency login): dpehlivanoglu

POSITION TITLE: Postdoctoral Associate

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Izmir University of Economics, Izmir, Turkey	BA	06/2010	Psychology
Bogazici University, Istanbul, Turkey	MA	07/2012	Psychology
Georgia Institute of Technology, Atlanta, USA	PHD	08/2018	Psychology
University of Florida, Gainesville, USA	Postdoctoral Associate	Ongoing	Psychology

A. Personal Statement

I am a Postdoctoral Associate in the Department of Psychology at the University of Florida.
My research examines the role of emotionally and motivationally relevant information on cognition at basic and applied contexts, with a special focus on understanding contributions of individual differences to cognition-emotion interactions. My training in experimental aging research combined with my background in cognitive and affective neuroscience allows to employ convergent measures, including behavioral (self-report, behavior-based tasks), physiological (eye-tracking), and neuroimaging (EEG/ERP) techniques, with the goal of comprehensively capture socioemotional and cognitive processes in adulthood and aging. I currently have 12 peer-review publications (eight first-authored) and serve as ad-hoc reviewer on numerous highly ranked journals in the field of aging (e.g., Neurobiology of Aging, The Journals of Gerontology, Psychology and Aging). My work has been recognized with multiple awards and scholarships (e.g., American Psychological Association Division 20 Postdoctoral Research Award; American Psychological Association Dissertation Award; Cluff Aging Research Award; The Scientific & Technological Research Council of Turkey National Scholarship).

Since I have started my postdoctoral studies, I have been core research personnel in an ongoing NIH R01 (PI Ebner; NIH/NIA - 1R01AG057764-01A1) on identifying the cognitive, socioemotional, and neurobiological profiles of online deception risk susceptibility in aging. I have been actively working with various members of the McKnight Brain Institute across the US, including Drs. Ebner, Wilson (University of Arizona), and Huentelman (TGen Institute). I have been closely working with Dr. Ebner for launching and implementing the R01 project as well as for supervising our research team at UF on various aspects of the project, including data collection, analysis, and manuscript preparation. Together with Dr. Wilson, I have been working on statistical data analysis and manuscript preparation on determining susceptibility profiles for online deception. I have also been in close contact with Dr. Huentelman to oversee data collection and analysis from the MindCrowd cohort to determine online deception susceptibility among diverse groups of older adults who are at risk for developing Alzheimer's disease.

Throughout my academic career, I have gained extensive experience in planning and conducting empirical research studies with older adults (including those with subjective cognitive decline and a family history of dementia), IRB protocols and research compliance, and supervision of research personnel and trainees, as well as diverse data analysis techniques, and results dissemination. These skills and my training background put me in an excellent position to serve as PI on the proposed pilot project, in which I will oversee the project including budget management, research regulatory activities, staff training, recruitment and logistics for data

collection, data analysis, and manuscript, report, and grant writing. I will work in close interaction with my mentors, Drs. Ebner and Wilson, and the participating postdoc at the University of Arizona site, Dr. Phelps, on these responsibilities. The proposed inter-institutional MBRF grant will provide us the unique opportunity for a multimethod approach by combining data-driven neural network modeling with an eye-tracker guided training to increase knowledge of the processes involved in susceptibility to deception via fake news and phishing in aging and design interventions to combat this significant risk among older adults. This grant will also generate pilot data and demonstrate feasibility of this line of research crucial for my R21 application on data-driven intervention research in aging.

Ongoing Research Support
Uncovering and Surveilling Financial Deception Risk in Aging
NIH/NIA - 1R01AG057764-01A1 (MPI: Natalie Ebner) 09/01/2018 – 06/30/2023
Role: Postdoctoral Associate

Representative Publications

a. **Pehlivanoglu, D.,** Lighthall, N. R., Lin, T., Chi, K. J., Polk, R., Perez, E., Cahill, B., & Ebner, N. C. (2022). Aging in an "infodemic": The role of analytical reasoning, affect, and news consumption frequency on news veracity detection. *Journal of Experimental Psychology: Applied.*

b. Ebner, N. C., **Pehlivanoglu, D.,** Polk, R., Turner, G. R., & Spreng, R. N. (2022). Aging online: Rethinking the aging decision-maker in a digital era. In Y. Hanock & S. Wood (Eds.), *A Fresh look at Fraud: Theoretical and Applied Perspectives* (pp. 58-87). Routledge Taylor Francis.

c. **Pehlivanoglu, D.** & Verhaeghen, P. (2019). Now you feel it, now you don't: Motivated attention to emotional content is modulated by age and task demands. *Cognitive, Affective, & Behavioral Neuroscience, 19*(5), 1299-1316.

d. **Pehlivanoglu, D.,** Jain, S., Ariel, R., & Verhaeghen, P. (2014). The ties to unbind: Age-related differences in feature (un)binding in working memory for emotional faces. *Frontiers in Psychology, 5,* 253

B. Positions, Scientific Appointment, and Honors

Positions and Scientific Appointments

2018 – Present	Ad-hoc Reviewer for: Journal of Experimental Psychology: General; Consciousness and Cognition; Journal of Gerontology: Psychological Sciences; Psychology and Aging; Perception; Cognition and Emotion; Psychological Bulletin; Aging, Neuropsychology, and Cognition; Physiology & Behavior; Frontiers in Psychology; International Journal of Psychophysiology; Neurobiology of Aging; Behavior Research Methods; Experimental Aging Research; Neuroimage
2018 – Present	Postdoctoral Associate, University of Florida, Department of Psychology, Gainesville, FL
2015 – 2018	Graduate Teaching Assistant, Georgia Institute of Technology, School of Psychology, Atlanta, GA
2012 – 2015	Graduate Research Assistant, Georgia Institute of Technology, School of Psychology, Atlanta, GA

Honors

2021	American Psychological Association Division 20 Postdoctoral Research Award
2021	Cluff Aging Research Award, Institute for Learning in Retirement at Oak Hammock
2018	The Georgia Tech Graduate Student Government Association Travel Award
2017	American Psychological Association Division 20 Dissertation Award
2010-2012	TUBITAK (The Scientific & Technological Research Council of Turkey) National Scholarship Program for Graduate Students
2005-2010	Full Tuition Merit Scholarship (Izmir University of Economics)

C. Contributions to Science

My training in experimental aging research combined with my background in cognitive and affective neuroscience allows to uncover age-related differences in socioemotional functioning and decision making at both behavioral and neural levels. My research agenda revolves around three primary areas:

1. Interindividual Differences in Susceptibility to Deception

The rapid shift towards a digitalized, globally connected world confronts individuals with drastically new contexts and decisions. Advances in technology and social media can result in the distribution of manipulation of opinions via misinformation and fake news. Our group is the first to systematically study the effects of age on susceptibility to fake news in adulthood and aging. We find that age-related decline in detecting fake news is only present in older adults above 70 years old and not in "young-old" (60-70 years) individuals. We have also shown that analytical reasoning ability predicts better detection of fake news in both young and older adults. Additionally, we find that analytical reasoning may typically enhance the ability to detect fake news but fails to confer a benefit for news articles with high urgency and emotional content, such as news related to the COVID-19 pandemic. These findings highlight the role of both interindividual differences (analytical reasoning ability, age) and contextual factors (e.g., news source, news content) on susceptibility to deception via fake news. Recently, we proposed a multi-faceted framework for organizing existing knowledge about influences on deception detection that can guide future work on the aging decision maker, including in the unsafe cyber space. This *Biopsychosocial Model of Deception Risk in Aging* capitalizes on interindividual differences in cognitive, socioemotional, and neurobiological factors to characterize risk profiles for designing age-tailored decision-supportive solutions to counter misinformation and fraud in later life.

a. **Pehlivanoglu, D.,** Lighthall, N. R., Lin, T., Chi, K. J., Polk, R., Perez, E., Cahill, B., & Ebner, N. C. (2022). Aging in an "infodemic": The role of analytical reasoning, affect, and news consumption frequency on news veracity detection. *Journal of Experimental Psychology: Applied.*

b. Ebner, N. C., **Pehlivanoglu, D.,** Polk, R., Turner, G. R., & Spreng, R. N. (2022). Aging online: Rethinking the aging decision-maker in a digital era. In Y. Hanock & S. Wood (Eds.), *A Fresh look at Fraud: Theoretical and Applied Perspectives* (pp. 58-87). Routledge Taylor Francis.

c. **Pehlivanoglu, D.,** Lin, T., Deceus, F., Heemskerk, A., Ebner, N. C., & Cahill, B. S. (2021). The role of analytical reasoning and source credibility on the evaluation of real and fake full-length news articles. *Cognitive Research: Principles and Implications, 6*(1), 1-12.

2. Cognition and Emotion Interactions

Much of my research revolves around cognition-emotion interactions across the adult lifespan. There is evidence in both young and older adults that relating information to one's self during encoding is an effective memory strategy, possibly due to involvement of specialized elaborative knowledge structures and associated motivational/social goals. Providing further insight on this self-referential processing memory-enhancement effect, my work has shown that self-relevant information enhances recollective experience and metamemory (awareness of one's memory content). In this context, I also investigate the degree to which emotion captures attention among young and older adults by employing ERP and eye tracking. My findings show that older adults (to the same extent as young adults) are able to flexibly allocate their attention to and away from emotional and/or salient stimuli based on specific task agendas. This age-comparative pattern, however, is limited to circumstances in which overall task difficulty is equated between the age groups. These findings make important contributions to the field by highlighting the importance of considering cognitive effort when examining age effects in the processing of socio-emotional information.

a. **Pehlivanoglu, D.,** & Verhaeghen, P. (2019). Now you feel it, now you don't: Motivated attention to emotional content is modulated by age and task demands. *Cognitive, Affective, & Behavioral Neuroscience, 19*(5), 1299-1316.

b. **Pehlivanoglu, D.,** Duarte, A., & Verhaeghen, P. (2020). Multiple identity tracking strategies vary by age: An ERP study. *Neuropsychologia, 138,* 107357.

c. **Pehlivanoglu, D.,** Jain, S., Ariel, R., & Verhaeghen, P. (2014). The ties to unbind: Age-related differences in feature (un)binding in working memory for emotional faces. *Frontiers in Psychology, 5*, 253.

d. Boduroglu, A., **Pehlivanoglu, D.,** Tekcan, A. İ., & Kapucu, A. (2015). Effects of self-referencing on feeling-of-knowing accuracy and recollective experience. *Memory, 23*(5), 736-747.

3. Impact of Oxytocin on Brain and Behavior

In this line of research, I investigate the role of the neuropeptide oxytocin on cognitive and socioemotional functioning in young and older adults both in the brain and in behavior. Current evidence suggests that oxytocin modulation of social-cognitive processes and behavior and their associated neurocircuitry depends on contextual (e.g., social stimuli) and interindividual factors (e.g., age, sex, clinical status). For example, we find that relative to placebo, intranasal administration of oxytocin enhances perceived trustworthiness of young faces among older adults; with this effect particularly pronounced for faces with direct gaze (relative to faces

with averted gaze). In our recent systematic review that focuses on oxytocin-related temporal modulation in the brain, we propose a novel conceptual framework that guides the study of oxytocin modulation on attention, starting very early in the processing stream. We conclude that modulation via oxytocin requires standardized, multi-method, longitudinal, and cross-sequential assessments in well-powered, controlled, and representative samples in line with an integrative lifespan approach, which considers development as a lifelong dynamic process involving both change and stability characterized by the interplay between genetic, neurobiological, and socio-behavioral factors.

a. **Pehlivanoglu, D.,** Myers, E., & ***Ebner, N. C.*** (2020). Tri-Phasic Model of Oxytocin (TRIO): A systematic conceptual review of oxytocin-related ERP research. *Biological Psychology,* 107917.

b. Horta, M., **Pehlivanoglu, D.,** & ***Ebner, N. C.*** (2020). The Role of Intranasal Oxytocin on Social Cognition: an Integrative Human Lifespan Approach. *Current Behavioral Neuroscience Reports,* 1-18.

c. Lin, T., **Pehlivanoglu, D.,** Ziaei, M., Liu, P., Woods, A. J., Feifel, D., Fischer, H., & Ebner, N. C. (in press). Age-related differences in amygdala activation associated with face trustworthiness but no evidence of oxytocin modulation. *Frontiers in Psychology.*

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Ebner, Natalie C

eRA COMMONS USER NAME (credential, e.g., agency login): NATALIE.EBNER

POSITION TITLE: Professor of Psychology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Free University Berlin, Berlin	BA	04/1998	Psychology
Free University Berlin, Berlin	MA	03/2001	Psychology
Free University Berlin, Berlin	PHD	05/2005	Psychology
Max Planck Institute for Human Development, Berlin	Postdoctoral	06/2007	Psychology
Yale University, Connecticut	Postdoctoral	07/2011	Psychology

A. Personal Statement

Given my extensive research expertise and my strong and diverse track record in training young scientists, I am in an excellent position to serve as mentor for Dr. Pehlivanoglu in this intervention pilot grant. I have a broad background in cognitive and socioemotional experimental research across the adult lifespan, and particular expertise in social-cognitive neuroscience and decision making in aging, including the study of processes involved in deception and exploitation in older adults (the broader topic area of this application). I use a multi-method approach in my research that includes self-report, cognitive-behavioral measures, neuroimaging techniques, and hormone/neuropeptide markers. I have a record of sustained and productive NIH, NSF, and foundation funding for researching cognitive and socioemotional aging. My mentoring portfolio includes 6 postdoctoral, 11 doctoral, > 10 post-bacs, and > 70 undergraduate students. I also serve currently as a mentor on 3 T32 programs (1 predoctoral, 2 postdoctoral) and I am currently a primary mentor on 2 junior faculty NIH K01 awards as well as on 2 NIH diversity supplements in two separate grants. Under my supervision, my students have published peer-reviewed work (> 45 of my publications are first- or co-authored by trainees; out of > 100 peer-reviewed publications in total), disseminated our research at numerous high-rank national and international conferences and scientific meetings, and have been awarded numerous recognitions, awards, and fellowships. I have served as a faculty mentor in the acquisition of > $1,000,000 in trainee awards, prizes, scholarships, and fellowships since I joined the University of Florida in 2011. My various affiliations on campus (e.g., the McKnight Brain Institute, the Institute on Aging) and my strong collaboration with Dr. Wilson, as the co-mentor on this team, and whom I know through the interdepartmental McKnight Brain Institute annual meetings, allows for an exceptionally well-composed mentoring team across two of the McKnight Brain Institute sites. As part of this grant, we will work very closely with Dr. Pehlivanoglu on the research aims, as well as on publication of the results and, importantly, on extramural grant submissions as detailed in the application.

<u>Ongoing projects that I would like to highlight include:</u>
NIH/NIA R01AG072658
Ebner/Lighthall/Wilson (MPI)
03/01/22-04/30/27
Characterizing and Modulating Neurocognitive Processes of Learning to Trust and Distrust in Aging

NIH/NIA R01AG057764
Ebner/Spreng (MPI)

09/01/2018-06/30/2023
Uncovering and Surveilling Financial Deception Risk in Aging

NIH/NIA R01AG059809
Cruz-Almeida/**Ebner** (MPI)
08/01/2018-04/30/2023
Mechanisms of Oxytocin's Analgesia in Older Adults

Representative Publications:

a. **Ebner NC**, Johnson MR, Rieckmann A, Durbin KA, Johnson MK, Fischer H. Processing own-age vs. other-age faces: neuro-behavioral correlates and effects of emotion. Neuroimage. 2013 Sep;78:363-71. PubMed Central PMCID: PMC3684564
b. Rana M, Varan AQ, Davoudi A, Cohen RA, Sitaram R, **Ebner NC**. Real-time fMRI in neuroscience research and its use in studying the aging brain. Front Aging Neurosci. 2016 Oct;8:239. PubMed Central PMCID: PMC5067937
c. Horta M, Ziaei M, Lin T, Porges EC, Fischer H, Feifel D, Spreng RN, **Ebner NC**. Oxytocin alters patterns of brain activity and amygdalar connectivity by age during dynamic facial emotion identification. Neurobio. Aging 2019 June; 78: 42-51. PubMed Central PMCID: PMC6545147
d. Pehlivanoglu D, Lin T, Deceus F, Heemskerk A, **Ebner NC**, Cahill B. The role of analytical reasoning and source credibility on the evaluation of real and fake full-length news articles. Cognitive Research: Principles and Implications 2021;6:24. PubmedCentral PMCID: PMC8012428

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-Present	Member, Study Section SPIP, National Institutes of Health
2021-Present	Editorial Board: Brain Aging
2020-Present	Professor, University of Florida, Department of Psychology
2020-Present	Affiliate Faculty, Center for Addiction Research & Education, University of Florida
2020	Ad-hoc Reviewer, Review Panel BBBP, National Institutes of Health
2019	Member, Steering Committee of National Academies of Sciences and National Institutes of Health Workshop
2018-Present	Affiliate Faculty, Pain Research and Intervention Center of Excellence (PRICE), Clinical and Translational Science Institute (CTSI), College of Medicine, University of Florida
2018-Present	Editorial Board: Journal of Experimental Psychology: General
2018-2020	Editorial Board: Cognition and Emotion
2018	Early Career Reviewer (ECR), Review Panel MESH, National Institute of Health
2018	Ad-hoc Reviewer, Review Panel SPIP, National Institutes of Health
2018	Ad-hoc Reviewer, Review Panel BBBP, National Institutes of Health
2018-Present	Editorial Board: Psychology and Aging
2018	Ad-hoc Reviewer, Austrian Science Foundation
2018	Ad-hoc Reviewer, Canada Research Chair
2017-2020	Associate Professor (with tenure), University of Florida, Department of Psychology
2017-2019	Member, Organizing Committee of the Indonesian-American Kavli Frontiers of Science Symposium
2016-Present	Ad-hoc Reviewer, National Science Foundation
2016-Present	Affiliate Faculty, Florida Institute for Cybersecurity Research (FICS), University of Florida
2013-Present	Affiliate Faculty, Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP) University of Florida
2013-2015	Junior Scholar in Claude D. Pepper Older Americans Independence Center Institute on Aging, Department of Aging & Geriatric Research, College of Medicine, University of Florida
2012-Present	Ad-hoc Reviewer, Swiss National Science Foundation
2012-2019	Editorial Board: Frontiers in Psychology: Emotion Science
2011-2017	Assistant Professor, University of Florida, Department of Psychology
2010-2011	Associate Research Scientist, Yale University, Department of Psychology
2007-2010	Postdoctoral Fellow, Yale University, Department of Psychology

2005-2007	Postdoctoral Fellow, Max Planck Institute for Human Development
2001-2005	Predoctoral Fellow, Free University Berlin & Max Planck Institute for Human Development

Honors

2020	UF College of Liberal Arts and Sciences Faculty Achievement Award
2019	UF Research Foundation Professorship Award
2016	UF College of Liberal Arts and Sciences International Educator of the Year Award
2016	UF Excellence Award -- Assistant Professors
2015	Kavli Fellow National Academy of Sciences
2014	International Max Planck Research School on the Life Course (LIFE) Outstanding Alumni Award, APA Board of Educational Affairs Award to Advance Interdisciplinary Education and Training in Psychology
2006	Heinz-Heckhausen-Jungwissenschaftlerpreis (Young Research Scientist Award), German Psychological Association

C. Contributions to Science

1. Own-Age Bias in Attention, Memory, and Emotion Perception

One line of my research builds on the fact that our environment is complex, and our cognitive system is limited, thus not all stimuli can be fully and simultaneously analyzed. There is evidence that emotional and self-relevant information is preferentially processed, possibly due to the highly practiced and elaborate knowledge structures associated with it as well as the greater personal and social costs of inattention or inaccurate memory. My research findings open new insights into how faces of different ages are processed and how they bias attention and memory. I show that this bias is affected by the emotional content of the faces and impacts memory for person-related information (e.g., personal goals and agendas). My results challenge and inform interpretations of face and emotion processing and age-related differences therein as older participants may be at a disadvantage relative to young participants when stimuli are faces of only young individuals. In our more recent work, we further demonstrate that brain regions involved in attentional biases can be trained via real-time functional magnetic imaging neurofeedback, including in older adults and individuals with Parkinson's disease or at risk for Alzheimer's disease. My findings are not only important from a developmental perspective, but they also place constraints on general theories of attention and memory and have various important implications for social interactions, emotional regulation, self-perceptions, psychological well-being, and health in adulthood and aging.

Representative Publications:

a. **Ebner NC**, He Y, Fichtenholtz HM, McCarthy G, Johnson MK. Electrophysiological correlates of processing faces of younger and older individuals. Soc Cogn Affect Neurosci. 2011 Sep;6(4):526-35. PubMed Central PMCID: PMC3150862.
b. **Ebner NC**, Johnson MR, Rieckmann A, Durbin KA, Johnson MK, Fischer H. Processing own-age vs. other-age faces: neuro-behavioral correlates and effects of emotion. Neuroimage. 2013 Sep;78:363-71. PubMed Central PMCID: PMC3684564.
c. Rana M, Varan AQ, Davoudi A, Cohen RA, Sitaram R, **Ebner NC**. Real-time fMRI in neuroscience research and its use in studying the aging brain. Front Aging Neurosci. 2016 Oct;8:239. PubMed Central PMCID: PMC5067937.
d. Strickland-Hughes CM, Dillon KE, West RL, **Ebner, NC**. Own-age bias in face-name associations: Evidence from memory and visual attention in younger and older adults. Cognition. 2020 Mar. PubMed PMID: 32192981

2. Decision Making and Aging

My lab aims at identifying adult age differences in cognitive, affective, and social influences on decision making, including in the applied contexts of health and computer security. We have shown that young and older adults differ in their use of future-time travel for healthy decision making. In addition, we have developed an infrastructure that allows us to determine internet users' susceptibility to cyberattacks (e.g., phishing emails) in the natural setting of the participants' homes. This research has found evidence of a particular vulnerability in older compared to young internet users, combined with very low susceptibility awareness in the elderly. We have also developed a conceptual framework for social decision making in aging, as well as novel deception-

related and social decision paradigms, which we submit to empirical testing in ongoing research (e.g., on phishing and misinformation/fake news).

Representative Publications:

a. Lin T, Capecci D, Ellis D, Rocha H, Dommaraju S, Oliveira DS, **Ebner NC**. Susceptibility to spear-phishing emails: Effects of internet user demographics and email content. ACM Transactions on Computer-Human Interaction, 2019 Jul; 26(5):1-28 PubMed Central PMCID: PMC7274040
b. **Ebner NC**, Ellis DM, Lin T, Rocha HA, Yang H, Dommaraju S, Soliman A, Woodard DL, Turner GR, Spreng RN, Oliveira DS. Uncovering susceptibility risk to online deception in aging. J Gerontol B Psychol Sci Soc Sci. 2020 Feb 14;75(3):522-533. PubMed PMID: 29669133
c. Grilli, MD, McVeigh, KS, Hakim, ZM, Wank, AA, Getz, SJ, Levin, BE, **Ebner, NC**, Wilson, RC. Is this phishing? Older age is associated with greater difficulty discriminating between safe and malicious emails. J Gerontol B Psychol Sci Soc Sci. 2021, 76:1711-1715. PubMed PMID PMCID: PMC8557838
d. Hakim, ZM, **Ebner, NC**, Oliveira, DS, Getz, SJ, Levin, BL, Lin, T, Lloyd, K, Lai, VT, Grilli, MD, Wilson, RC. Evaluating the cognitive mechanisms of phishing detection with PEST, an ecologically valid lab-based measure of phishing susceptibility. Behavior Research Methods, 2021. PubMed Central PMCID: PMC8188181

3. Oxytocin and Socioemotional Aging

As summarized in recent theoretical papers, oxytocin is a neuropeptide with beneficial effects in social and emotional domains, mostly studied in healthy young adults, schizophrenia, and autism. Our group is the first to comprehensively study acute and chronic oxytocin effects in the context of emotional, motivational, and social-cognitive aging. We have developed a theoretical framework that allows us to examine the extent to which the neuropeptide oxytocin is associated with improved functioning in aging, considering gene-brain-behavior relationships using behavioral, (epi)genetic, pharmacological, and neuroimaging techniques. In this line of work, we have generated supportive evidence of good tolerability and benefits of oxytocin intranasal intervention on various functions in aging (e.g., affect, social decision making, resting brain activity)

Representative Publications:

a. **Ebner NC**, Chen H, Porges, E, Lin T, Fischer H, Feifel D, Cohen RA. Oxytocin's effect on resting-state functional connectivity varies by age and sex. Psychoneuroendocrinology. 2016 Jul;69: 50-59. PubMed Central PMCID: PMC4942126
b. **Ebner NC**, Horta M, Lin T, Feifel D, Fischer H, Cohen RA. Oxytocin modulates meta-mood as a function of age and sex. Front Aging Neurosci. 2015 Sep;7:175. PubMed Central PMCID: PMC4565056.
c. Horta M, Kaylor K, Feifel D, **Ebner NC**. Chronic oxytocin administration as a tool for investigation and treatment: A cross-disciplinary systematic review. Neurosci & Biobehav Rev. 2020 Jan; 108: 1-23. PubMed Central PMCID: PMC6949379
d. Pehlivanoglu D, Myers E, **Ebner, NC**. Tri-Phasic Model of Oxytocin (TRIO): A systematic conceptual review of oxytocin-related ERP research. *Biological Psychology* 2020;*154*:107917. PubmedCentral PMCID: PMC7556712

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/natalie.ebner.1/bibliography/public/

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Phelps, Caroline Emily

eRA COMMONS USER NAME (credential, e.g., agency login): CPHELPS

POSITION TITLE: Researcher/Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Oxford	BA	08/2012	Physiological Sciences
University of Bristol, UK	PhD	01/2017	Neuroscience and Pharmacology
University of Arizona, USA	Postdoctoral Training	10/2021	Pharmacology
University of Arizona, USA	Researcher/ Scientist	Ongoing	Psychology

A. Personal Statement

I have a strong background in cognition research. I have published a number of studies investigating the nature and mechanisms underlying cognitive deficits seen in animal models of chronic pain. Through this I became interested in using computational modelling for a greater understanding of cognitive processes, beyond overt behavioral measures. Under the mentorship of Dr Robert Wilson, I have been learning and applying computational modelling to understand how aging effects decision making, including in a phishing task.

In this grant, I will be working with Dr. Pehlivanoglu in developing experimental stimuli and tasks as well as undertaking data processing and analysis. Under the supervision of Dr Wilson, I will be working on the neural network model and supervising other personnel involved with this. In year 2, I will also be actively involved in manuscript write-up and R21 and R01 grant submission.

Most relevant publications to the current proposal include my work on memory and executive function deficits in chronic pain, listed below.

1. **Phelps CE**, Navratilova E, Porreca F. Cognition in the Chronic Pain Experience: Preclinical Insights. Trends in Cognitive Sciences 2021
2. **Phelps CE**, Navratilova E, Porreca F. Chronic pain produces reversible memory deficits that depend on task difficulty in rats. Journal of Pain 2021
3. Cowen SL, **Phelps CE**, Navratilova E, McKinzie DL, Okun A, Husain O, Gleason SD, Witkin JM, Porreca F. Chronic pain impairs cognitive flexibility and engages novel learning strategies in rats. Pain (2018) PMCID: PMC6008204

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2021- Researcher/Scientist, University of Arizona, USA
2017-2021 Postdoctoral Researcher, University of Arizona, USA
2013-2015 Tutor and Laboratory Demonstrator, Physiology and Pharmacology, University of Bristol, UK
2012- 2017 PhD in Physiology, Pharmacology and Neuroscience, University of Bristol, UK

Other Experience and Scientific Appointments

- 2021- Ad hoc internal reviewer for grants at the University of Arizona
- 2021- Postdoctoral member on Academic Personnel Policy Committee of University Faculty Senate.
- 2021- Review Editor on the Editorial Board of Frontiers in Pain Research
- 2015 Internship at biopharmaceutical start-up Exonate. Nottingham, UK
- 2011 Internship at the University of Oxford, UK. Funded by The Physiological Society, UK

Memberships: International Association for the Study of Pain (IASP), US Association for the Study of Pain (USASP)

Honors

- 2020-2021 Chosen to be a Virtual Correspondent for the IASP, Pain Research Forum
- 2020 University of Arizona Sursum Fellow, received the Postdoctoral Research Development Grant
- 2019 Postdoctoral Yamamura/Pfizer 1st Place in University of Arizona, Pharmacology Data Blitz
- 2015 Awarded British Association of Psychopharmacology Poster Prize

Awarded bursaries to attend conferences from: British Pharmacology Society, World Congress of Basic and Clinical Pharmacology 2014, British Association for Psychopharmacology, University of Bristol Alumni, and Guarantors of BRAIN.

C. Contributions to Science

1. Pain induced cognitive impairments: Pain is a vital learning experience. Alongside the sensory and affective dimensions of pain, the cognitive element of acute pain protects an individual from injury due to a current noxious stimulus (through seizing attention) or future similar threats (due to strong learning and memory). However, in chronic pain, pain no longer serves this protective purpose and pain seizing of limited cognitive resources may now manifest as cognitive deficits in chronic pain patients. Yet, in patients it is difficult to ascertain if these cognitive deficits are the result of the pain itself, or a plethora of other factors such as medications and emotional disorders. Therefore, animal models are needed to determine if the pain itself is causing the cognitive impairment as well as to develop new therapies to ameliorate this. During my PhD, I conducted some preliminary studies on this and then, upon commencement of my postdoctoral training, I became involved in work on cognitive flexibility ongoing in the Porreca laboratory in collaboration with Dr. Stephen Cowen and Eli Lilly. In this study, we found that animals with spinal nerve ligation (SNL) induced pain, could learn the initial association between a lever press and reward but were slower to switch responding when a higher reward was secondarily attached to the alternate lever. This suggested a pain-induced deficit in cognitive flexibility. Furthermore, SNL animals appeared to be using an alternative learning strategy, potentially due to a reliance on habitual rather than defective cognitive learning mechanisms. Habitual learning strategies have been linked to addiction, which is a prominent comorbidity of pain, so having a task to measure this is an important step in pain and comorbid addiction research. I am also interested in short and long term memory impairments in SNL rats, which we have observed in a non-rewarded spontaneous behavioral task. I found that rats with nerve ligation induced chronic neuropathic pain only showed impairments in short term memory retention and memory consolidation under difficult conditions, whilst sham controls could remember the objects under both conditions. The memory consolidation deficits were relieved by acute administration of the analgesic, duloxetine. Together this suggested that chronic pain reduces cognitive resources available for memory tasks and this can be reversed by acute analgesia.

a. **Phelps CE**, Navratilova E, Porreca F. Cognition in the Chronic Pain Experience: Preclinical Insights. Trends in Cognitive Sciences 2021

b. **Phelps CE**, Navratilova E, Porreca F. Chronic pain produces reversible memory deficits that depend on task difficulty in rats. Journal of Pain 2021
c. Cowen SL, **Phelps CE**, Navratilova E, McKinzie DL, Okun A, Husain O, Gleason SD, Witkin JM, Porreca F. Chronic pain impairs cognitive flexibility and engages novel learning strategies in rats. Pain (2018)
d. **Phelps CE,** Lumb BM, Donaldson LF, Robinson ES. The Partial Saphenous Nerve Injury (PSNI) Induced Model of Pain Impairs Reward Related Learning but not Reward Sensitivity or Motivation. Pain 2021

2. The role of kappa opioids in the pain experience: Pain is a physiological stressor, yet unlike functional pain disorders triggered by psychological stress, the role of stress related neurobiology in chronic ongoing pain conditions has been little studied. Activation of kappa opioid signaling is a fundamental response to stress and in Dr. Porreca's laboratory I conducted a series of experiments investigating the role of kappa opioids in the three fundamental elements of pain: sensory, affect and cognition. I was involved in conducting experiments for our published work, which found that blocking kappa opioid signaling, either systemically or directly in the right central nucleus of the amygdala (rCeA) does not alleviate hindpaw allodynia in SNL rats but does alleviate the affective component of the pain. In my primary work, we found that SNL-induced deficits in descending modulation of pain, are ameliorated by either systemic or direct microinjection of a kappa opioid antagonist into the rCeA. This suggests heightened kappa opioid signaling may be involved in the vulnerability to or maintenance of chronic pain.
I also conducted preliminary work to determine if kappa opioid signaling in the rCeA of naïve rats is sufficient to cause a pain-like sensory and affective experience. Acute pharmacological activation of kappa opioid signaling in this region is sufficient to induce periorbital but not hindpaw allodynia, as well as a pain-like negative affective state. I've also conducted preliminary experiments to determine the role of kappa opioid signaling in cognitive deficits, results so far suggest heightened kappa opioid signaling is responsible for pain induced short-term but not long-term memory deficits.
As kappa opioid antagonists are currently in clinical trials for major depressive disorder, together this work could aid their development as analgesics that could ameliorate or perhaps prevent chronic pain and related comorbidities.

a. **Phelps CE**, Navratilova E, Dickenson AH, Porreca F, Bannister K. Kappa Opioid Signaling in the Right Central Amygdala Causes Hindpaw Specific Loss of Diffuse Noxious Inhibitory Controls (DNIC) in Experimental Neuropathic Pain. Pain (2019)
b. Navratilova E, Ji G, **Phelps C**, Qu C, Hein M; Yakhnitsa V, Neugebauer V, Porreca F. Kappa opioid signaling in the central nucleus of the amygdala promotes disinhibition and aversiveness of chronic neuropathic pain. Pain (2019)
c. **Phelps CE**, Navratilova E, Neugebauer V, Porreca F. Kappa Agonist Aversive Effects in Right Central Amygdala in Uninjured Rats. IASP World Congress on Pain, 2021

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Robert C. Wilson

eRA COMMONS USER NAME (credential, e.g., agency login): BOBWILSON

POSITION TITLE: Associate Professor of Psychology and Cognitive Science

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Cambridge	B.A.	06/2002	Natural Sciences
University of Cambridge	M.Sci.	06/2002	Chemistry
University of Pennsylvania	M.S.E.	05/2003	Bioengineering
University of Pennsylvania	Ph.D.	05/2009	Bioengineering
Princeton University	Postdoc	12/2014	Psychology and Neuroscience

A. Personal Statement

I am an expert in computational neuroscience and mathematical psychology. I have modeled learning and decision making at a variety of levels – from low level neural networks to high level Bayesian inference – and have extensive experience linking theoretical models to experimental data. Most relevant to this grant is my work building cognitive models of complex tasks (Wilson & Collins, 2019), my work on neural networks (Wilson et al. 2019), and my work on phishing email detection (Hakim et al. 2020; Grilli et al 2021).

In this grant I will act as mentor for the University of Arizona PI Caroline Phelps. Dr Phelps is a postdoctoral research associate in my lab and we have already worked together for 1 year. As part of her training, I will advise Dr Phelps on the details of the computational modeling, meeting with her weekly to discuss any issues as they arise. Approximately once per month, these meetings will also take in the bigger picture including strategies for publication, management of personnel and the project more generally, and the approach and (in Year 2) the writing of the R21 proposal on which Dr Phelps (and Dr Pehlivanoglu) will be co-PIs.

In addition to working with Dr Phelps, I will also coordinate closely with Dr Pehlivanoglu and her mentor Dr Ebner. I already have a strong working relationship with Dr Ebner, having worked with her for over 4 years, publishing two papers and receiving two grants (including an R01 from NIA). In addition, along with Dr Ebner, I will spearhead the R01 application to be written in Year 2 of the award.

Wilson, R. C. & Collins, A. G. E. (2019). Ten simple rules for the computational modeling of behavioral data. *eLife* 8, e49547

Wilson, R. C., Shenhav, A., Straccia, M., & Cohen, J. D. (2019). The eighty five percent rule for optimal learning. Nature communications, 10(1), 1-9.

Hakim, Z. M., Ebner, N. C., Oliveira, D. S., Getz, S. J., Levin, B. E., Lin, T., ... & **Wilson, R. C.** (2020). The Phishing Email Suspicion Test (PEST) a lab-based task for evaluating the cognitive mechanisms of phishing detection. *Behavior Research Methods*, 1-11. doi: 10.3758/s13428-020-01495-0. Epub 2020 Oct 19. PubMed PMID: 33078362; PubMed Central PMCID: PMC8188181.

Grilli, M. D., McVeigh, K. S., Hakim, Z. M., Wank, A. A., Getz, S. J., Levin, B. E., ... & **Wilson, R. C.** (2021). Is this phishing? Older age is associated with greater difficulty discriminating between safe and malicious emails. *The Journals of Gerontology: Series B*.

B. Positions, Scientific Appointments, and Honors

Chronology of Employment

2021-present Associate Professor of Psychology and Cognitive Science, University of Arizona
2015-2021 Assistant Professor of Psychology and Cognitive Science, University of Arizona
2009-2014 Postdoctoral Research Associate, Princeton Neuroscience Institute
2003-2009 Graduate Student, Department of Bioengineering, University of Pennsylvania

C. Contributions to Science

1. How humans and animals solve the explore-exploit dilemma

Many decisions in life involve a tradeoff between exploring new options for information and exploiting known options for reliable reward. For example, when dining at a favorite restaurant do you explore the new ravioli that is sure to be informative, or exploit the known pizza that is sure to be good? Beyond eating out, the explore-exploit dilemma occurs at all levels of decision making, from picking a TV show to watch or a person to marry, and there are real advantages to solving it well. Yet despite its importance, solving the dilemma optimally is intractable in all but the simplest settings and so the question arises as to how we balance exploration and exploitation in practice. In this work I have shown that humans use two distinct strategies for solving the explore-exploit dilemma: a directed strategy in which information seeking drives exploration by choice, and a random strategy in which behavioral variability drives exploration by chance. In addition, studies from my lab and my collaborators suggest that these two strategies rely on dissociable neural networks, with directed exploration dependent of frontal pole, developing over the course of adolescence, and being impaired in schizophrenia, while random exploration appears to be tied to norepinephrine. The identification of the two strategies, in addition to experiments with which to quantify them, has had a significant impact on the field with the original paper (Wilson et al. 2014) over 200 times.

Wilson, R. C., Geana, A., White, J. M., Ludvig, E. A., & Cohen, J. D. (2014). Humans use directed and random exploration to solve the explore-exploit dilemma. *JEP:General, 143* (6), 2074-2081. doi: 10.1037/a0038199. Epub 2014 Oct 27. PubMed PMID: 25347535; PubMed Central PMCID: PMC5635655.

Zajkowski, W. K., Kossut, M., & **Wilson, R. C.** (2017). A causal role for right frontopolar cortex in directed, but not random, exploration. eLife, 6. doi: 10.7554/eLife.27430. PubMed PMID: 28914605; PubMed Central PMCID: PMC5628017.

Somerville, L. H., Sasse, S. F., Garrad, M. C., Drysdale, A. T., Abi Akar, N., Insel, C., & **Wilson, R. C.** (2017). Charting the Expansion of Strategic Exploratory Behavior During Adolescence. *JEP:General, 146* (2), 155. doi: 10.1037/xge0000250. Epub 2016 Dec 15. PubMed PMID: 27977227.

Wilson, R. C., Bonawitz, E., Costa, V. D., & Ebitz, R. B. (2021). Balancing exploration and exploitation with information and randomization. *Current Opinion in Behavioral Sciences*, *38*, 49-56. doi: 10.1016/j.cobeha.2020.10.001. Epub 2020 Nov 6. PubMed PMID: 33184605; PubMed Central PMCID: PMC7654823.

2. Learning in the presence of abrupt change

Whether getting a new job or a new president, life is full of “change points” that cause the rules of the game to shift abruptly. Learning and making predictions in such circumstances can be challenging because change points can render much of the past irrelevant. In this work I developed a series of computational models to look at how humans and animals learn in the face of such environmental change points. These models ranged in scale from low level neural network models to high level cognitive models. All of these models made detailed experimental predictions some of which have been tested, and borne out, in experiments by my collaborators.

Wilson, R. C., Nassar, M. R., & Gold, J. I. (2010). Bayesian online learning of the hazard rate in change-point problems. *Neural Computation, 22* (9), 2452-2476. doi: 10.1162/NECO_a_00007. PubMed PMID: 20569174; PubMed Central PMCID: PMC2966286.

Wilson, R. C., & Niv, Y. (2012). Inferring relevance in a changing world. *Front Hum Neurosci, 5*:189. doi: 10.3389/fnhum.2011.00189. eCollection 2011. PubMed PMID: 22291631; PubMed Central PMCID: PMC3264902.

Wilson, R. C., Nassar, M. R., & Gold, J. I. (2013). A mixture of delta-rules approximation to Bayesian inference in change-point problems. *PLoS Comp Biol, 9* (7), e1003150. doi: 10.1371/journal.pcbi.1003150. Epub 2013 Jul 25. PubMed PMID: 23935472; PubMed Central PMCID: PMC3723502.

3. <u>The role of orbitofrontal cortex in learning and decision making</u>

Orbitofrontal cortex (OFC) has long been known to play an important role in learning and decision making. However, the exact nature of that role has remained elusive. In 2014, I proposed a new unifying theory of OFC function in which the OFC provides an abstraction of currently available information in the form of a labeling of the current task state. This "cognitive map" of "task space" in OFC is then used as a scaffold for learning and decision making throughout the brain. The theory accounts for many of the puzzling findings related to OFC such as its role in a number of behavioral tasks, as well as more recent findings showing the effect of OFC lesions on the firing of dopaminergic neurons in ventral tegmental area (VTA). This work has been well received by the field and has been cited over 500 times since 2014.

Takahashi, Y. K., Roesch, M. R., **Wilson, R. C.**, Toreson, K., O'Donnell, P., Niv, Y., & Schoenbaum, G. (2011). Expectancy-related firing of midbrain dopamine neurons depends on orbitofrontal cortex. *Nature Neuroscience, 14*, 1590-1597. doi: 10.1038/nn.2957. PubMed PMID: 22037501; PubMed Central PMCID: PMC3225718.

Wilson, R. C., Takahashi, Y. K., Schoenbaum, G. & Niv, Y. (2014). Orbitofrontal cortex as a cognitive map of task space. *Neuron, 81* (2), 267-279. doi: 10.1016/j.neuron.2013.11.005. PubMed PMID: 24462094; PubMed Central PMCID: PMC4001869.

Schuck, N. W., Cai, M. B., **Wilson, R. C.**, & Niv, Y. (2016). Human orbitofrontal cortex represents a cognitive map of state space. *Neuron*, *91*(6), 1402-1412. doi: 10.1016/j.neuron.2016.08.019. PubMed PMID: 27657452; PubMed Central PMCID: PMC5044873.

4. <u>The cognitive neuroscience of phishing susceptibility</u>

Phishing emails – malicious emails that attempt to lure victims into taking actions that benefit an attacker – constitute a major public health problem, linked to decreased quality of life and negative health outcomes due to fraud and exploitation. Because of their sheer volume and because phishing emails are designed to deceive, purely technological solutions such as filters and blacklists only go so far, leaving human decision making as the last line of defense against phishing. However, in part because it is difficult to phish people under controlled laboratory conditions, little is known about the cognitive and neural mechanisms underlying phishing susceptibility. In this line of work I have begun to develop behavioral tasks and computational models that can be used within the lab to investigate the cognitive neuroscience of phishing email evaluation in an ecologically valid manner. In our first paper, we showed that phishing emails rated as less suspicious in the lab were more effective in the real world, a key first step to establish the ecological validity of our tasks. In the second paper, we showed that older adults are less able to distinguish between safe and phishing emails that adults in late midlife.

Hakim, Z. M., Ebner, N. C., Oliveira, D. S., Getz, S. J., Levin, B. E., Lin, T., ... & **Wilson, R. C.** (2020). The Phishing Email Suspicion Test (PEST) a lab-based task for evaluating the cognitive mechanisms of phishing detection. *Behavior Research Methods*, 1-11. doi: 10.3758/s13428-020-01495-0. Epub 2020 Oct 19. PubMed PMID: 33078362; PubMed Central PMCID: PMC8188181.

Grilli, M. D., McVeigh, K. S., Hakim, Z. M., Wank, A. A., Getz, S. J., Levin, B. E., ... & **Wilson, R. C.** (2021). Is this phishing? Older age is associated with greater difficulty discriminating between safe and malicious emails. *The Journals of Gerontology: Series B*.

5. <u>Computational modeling of spatial navigation</u>

The ability to navigate—to food, to water, to breeding grounds, to work—is essential for survival in many species. To navigate effectively we need to continuously update our estimates of location and heading in the environment from incoming multisensory information. This multisensory input comes in two forms: idiothetic cues, from one's own rotations and translations (including body-based cues from the vestibular, proprioceptive, and motor efferent copy systems, as well as visual optic flow), and allothetic cues, from the environment

(usually visual landmarks). This line of work investigates how people combine these two sources of information to navigate effectively. In graduate school, I developed a neural network model that integrates idiothetic and allothetic cues in an approximately Bayesian manner – combining them optimally when the mismatch between them is small and basing the estimate only on one cue when the mismatch is large. More recently, in collaboration with Dr Ekstrom, I have begun to test the predictions of this model with behavioral experiments in immersive virtual reality. Our latest paper finds that human behavior is consistent with the predictions of the neural network model.

Wilson, R. C., & Finkel, L. (2009). A neural implementation of the Kalman filter. Advances in neural information processing systems, 22.

Harootonian, S. K., **Wilson, R. C.**, Hejtmánek, L., Ziskin, E. M., & Ekstrom, A. D. (2020). Path integration in large-scale space and with novel geometries: Comparing vector addition and encoding-error models. PLoS computational biology, 16(5), e1007489.

Harootonian, S. K., Ekstrom, A. D., & **Wilson, R. C.** (2022). Combination and competition between path integration and landmark navigation in the estimation of heading direction. PLoS computational biology, 18(2), e1009222.

Links to a complete list of published work

- NCBI My Bibliography
    - www.ncbi.nlm.nih.gov/sites/myncbi/robert.wilson.3/bibliography/48037481/public

Matt Huentelman, PhD
Professor, Neurogenomics
Scientific Director, Center for Rare Childhood Disorders
The Translational Genomics Research Institute
445 N Fifth Street, 5th Floor
Phoenix, Arizona 85004

RE: The MBRF Cognitive Aging and Memory Intervention Core Inter-Institutional Pilot Program Application: Team Collaboration Support Letter for Dr. Didem Pehlivanoglu

June 29, 2022

Dear Didem,

I am writing this letter to express my enthusiasm and support for this innovative research proposal, “A Neural Network and Guided Eye-Tracking Approach for Characterizing and Combating Fake News Detection in Aging”, in response to the McKnight Research Foundation (MBRF) call on Inter-Institutional MBRF Applications for Pilot Studies. The project you propose constitutes a novel direction of investigation on characterizing attentional and neurocognitive mechanisms driving susceptibility to fake news in aging using artificial intelligence and developing an attentional nudging intervention to enhance fake news detection. Healthy older adults and those with dementia (e.g., Alzheimer’s disease) are at particular risk for deception given cognitive changes associated with age and the disease. These at-risk individuals, however, are understudied in research on deception. Additionally, the literature on characterization of susceptibility to deception in aging has exclusively focused on comparisons between homogenous groups of young and older adults, thus limiting representation of adult lifespan sample from diverse backgrounds in deception research.

MindCrowd (mindcrowd.org) was launched in 2013 and has since recruited just under 300,000 participants from around the world. This includes individuals from across the aging spectrum (18+) and over 50% of the cohort is 50 years of age and older. Benefits of our collaborative teamwork will be twofold. First, collaboration with my group at TGen will directly contribute to your project’s goal of expanding your data collection to nationally representative lifespan sample of a diverse group of individuals recruited from the MindCrowd. Second, recent funding from the National Institutes of Health supported the creation of an expanded version of MindCrowd that includes a dashboard of various cognitive tasks. Integrating short fake news task into the MindCrowd platform will make a great methodological addition to the newly developed dashboard.

In sum, as a co-founder of MindCrowd, I agree to commit the necessary support and additional expertise needed for incorporating of short fake news task into the MindCrowd dashboard and for expansion of data collection to the Mindcrowd cohort at no cost. Your proposal is conceptually very strong, scientifically well-founded, innovative, methodologically rigorous, and has the potential for solid clinical impact among individuals at-risk for developing Alzheimer’s disease. The data you plan to collect as part of this pilot grant are essential for submission of your future NIH grant proposal on developing a comprehensive intervention approach and testing its effectiveness. Your track record of research productivity and my direct experience in working with you over the last 2 years for collecting and analyzing data from the MindCrowd cohort as part of our AD/ADRD supplement with Dr. Ebner make me highly confident that you will be successful in completion of this project and a follow-up extramural grant proposal to NIH.

Sincerely,

Professor of Neurogenomics, The Translational Genomics Research Institute

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: A Neural Network and Guided Eye-Tracking Approach for Characterizing and Combating Fake News Detection in Aging

Principal Investigator(s): Didem Pehlivanoglu

Institutions: U. FL, U. AZ

OVERALL IMPACT

Please provide your assessment of the strengths and weaknesses of the application using brief bullet points to reflect the project's likelihood to exert a sustained, powerful impact on the research field(s) involved, using the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact. Please score the application's potential using the following 1 (Highest Impact) to 9 (Lowest Impact) rating scale for each review criteria section:

Impact	High	Medium	Low
Score: 4	1 2 3	**4** 5 6	7 8 9

Overall Impact *Write a brief paragraph summarizing the factors that informed your Overall Impact score.*

The topics is clearly important and in need of research. If the project is successful and it meets the scientific standard of reproducibility, then the overall impact is quite high. There is, however, quite a lot of research (not cited) that suggest that either it wont be successful or it won't hold up to replication. There are also concerns with the validity of the approach related to the headline selection.

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance 2

Strengths

- The topic is urgent and the need for research is great.
- Question: given that normal adults with experience in lies detection are typically only 54% accurate at deception detection, how much worse can the cognitively impaired be given the 50% pure guess basement? Research not mentioned might under cut the arguments. These finging appear to apply to fake news, e.g., doi.org/10.1177/0093650220921321
- If successful, the aims are very significant.

Weaknesses

- Not especially theorical, but it could be (e.g., Truth-default Theory seems relevant)
- Suggested reference: doi.org/10.1016/j.copsyc.2022.101380

2. Investigator(s) 3

Strengths

- Have done previous work on the topic
- Have worked together before
- Credentials suggest that they are qualified and capable

Weaknesses

- Do not seems to cover a wide sprectum of relevant academic disiplines

3. Innovation 2

Strengths

- Very innovative

Weaknesses

- None apparent

4. Approach 6

Strengths

- Good ecological validity

Weaknesses

- Need more attention to establishing ground truth of headlines.
- Is plausibility a confound?
- Results likely impacted by approach to selecting headlines

5. Environment 3

Strengths

- Meets the needs of the research

Weaknesses

- Nothing

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes:

Strengths

- Collaboration among two

Weaknesses

- NA

2. Potential for clinical translational impact of the intervention on cognitive aging and memory

Strengths

- Yes, if valid and successful

Weaknesses

- The probability of valid and success is questionable due to concerns with the approach and deeper theoretical issues.

3. Potential for future NIH funding of the research
• Moderate to High. This is a strength.

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: A Neural Network and Guided Eye-Tracking Approach for Characterizing and Combating Fake News Detection in Aging

Principal Investigator(s): Didem Pehlivanoglu, PhD

Institutions: UF

OVERALL IMPACT

Please provide your assessment of the strengths and weaknesses of the application using brief bullet points to reflect the project's likelihood to exert a sustained, powerful impact on the research field(s) involved, using the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact. Please score the application's potential using the following 1 (Highest Impact) to 9 (Lowest Impact) rating scale for each review criteria section:

Impact	High	Medium	Low
Score:7	1 2 3	4 5 6	7 8 9

Overall Impact *Write a brief paragraph summarizing the factors that informed your Overall Impact score.*

The overall goal of this proposal is to combat the lack of ability to identify fake news, especially by older adults who are particularly vulnerable to deception via fake news. The first aim of the proposal is to develop a neural network model to identify the features in the news headline and the cognitive characteristics of the individual that influence fake news detection. The proposal provides no evidence that the neurocognitive mechanisms associate with comprehension of news is different between "fake" and "non fake" news. This is a serious flaw. No AI system can overcome this problem if the mechanisms are identical in both.

The second aim is to develop **a brief fake news detection paradigm for integration into large-scale data collection from a nationally representative, diverse adult lifespan sample.**

This aim will be informed by the neural network modeling. While I am not an AI expert, AI architecture does not provide an algorithm or a model by which the network discriminates between states. Thus, this is another weakness of the proposal.

The 3rd aim will determine behavioral benefits of eye tracking. The rationale is based on literatures that show that age-related deficits in deception detection is associated with greater reliance on superficial features (i.e., reputation of news sources) than central features (i.e., news content).

This reliance can be utilized for the most promising approach. Providing the elder individuals with a list of reliable news sources can be much more effective than developing an AI system that would need to identify fake news which may not have different features than non-fake news. A safe way to make sure the individual is reaching a reliable source is to have this individual initiate the contact and ignore messages from other sources that cannot be verified at the time of the contact.

The fact that Neural networks can filter malicious content does not necessarily imply that the same approach can be used to distinct between fake from non-fake news.

Finally, and most importantly, no preliminary evidence was provided to demonstrate that eye tracking is critical to the process and would add a relevant information.

Based on these observations the overall merit of this proposal is low.

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance 6

Strengths

- Efforts toward reducing the vulnerability of elderly subjects and other individuals who have reduced cognitive capacity is of high significance.

Weaknesses

- No convincing arguments that rely on facts were provide to show that the proposed work would be able to make a significant contribution toward this goal.
-

2. Investigator(s) 3

Strengths

- **Excellent track record. The pioneering work by the PI demonstrated (a somewhat trivial and well-recognized reality) that older** adults, and particularly the oldest-old individuals, experience difficulties with fake news detection. These results are expected as except vocabulary, performance in most cognitive domains decline with age

Weaknesses

- The authors over estimates the importan of their obvious findings

3. Innovation 6

Strengths

-

Weaknesses

- Instead of focusing on using eye tracking to record what the individuals are focusing. The researcher can simply inquire with the individual regarding his/her focus areas. Another simpler way is to remove the heading which will assure that subjects will focus on the content
-

4. Approach 8

Strengths

-

Weaknesses

- No preliminary results or rationale provided to support the feasibility of the proposed approach, especially the contribution of tracking of eye movements. See additional comments in the overall impact section.

5. Environment 2

Strengths

- **Both UA and UF are outstaning members of the McKnight Institute for aging related cognitive decline with excellent funding and publication records.**

Weaknesses

- None noted

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes:

Strengths

- Satisfectory

Weaknesses

-

2. Potential for clinical translational impact of the intervention on cognitive aging and memory

Strengths

-

Weaknesses

- Too preliminary to provide an educated guess.

3. Potential for future NIH funding of the research

- Hard to estimate, I have ecently witnessed very high score given to poor quality applications and the other way around.

Why was the speller disabled????? Sory for the typos!

THE UNIVERSITY OF
ALABAMA AT BIRMINGHAM

June 29, 2022

Dr. Ronald Lazar
Evelyn F. McKnight Endowed Chair
Professor of Neurology and Neurobiology
Director, Evelyn F. McKnight Brain Institute at UAB
Director, Division of Neuropsychology
MBRF Inter-Institutional Cognitive Aging and Memory Intervention Core member
University of Alabama at Birmingham
Birmingham AL 35294

Dr. Bonnie Levin
Director, Division of Neuropsychology
University of Miami, Miller School of Medicine
MBRF Inter-Institutional Cognitive Aging and Memory Intervention Core member
University of Miami
Miami, FL 33136

Dear Dr. Lazar and Dr. Levine,

I am writing to express our interest in undertaking clinical research in the field of non-pharmacological cognitive interventions to prevent or delay cognitive deficits in older adults, specifically in regard to the relationships between personality traits, subjective cognitive decline, and processing speed training. I am pleased to submit the enclosed pilot study proposal, "A Single Arm Intervention Study to Evaluate Effects of Personality Traits on Efficacy of Processing Speed Training in Individuals with Subjective Cognitive Decline", as an application for funding from The MBRF Cognitive Aging and Memory Intervention Core Inter-Institutional Pilot Program.

The proposed pilot study of the influence of personality traits on Processing Speed Training in individuals with SCD is a crucial step in the understanding of factors that may moderate cognitive and functional benefits and efficiency of cortical networks of computerized cognitive training (CCT). This is an unexplored area in CCT. If the selected personality traits are found as moderators of the efficacy of the intervention, then the pilot data will be used as preliminary data for an NIH application examining the longitudinal benefits of PST on cognitive and functional performance and efficiency of cortical networks and the effect of PST is moderated by personality traits. Since SCD is a risk factor for incident dementia due to Alzheimer's disease, clinical research of this nature should help to elucidate the role of individual-level factors and

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Phone: 205.996.3679 | www.uab.edu/medicine/neurology

their effect on CCT response, providing insights into the benefits of precision-medicine-guided approaches among older adults with SCD.

Please find below the names and contact information of potential qualified reviewers:

Benjamin Hampstead, Ph.D., ABPP/CN-University of Michigan
bhampste@umich.edu

Joel Kramer, PsyD- University of California San Francisco
joel.kramer@ucsf.edu

Duke Han, Ph.D. - University of Southern California
Duke.Han@med.usc.edu

Thank you in advance for your consideration of this proposal. I look forward to the opportunity to conduct further research in the field of cognitive aging and intervention clinical trials.

Sincerely yours,

Giovanna Pilonieta

Giovanna Pilonieta, DMD MPH
Scientist I
Department of Neurology Heersink School of Medicine

UF UNIVERSITY of FLORIDA

College of Public Health and Health Professions
Department of Clinical and Health Psychology
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June 15, 2022

Re: Cognitive Aging and Memory Intervention Core Pilot Application (PIs: Pilonieta, Gullett)

Dear McKnight Cognitive Aging and Memory Intervention Core,
I write this letter to express my enthusiastic support for Drs. Pilonieta and Gullett's proposal to execute a small pilot clinical trial investigating personality and neuroimaging predictors of cognitive training gains in older adults. I will serve as a collaborator on the project to help guide the scientific direction of the study and ensuring accomplishment of the clinical trial goals. Drs. Pilonieta and Gullett's expertise overlap perfectly on this project. Dr. Pilonieta's expertise in personality assessment and strong interest in remediating cognitive aging and Dr. Gullett's specific interest in cognitive training and prediction of gains from neuroimaging measures make for an excellent early career investigator team to lead this project.

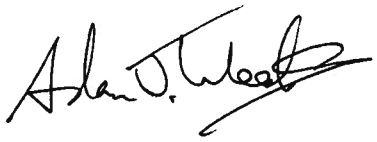
Furthermore, this project directly leverages infrastructure created as part of the McKnight Brain Aging Registry study. Specifically, we will use the multisite imaging sequences already deployed in the MBAR study for the proposed pilot clinical trial. Further still, this work will also create a foundation for future examination of ongoing large cohort cognitive training trials across McKnight sites (e.g., the ACT trial) and creates a new collaboration between investigators at two of the MBIs.

As Associate Director of the Center for Cognitive Aging and Memory Clinical Translational Research (CAM) in the UF McKnight Brain Institute, director of one of the most well-funded neuromodulation and aging labs in the US (~18 million in ongoing PI funding across 4 active R01s), and director of several research cores within the CAM (clinical trial, recruitment, neuromodulation, etc.), I will work with the study team to ensure the success of the proposed study. Further still, the CAM Clinical Translational Research arm of the Center will provide any additional support needed at the UF site to meet the proposed study goals.

Drs. Pilonieta and Gullett are strongly motivated to achieve the goals of the proposed study. I look forward to this collaboration and will continue to provide ongoing guidance and all

assistance needed to ensure the success of the proposal. The study will have the full support of the Center for Cognitive Aging and Memory. If you have any questions, please feel free to contact me.

Sincerely,



Adam J. Woods, PhD

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Project Title: A Single Arm Intervention Study to Evaluate Effects of Personality Traits on Efficacy of Processing Speed Training in Individuals with Subjective Cognitive Decline

Senior/Key personnel

PI: Giovanna Pilonieta, DMD MPH
CO- I: Joseph M. Gullett, PhD
David S. Geldmacher, MD
Adam J. Woods, PhD
Kristina M. Visscher, PhD

Project/Performance sites

University of Alabama at Birmingham
University of Florida

Contact PI

Giovanna Pilonieta DDS MPH

(CONTACT Pi information)

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Research Plan

Summary

This single arm clinical trial will test whether personality traits moderate the effects of Processing Speed Training (PST) on cognitive and functional outcomes in older adults with subjective cognitive decline (SCD). SCD has been associated with a subclinical decline in processing speed, as well as immediate and delayed verbal recall. In addition, recent studies found relationships between personality traits, subjective cognitive decline, and cognitive performance. A negative association between personality traits such as neuroticism and cognitive performance was reported. Higher levels of psychological resilience were associated with lower levels of subjective memory and executive functioning complaints. We will therefore evaluate personality traits such as neuroticism, mastery and resilience as baseline characteristics. Changes from baseline in measures of cognitive function and everyday abilities will serve as outcome measures. Functional and structural neuroimaging biomarkers will measure intervention-associated alterations in the efficiency of cortical networks (overall system segregation). This study will leverage the existing infrastructure created as part of the McKnight Brain Aging Registry study. We propose use the multisite imaging sequences utilized in the MBAR study for this trial. Further, this research will leverage the multisite clinical trial infrastructure at McKnight Brain Institutes located at the University of Alabama at Birmingham and the University of Florida creating a foundation for future studies. A single arm multisite clinical trial will examine the effects of personality traits on cognitive training in older adults experiencing SCD (n = 40; 20 per site). Participants will be women and men 65-85 years of age with subjective cognitive complaints but no evidence of Mild Cognitive Impairment (MCI) or Alzheimer's disease or dementia. We will compare changes from baseline on cognition, function, and brain function resulting from PST using a comprehensive neuropsychological battery and neuroimaging evaluation of brain structure and function. Within and between-network resting-state functional magnetic resonance imaging (rsfMRI) connectivity will be calculated for the seven common networks in the Yeo et al. atlas. We hypothesized that: 1) Baseline variables, including personality traits of mastery, neuroticism, and resilience, will be associated with the magnitude of PST response, 2) A 12-week single arm study using Processing Speed Training (PST) will improve performance on the Pattern Comparison Processing Speed test by a z-score of 0.5 or more, measures of cognitive performance measured as overall cognitive composite score and raw scores, 3) The intervention will result in benefits on the Functional Composite Score at 12 weeks of intervention, and, 4) Based on the hypothesis that PST improves the efficiency of cortical networks, we predict that overall system segregation will get larger after the intervention. To date, no studies have evaluated the relationships between personality traits and PST outcomes in older adults. This study will provide insights into the benefits of precision-medicine-guided approaches to increase the efficacy and sustained effects of computerized cognitive training.

Specific Aims

A growing body of research suggests that subjective cognitive decline (SCD) is a risk factor for incident dementia due to Alzheimer's disease (AD) (1). Recent studies found that SCD was preceded by a subclinical decline in processing speed, as well as immediate and delayed verbal recall (2). In addition, increasing evidence indicates associations between personality characteristics, cognitive abilities, and SCD in older adults(3)(4). Higher levels of neuroticism were associated with worse cognitive performance (e.g., memory, speed-attention-executive task, fluency)(3). Higher levels of neuroticism, anxiety, and depression were associated with a higher level of SCD (4). Therefore, the cognitive and functional benefits of cognitive training may depend on personality traits. Then, differences in structure and functional connectivity (FC) of the brain networks occur among individuals with SCD (5). Segregation describes the organization of a network both within- and between network connectivity (6). Recent studies evaluated the relationships between network segregation and cognitive performance in older healthy adults (7). Their findings reported that segregation of the fronto-parietal network (FPN) and the segregation of the cortical association system were strong predictors of cognition and processing speed (7). While previous studies have explored the relationships between personality characteristics and social networking training (8, 9), to our knowledge, there are no data about the influence of personality traits on cognition and function after training on PST. A better characterization of the relationship between personality traits, SCD, and CCT may allow precision-medicine-guided approaches to increase the efficacy and sustained effects of the training. In addition, previous studies rarely ascertain brain

structure and function as predictors of cognitive training outcomes for those at high risk of cognitive decline. We propose these aims:

Specific Aim 1: To explore the influence of personality traits on cognitive and functional benefits of PST in individuals with SCD. The objective is to determine how personality traits interplay to impact PST effects to improve efficacy for targeted processing speed tasks in individuals with SCD.

- H1: Baseline variables, including personality traits of mastery, neuroticism, and resilience, will be associated with the magnitude of PST response.
- H2: Individuals will demonstrate improvement immediately following the 12-week training on the Pattern Comparison Processing Speed test by a z-score of 0.5 or more
- H3: A 12-week single arm study using Processing Speed Training (PST) will improve measures of cognitive performance measured as overall cognitive composite score and raw scores
- H4: The intervention will result in benefits on the Functional Composite Score at 12 weeks of intervention

Specific Aim 2: To examine the effects of Processing Speed Training (PST) on overall system segregation of subjects with subjective cognitive decline after 12 weeks of intervention.

- H5: Based on the hypothesis that PST improves the efficiency of cortical networks, we predict that overall system segregation will get larger after the intervention.
- We further hypothesize that the same personality traits examined in specific aim 1 will be related to the efficiency of cortical networks. These data will be used as preliminary data for an NIH application examining the hypothesis that PST improves performance by improving the efficiency of cortical networks, and that the effect of PST is moderated by personality traits.

Research Strategy

Significance

Converging evidence has shown that SCD is related to several conditions, such as personality characteristics and cultural background(10). Higher levels of psychological resilience were associated with lower levels of subjective memory and executive functioning complaints (11). Additionally, self-efficacy was negatively associated with subjective cognitive complaints (12). However, their influence on cognitive training has not been ascertained. There is evidence, although mixed about the effects of computerized cognitive training (CCT) in improvement of cognition (13-15). While previous studies found that computerized cognitive training (CCT) has a moderate effect in long-term improvement of cognition (13, 14). In a systematic review by Gates et al. (2019), the authors investigated the effects of CCT for the preservation or improvement of cognitive function in healthy older adults. The study found no effects of computerized cognitive training (CCT) on global cognition or secondary outcomes of episodic memory, speed of processing, executive function, and working memory (15), these results may suggest that individual level factors such as personality characteristics might have adversely moderated potential benefits of CCT. As personality traits may play an important role in the individuals' outcomes, further research is needed about their influence on cognitive and functional training outcomes.

Innovation:

This proposed pilot study will advance prior research by first, ascertaining the influence of personality traits on the effects of PST cognitive and functional outcomes. Then, exploring brain structural and functional predictors of cognitive improvement by PST in subjects with SCD. Additionally, we will leverage the existing infrastructure created as part of the McKnight Brain Aging Registry study. We propose use the multisite imaging sequences utilized in the MBAR study for this trial. Leveraging robust and comprehensive neuroimaging data, the proposed study will provide critical information for heterogeneity of CCT response among older adults and a pathway to tailor the dose and intensity of cognitive interventions to prevent or delay cognitive deficits, which is critical for individuals with SCD.

Approach:
Research Type: Stage II behavioral intervention
Target Population: Potential participants will be individuals with self-reported memory complaints recruited from the Alzheimer's Disease Research Center at UAB- the University of Florida, primary care clinics, and the community (i.e., Senior's center)
Sample size: We will enroll 40 subjects
Eligibility
Inclusion Criteria:
1. Male or female, age 65-85 years
2. Memory and other cognitive complaints consistent with SCD defined by the National Institute on Aging:
SCD will be defined as i. any subjective concern of change in cognitive functioning without objective evidence of cognitive impairment, and ii. Complete preservation of functional abilities and independence in instrumental activities of daily living
3. Montreal Cognitive Assessment (MoCA) normal score adjusted for age, sex, and education.
4. Stable medications for at least 30 days (i.e., anti-depressants)
5. Willing and able to complete all assessment and study procedures.
Exclusion criteria:
1. Objective cognitive impairment present on UDS-III Neuropsychological battery (any test score within a specific cognitive domain >1·5 SD below the normative mean, (age, sex, education).
2. Beck Depression Inventory score >20
3. Medical comorbidities likely to affect cognition (e.g., brain trauma, history of major psychiatric conditions, neurological disorders, or other systemic diseases that can cause cognitive impairment, such as thyroid dysfunction, severe anemia, syphilis, HIV, etc.)
4. Severe hearing or visual impairment, language communication disorders.
5. MRI contraindications (e.g., metal dentures or other metal implants that cannot be removed, severe claustrophobia, etc.)

Description of Intervention: The study will be a single intervention crossover design studying effects of a 12-week, computer-based intervention among subjects with self-reported Subjective Cognitive decline and their moderation by baseline personality factors. Participants will complete baseline cognitive assessments to determine their initial cognitive processing speed skills, cognition, and functional status and to compare to the training responses in cognitive and functional endpoints. Similarly, the effects of cognitive training on neural activity and connectivity will be ascertained at baseline and after training by a resting-state fMRI. Cognitive training (CT) will be delivered via Posit Science's BrainHQ suite. Training will target processing speed/attention (double decision, and hawk-eye tasks, divided attention, and target tracker) and working memory (memory grid, to-do list training, card shark, and auditory aces). All participants will complete a total of five weekly sessions of cognitive training over a 12-week period. Each session will last 60 minutes. Cognitive and functional assessments and resting-state fMRI will be performed after training completion for post-testing. Adherence and dose exposure for the training will be evaluated by usage tracking.

Participant measures:
Self-reported questionnaires
- Memory Functioning Questionnaire (MFQ)-Frequency of Forgetting-10 Scale
- Eysenck Personality Inventory
- Pearlin mastery scale
- University of Washington Resilience Scale 8-item short form (UWRS-8)

Primary outcome:
- Speed of processing (Pattern Comparison Processing Speed Test)

Cognitive outcomes:
- MoCA: Global cognition
- Trail Part A
- Trail Making, Part B
- WAIS-IV coding (Wechsler Adult Intelligence Scale)

- WAIS-IV symbol search
- Semantic Fluency (Animal naming) from the Consortium to Establish a Registry for Alzheimer's Disease battery
- The Benton Controlled Oral Word Association Test (COWAT): V1-stimulus letters C F L
- DKEFS battery: Color-word interference task
  Color word reading
- Composite score will be computed by averaging the z-scores from the Coding subtest of the Wechsler Adult Intelligence Scale, fourth edition (WAIS-IV); Semantic Fluency (animals) from the Consortium to Establish a Registry for Alzheimer's Disease battery; the Benton Controlled Oral Word Association Test (COWAT); Trail Making, Part B; and the Brain HQ Useful Field of View (UFOV®), subtest 2 (normalized and reversed).

Function IADLs:

- Functional Assessment Scale (FAS)
- Composite score will be computed by averaging the z-scores from the participants' scores on the Timed IADL and the total UFOV®. – (UFOV Assessment)

Neuroimaging measures:

BOLD imaging (12 minutes)
T1-weighted anatomical images
FLAIR anatomical images

Power and Sample Size Considerations: We will enroll a total of 40 participants. There are no preliminary studies on personality traits' effects on PST to estimate effect size. Studies of cognitive training have used an effect size of 0.42 (Cohen's d) to detect the benefits of processing speed training on cognitive outcomes (16). The sample size of 40 subjects will provide >80% power to detect differences at alpha level 0.05 on the primary outcome, the Pattern Comparison Processing Speed test. We will have similar power for cognitive, functional, and neuroimaging measures of brain change among older adults.

Statistical Analyses: Baseline and post-intervention characteristics of participants will be described using means and standard deviations (SD) for continuous variables and frequencies (percentages) for categorical variables. Linear regression models will examine the relationships of personality traits, processing speed training to cognitive and functional outcomes, and neuroimaging measures (pre-test: post-test design). We will estimate the effect of personality traits on the outcomes by controlling for participants' demographic characteristics. In addition, for fMRI analyses, Cohen's d effect sizes will be calculated for any significant training effects.

Multisite MBI Collaborations: This study will leverage the existing multisite clinical trial infrastructure at McKnight Brain Institutes located at the University of Alabama at Birmingham and the University of Florida. PI. Dr. Giovanna Pilonieta (UAB) will lead the collaboration and coordinate efforts. She will directly supervise the overall implementation of this project. Co-I Dr. Joseph M. Gullett, Ph.D., will lead studies-related activities at the University of Florida. Co-Investigators Dr. Adam J. Woods, Ph.D., and Dr. David S. Geldmacher, MD, will oversee the overall project and advise the PI on implementing study-related activities. Zoom meetings will be held at least monthly. Dr. Kristina M. Visscher will play an advisory role in final designs and interpretations of this study.

Timeline and Future Directions

Project Milestones	
Month	Activities/Milestones
1-3	Institutional agreements-IRB submission, database creation, IT/technical development (BrainHQ)
1-3	IRB approval- recruitment
5-22	Recruitment, enrollment, cognitive intervention, MRIs, data collection, and entry
22	Last subject-last assessment; data verification/cleaning
22-23	Statistical analysis and interpretation
24	Interpretation and Dissemination of findings (abstracts, presentation, publications)
1-24	Monthly research staff meetings-Investigators/Consultant meetings
	Future grants-Follow-on R01

Future research will add task-driven fMRI to examine brain activity and connectivity changes in older adults with SCD and test the efficacy of the intervention in community settings. Support of the hypotheses will also lead to a collaborative R01 application to examine the longitudinal benefits of PST on cognitive and functional performance and efficiency of cortical networks, and the effect of PST is moderated by personality traits.

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16. Woods AJ, Cohen R, Marsiske M, Alexander GE, Czaja SJ, Wu S. Augmenting cognitive training in older adults (The ACT Study): Design and Methods of a Phase III tDCS and cognitive training trial, Contemporary Clinical Trials, Volume 65,2018,Pages 19-32,ISSN 1551-7144,https://doi.org/10.1016/j.cct.2017.11.017.

Principal Investigator Giovanna Pilonieta OSP Number

DETAILED BUDGET	FROM 9/1/22	THROUGH 8/31/23

List PERSONNEL *(UAB Personnel Only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts *(omit cents)* for Salary and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Giovanna Pilonieta	PD/PI	1.7				9,195.00	3,356.00	$ 12,551.00
TBD	Research Asst.	1.8				7,956.00	2,904.00	$ 10,860.00
								$ 0.00
								$ 0.00
								$ 0.00
								$ 0.00
								$ 0.00
SUBTOTALS →						$ 17,151.00	$ 6,260.00	$ 23,411.00

CONSULTANT COSTS	
EQUIPMENT *(Itemize)* 3 IPads @ $362 each	$ 1,086.00
SUPPLIES *(Itemize by category)* Cognitive measures $ 216 NIH Toolbox® app $ 535	$ 751.00
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS MRIs	$ 3,167.00
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)* Participant stipends $150 x 10 = $1,500	$ 1,500.00
OUTGOING SUB-CONTRACT COSTS	$ 29,650.00
SUBTOTAL COSTS	$ $ 59,565.00
F&A / INDIRECT COSTS @ 0% If indirect costs are not allowed, leave it "0"	$ 0.00
TOTAL COSTS	$ $ 59,565.00

Comments:

Principal Investigator Giovanna Pilonieta OSP Number

DETAILED BUDGET	FROM 9/1/23	THROUGH 8/31/24

List PERSONNEL *(UAB Personnel Only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts *(omit cents)* for Salary and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Giovanna Pilonieta	PD/PI	1.7				9,195.00	3,356.00	$ 12,551.00
TBD	Research Asst.	1.8				7,956.00	2,904.00	$ 10,860.00
								$ 0.00
								$ 0.00
								$ 0.00
								$ 0.00
								$ 0.00
	SUBTOTALS →					$ 17,151.00	$ 6,260.00	$ 23,411.00

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)* Cognitive measures $216 NIH Toolbox® app $ 535	$ 751.00
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS MRIs	$ 3,167.00
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)* Participant stipends $150 x 10 = $1,500	$ 1,500.00
OUTGOING SUB-CONTRACT COSTS	$ 28,278.00
SUBTOTAL COSTS	$ $ 57,107.00
F&A / INDIRECT COSTS @ 0% If indirect costs are not allowed, leave it "0"	$ 0.00
TOTAL COSTS	$ $ 57,107.00

Comments:

Budget Justification
The proposed budget requests funds for a 2-year study period. Benefits are calculated at the UAB-mandated rates. Participant incentives are fixed per participant but will vary based on the number of contacts per annum. Costs to enroll each participant are budgeted throughout the award period and based upon a maximum recruitment of 20 total participants at the UAB Site.

KEY PERSONNEL
Giovanna Pilonieta, DMD, MPH. (Principal Investigator) (Effort:14 %, 1.7 Calendar Months Years 1-2)
Dr. Pilonieta will be responsible for overall project oversight. She will facilitate interactions between investigators, supervise study staff and recruitment, and monitor progress toward milestones. She will be responsible for study development and oversight, guiding all aspects of the study's conduct to ensure its advancement, integrity, and scientific rigor. She has extensive experience in the design and implementation of human subject research as she serves as the primary statistical analyst for the Division and has been responsible for the analytic design and execution of numerous studies for Division faculty since 2013.

Clinical Studies Research Assistant (TBN): (Effort 15%, 1.8 calendar months, Years 1-2) The clinical study coordinator will conduct the clinical study operations of the study, including scheduling participant activity, data entry, maintaining participant records and performing neurocognitive and functional assessments according to study protocol. He/She will oversee the completion and submission of local regulatory paperwork and coordinate safety reporting. He /She will report directly to Site PI and Co-I's Drs. Pilonieta and Geldmacher and meet with the entire team.

OTHER EXPENSES
Computing resources ($1,086 total cost). Funds are requested to purchase three iPad devices for administration of the take-home cognitive training paradigm to accommodate a maximum estimated concurrent enrollment of up to two participants at any given time. This is based on the estimate of 20 total participants over the two years of planned participant recruitment, or an average of 10 participants per year, totaling two participants per 12-week period for completion of the intervention. Funds requested include a third additional iPad device that will be utilized to administer baseline assessments without requiring the use of a participant iPad for administration. Each base model iPad currently costs $362 with free shipping. Thus, the total costs for equipment are solely in year one and equal to $1,086

Cognitive measures ($1502 total cost). Our division either has a sufficient number of copies of the proposed traditional neuropsychological measures, or they are available through public domain. The exception to this is a single installation of the NIH Toolbox required to fulfill the research aims. The funds requested for this license include $499.99+ tax on a yearly basis over the two years of the study for a total of $1070 ($535/year).
We request funds to purchase the licenses required to administer the Post Science Brain HQ Suite cognitive training, which is granted on a yearly, per-user/device basis. There may be up to three users/devices running at any given period, so three user accounts are required. The funds requested for this include $72 for each of the three participant iPads renewed on a yearly basis over the two years of active data collection for a total of $432 ($216/year).

MRI ($6,334 total cost). Funds are requested to complete a baseline and post-training MRI sequence. These funds are based upon a fee of 158.35 per MRI across a maximum of 20 study participants at the baseline time and post-training points. This equates to $6,334across both years (40 x $158.35), or $3,167 per year.

Participant incentives ($3,000 total cost). For this study, participants will receive $150 for completion of the entire study ($75 at the end of the baseline MRI+ neurocognitive visit and $75 after the 12-week follow-up visit), equivalent to a total cost of $1500 for year one and $1500 for year two.

Principal Investigator Joseph Gullett OSP Number

DETAILED BUDGET

FROM 9/1/22 THROUGH 8/31/23

List PERSONNEL
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts *(omit cents)* for Salary and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Joseph Gullett	PD/PI	0						$ 0.00
TBD	Research Asst.	6				15,000.00	1,080.00	$ 16,080.00
								$ 0.00
								$ 0.00
								$ 0.00
								$ 0.00
								$ 0.00
SUBTOTALS →						$ 15,000.00	$ 1,080.00	$ 16,080.00

CONSULTANT COSTS	
EQUIPMENT *(Itemize)* Computing resources (3 IPads @ $426 each)	$ 1,278.00
SUPPLIES *(Itemize by category)* Cogntive measures $216/year Binders adn Printing $576	$ 792.00
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS MRIs	$ 5,000.00
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)* Recruitment costs $2,500 per year Transportation $3,000 Participant incentives $1,000	$ 6,500.00
OUTGOING SUB-CONTRACT COSTS	
SUBTOTAL COSTS	**$ $ 29,650.00**
F&A / INDIRECT COSTS @ 0% If indirect costs are not allowed, leave it "0"	$ 0.00
TOTAL COSTS	**$ $ 29,650.00**

Comments:

Principal Investigator Joseph Gullett OSP Number

DETAILED BUDGET

FROM 9/1/23 THROUGH 8/31/24

List PERSONNEL
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts *(omit cents)* for Salary and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Joseph Gullett	PD/PI	0						$ 0.00
TBD	Research Asst.	6				15,450.00	1,112.00	$ 16,562.00
								$ 0.00
								$ 0.00
								$ 0.00
								$ 0.00
								$ 0.00
SUBTOTALS →						$ 15,450.00	$ 1,112.00	$ 16,562.00

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)* Cogntive measures $216/year	$ 216.00
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS MRIs	$ 5,000.00
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)* Recruitment costs $2,500 per year Transportation $3,000 Participant incentives $1,000	$ 6,500.00
OUTGOING SUB-CONTRACT COSTS	
SUBTOTAL COSTS	$ $ 28,278.00
F&A / INDIRECT COSTS @ 0% If indirect costs are not allowed, leave it "0"	$ 0.00
TOTAL COSTS	$ $ 28,278.00

Comments:

Budget Justification
The proposed budget request funds for a 2-year study period. Salary estimates include a 3% cost of living increase per year. Benefits are calculated at the UF-mandated rates for the part-time research assistant study interventionist. Participant incentives are fixed per participant but will vary based on number of contacts per annum. Costs to enroll each participant are budgeted throughout the award period and based upon maximum recruitment of 20 total participants at the UF Site.

KEY PERSONNEL
Joseph M. Gullett, Ph.D. (Co-Investigator, 0% full-time effort, 9 person-months salary support requested) is a licensed neuropsychologist trained in the scientist-practitioner model. He has over 11 years of clinical experience in assessment, diagnosis, and intervention of neurodegenerative disorders in addition to research-related experience in the neuropsychological and neuroanatomical correlates of aging and clinical disorders. Dr. Gullett will be responsible for study development and oversight, guiding all aspects of the study's conduct to ensure its advancement, integrity, and scientific rigor. He has gained extensive experience in the design, creation, and implementation of human subjects research, and will use these skills in concert with expert collaborators to serve as the UF Site PI and ensure the success of the project.

Clinical Studies Research Assistant and Coordinator (TBN): (50% Effort, 6 calendar months, Years 1-2) The clinical study coordinator will conduct the clinical study operations of the study, including scheduling participant activity, data entry, maintaining participant records and performing neurocognitive and functional assessments according to study protocol. They will oversee the completion and submission of local regulatory paperwork and coordinate safety reporting. They will report directly to Site PI and Co-I's Drs. Gullett and Woods and meet with the entire team.

OTHER EXPENSES
Computing resources ($1,277.58 total cost). Funds are requested to purchase three iPad devices for administration of the take-home cognitive training paradigm to accommodate a maximum estimated concurrent enrollment of up to two participants at any given time. This is based on the estimate of 20 total participants over the two years of planned participant recruitment, or an average of 10 participants per year, totaling two participants per 12-week period for completion of the intervention. Funds requested include a third additional iPad device that will be utilized to administer baseline assessments without requiring the use of a participant iPad for administration. Each base model iPad currently costs $329 with free shipping, and UF IT requires AppleCare+ added to each Apple device at the price of $69 each. Thus, the total costs for equipment are solely in year one and equal to $1,277.58.

Cognitive measures ($432 total cost). Our center either has a sufficient number of copies of the proposed traditional neuropsychological measures, or they are available through public domain. The exception to this is a single installation of the NIH Toolbox required to fulfill the research aims. However, a license for the NIH toolbox will be provided to the applicant by the Center for Cognitive Aging & Memory, and thus no funds are requested for installation. In addition, we request funds to purchase the licenses required to administer the Post Science Brain HQ Suite cognitive training, which is granted on a yearly, per-user/device basis. There may be up to three users/devices running at any given period, so three user accounts are required. The funds requested for this includes $72 for each of the three participant iPads renewed on a yearly basis over the two years of active data collection for a total of $432 ($216/year).

Binders and Printing ($576 total cost). Given the clinical trials nature of this project, costs associated with the printing and organization of study administration materials are to be expected. This includes consent forms, participant screening forms, printing of public domain neuropsychological tests, self-

report measures, and printed materials given to participants to take home for Cognitive Training guidance. Based on experience garnered from the parent trial, we anticipate these costs to be $14.40 per participant. When including costs of printing initial phone screening forms and materials for up to 20 additional participants who may ultimately drop-out prior to inclusion in the study, this equates to $14.40 x 40 = $576 total, implemented at year one only.

Media and Mass Mailing – Recruitment Strategies ($5,000 total cost). The University of Florida Recruitment Core has several years of experience in recruiting community elders for Clinical Trials such as the proposed study. This group has a proven track record for the creation and distribution of television and radio ads, as well as printed media. This budget will be crucial for ensuring enrollment of enough participants to supplement the clinically-based recruitment efforts of the PI. This includes large half-page advertisements at study initiation, classified ads, recruitment flyers, informational brochures, mailed postcards to the local catchment area based on voter registration information, and television and radio ads. $2500 per year is requested.

MRI ($10,000 total cost). Funds are requested to complete a half-hour baseline MRI sequence within the AMRIS facility at the neighboring McKnight Brain Institute. These funds are based upon an hourly rate of $500 across a maximum of 20 study participants at the baseline time and post training points. This equates to $10,000 across both years (40 x $250), or $5,000 per year.

Transportation service ($6,000 total cost). Transportation is often a major barrier for participation in research for minorities and individuals of lower socioeconomic status. To overcome this barrier, our standard of practice in our Center has been to provide round-trip travel through ride-sharing services to all participants. Participants who are included after completion of the initial phone screening will travel on-site for additional in-person screening and clinical interview at visit one. Those who remain included in the study subsequent to the first in-person visit will return for baseline neurocognitive testing, MRI, and cognitive training instruction at visit two. Two additional in-person visits will occur for continued training on use of the Cognitive Training instrument. The fifth in-person visit will occur after completion of the 12-week intervention, when participants will return for follow-up neurocognitive testing. Given that our participants are located within the local Alachua county region, the average ride-share cost on a round trip basis is estimated at $30 per participant. Thus, the total cost of transportation for Intervention participants in each year is 10 participants X 5 visits X $30 = $1,500. Further, we anticipate there to be approximately 20 total additional participants who either pass initial phone screening and do not pass the first in-person screening, or who are included but do not return for visit 2. Thus, we have budgeted for double to adjust for recruitment and retention/dropout incidence. This results in $3,000 anticipated travel expenses for year one, and $3,000 in anticipated travel expenses for year two.

Participant incentives ($2,000 total cost). To maximize adherence to the intervention protocols and retention to study visits, participants will be compensated (at a reasonable monetary value) for the time spent during each assessment visit. For this study, participants will receive $150 for completion of the entire study ($75 at the end of the baseline MRI+neurocognitive visit, and $75 after the 12-week follow-up visit), equivalent to a total cost of $750 for year one and $750 for year two. Given that we plan for up to 20 participants to complete the baseline assessment but to not continue the study due to dropout or exclusion, an additional $25 x 20 = $500 is included for a total of $2,000 in anticipated participant incentives, or $1,000 per year.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Pilonieta, Giovanna

eRA COMMONS USER NAME (credential, e.g., agency login): GPILONIETA

POSITION TITLE: Scientist I, Division of Memory Disorders and Behavioral Neurology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Santo Tomas University, Bucaramanga, COL	DDS	12/1994	Dentistry
Javeriana University, Bogota, COL	Specialist	12/1998	Pediatric Dentistry
University of Alabama at Birmingham, BHM, AL	MPH	04/2014	Public Health-Epidemiology
University of Alabama at Birmingham, BHM, AL	PhD	08/2022 (anticipated)	Health Services Administration

A. Personal Statement

I am a Scientist working in the UAB Department of Neurology Division of Memory Disorders and Behavioral Neurology. Undertaking a Master of Public Health at UAB with a focus on Epidemiology accentuated my passion for understanding how elements at the individual and community level influence the wellbeing of the populations and pursue an academic research career. I serve as a statistical analyst for the Division and have been responsible for the analytic design and execution of numerous studies for Division faculty since 2013. I also work as co-mentor to fellows, students, and new employees of diverse backgrounds in conducting studies and analyses. During my research training, I took part in community-based research to prevent chronic disease in minority groups, an opportunity to learn culturally tailored approaches to overcome barriers to access and delivery of care. My primary goals are to improve the quality of life of individuals at high risk of developing ADRD through adequate processes of care, including diagnosis and severity assessments, as well pharmacological and non-pharmacological interventions, to prevent and reduce cognitive and functional decline. This aligns with my research interest in assessing the influence of social determinants of health and other risk factors at the individual level in cognitive impairment and the differences in the cognitive outcomes among communities in special minorities and their effect on the quality of life. I look forward to the opportunity to develop this study of the effects of personality traits on efficacy of cognitive training in individuals with Subjective Cognitive Decline to identify novel approaches to maintain their functional independence and improve their quality of life.

Citations:

1. Wadley VG, Bull TP, Zhang Y, Barba C, Bryan RN, Crowe M, Desiderio L, Deutsch G, Erus G, Geldmacher DS, Go R, Lassen-Greene CL, Mamaeva OA, Marson DC, McLaughlin M, Nasrallah IM, Owsley C, Passler J, Perry RT, **Pilonieta G,** Steward KA, Kennedy RE. Cognitive Processing Speed Is Strongly Related to Driving Skills, Financial Abilities, and Other Instrumental Activities of Daily Living in Persons With Mild Cognitive Impairment and Mild Dementia. J Gerontol A Biol Sci Med Sci. 2021 Sep 13;76(10):1829-1838. doi: 10.1093/gerona/glaa312. PMID: 33313639; PMCID: PMC8522472.
2. **Pilonieta G**, Jablonski RA, Winstead V, Geldmacher D Family Quality of Life in Dementia and Caregiver Burden are Associated with Different Caregiver Personal Characteristics. Alzheimer's Dement. 2020;16(Suppl. 7): e045333. Available from: https://doi.org/10.1002/alz.045333

3. Natelson Love, MC, **Pilonieta, G**, Geldmacher, DS. "Alabama Brief Cognitive Screener". Prim Care Companion CNS Disord. 2019 Mar 14; 21(2). pii: 18m02336. Available from: https://DOI: 10.4088/PCC.18m02336
4. Nguyen, M; **Pilonieta, G;** Geldmacher, DS. Family Quality of Life and Caregiver Self-Efficacy among African American Families. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, Vol. 13, Issue 7, P539. Available from: **https://doi.org/10.1016/j.jalz.2017.06.644**

B. Positions, Scientific Appointments, and Honors

Positions

2019- Present	Scientist I, Department of Neurology, Division of Memory Disorders and Behavioral Neurology, University of Alabama-Birmingham
2015- 2019	Research Associate, Department of Neurology, Division of Memory Disorders and Behavioral Neurology, University of Alabama-Birmingham
2014-2015	Research Assistant, Department of Neurology, Division of Memory Disorders and Behavioral Neurology, University of Alabama-Birmingham.
2013-2014	Graduate Student Assistant, Department of Neurology, Division of Memory Disorders and Behavioral Neurology, University of Alabama-Birmingham.
2004-2008	Department Director -Department of Pediatric Dentistry, School of Dentistry, Santo Tomas University, Bucaramanga, Colombia.
2002-2012	Professor, Department of Pediatric Dentistry, School of Dentistry, Santo Tomas University, Bucaramanga, Colombia.

Honors

Honor Society of Phi Kappa Phi April 2019-present
American Association of University Women (AAUW) International Fellowship 2013

C. Contributions to Science

1. My primary contribution to the science of Alzheimer's disease has been in the development and analysis of cognitive assessment instruments to facilitate timely diagnosis in the setting of ambulatory care of people with dementia and MCI. I have served as the statistical analyst during the development of the scale.

a. Pilonieta, G. Geldmacher, DS. Internal Consistency by Diagnosis of the Alabama Brief Cognitive Screener (ABCs) in a Memory Disorders Clinic. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, Vol. 12, Issue 7, Supplement, P499. Available from; **https://doi.org/10.1016/j.jalz.2016.06.989**
b. Natelson Love, M. Pilonieta, G. Geldmacher, DS. Alabama Brief Cognitive Screener Scores Predict Level of Impairment in Instrumental Activities of Daily Living and Dementia Diagnosis in a Memory Disorders Clinic, Alzheimer's & Dementia: The Journal of the Alzheimer's Association, Volume 11, Issue 7, P662. Available from: **https://doi.org/10.1016/j.jalz.2015.06.977**
c. Natelson Love, M. Pilonieta, G. Geldmacher, DS. Alabama Brief Cognitive Screener Scores Vary Appropriately by Diagnosis and Resemble MMSE Scoring Distributions. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, Volume 11, Issue 7, P523 - P524. Available from: **https://doi.org/10.1016/j.jalz.2015.06.641**
d. Mehra, N. Pilonieta, G. Geldmacher, DS. Comparison of two brief cognitive screening tests and relationship to subjective cognitive complaints in a primary care setting. The Journal of the Alzheimer's Association, Volume 13, Issue 7S, P729. Available from: **https://doi.org/10.1016/j.jalz.2017.06.948**

2. In addition to the contributions described above, with a team of collaborators, as a data scientist I have been responsible for the statistical analysis in the assessment of clinical effectiveness for personalized medicine approaches and distant-learning training and coaching program for caregivers. These studies look for using patient-specific genetic information to select medications to help attenuate behavioral and psychiatric symptoms in patients with dementia. The latter explored an innovative approach to reducing care-resistant behaviors in people with dementia. Both have already been implemented in the clinical setting to complement the existing approaches and to provide real value in addressing the unmet needs of people with AD/ADRD.

a. Pilonieta G, Geldmacher D. Dementia Caregiver Surrogate Decision Making Self-Efficacy: Distress, and Quality of Life. Innov Aging. 2021 Dec 17;5(Suppl 1):742. doi: 10.1093/geroni/igab046.2756. PMCID: PMC8681494.

b. Feasibility of Online Synchronous Caregiver Dementia Coaching for Rejection-of-Care Behaviors. Jablonski RA1, Vicki W, **Pilonieta G,** Geldmacher D. Innovation in Aging, Volume 3, Issue Supplement_1, November 2019, Pages S924–S925. Available from: https://doi.org/10.1093/geroni/igz038.3367.
c. Daut R, Yu K, Li J, Burns L, Brown K, Pollack M, Tanner JA, Geldmacher D, **Pilonieta G**, Anderson A.Pharmacogenomic Testing to Inform Prescribing in Patients with Behavioral and Psychiatric Symptoms of Dementia (BPSD): Results from Two Small, Randomized, Controlled Trials, The American Journal of Geriatric Psychiatry, Volume 29, Issue 4, Supplement,2021, Pages S113-S115, ISSN 1064-7481.Available from: https://doi.org/10.1016/j.jagp.2021.01.110

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Joseph M. Gullett

eRA COMMONS USER NAME (credential, e.g., agency login): gullettj

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Florida	B.S.	05/2008	Psychology
University of Florida	M.S.	05/2013	Clinical Psychology
West Los Angeles VAMC	-	08/2017	APA Internship in Clinical Psychology
University of Florida	Ph.D.	08/2017	Clinical Psychology
University of Florida	Postdoctoral	08/2019	Neuropsychology

A. Personal Statement

I am a licensed neuropsychologist and tenure-track Assistant Professor in AI with the University of Florida Center for Cognitive Aging and Memory. I received my Ph.D. in clinical psychology from the University of Florida in August of 2017 after the completion of a one-year clinical internship in psychology at the West Los Angeles VA Medical Center. My early research focused on the use of diffusion tensor imaging methods to study white matter in Veterans with co-morbid mild traumatic brain injury (mTBI) and posttraumatic stress disorder (PTSD) at the Malcom Randall VA. Since that time, I have continued to apply imaging and neuropsychology methods to the study of various clinical disorders, including neurodegenerative disorders, and formed clinical expertise in neurodegenerative disease with a research interest in Alzheimer's disease interventions. After becoming involved with the 1Florida Alzheimer's Disease Research Center (ADRC), I was the awardee of their 2019 Pilot Grant to investigate the ability of baseline neuroimaging to predict worsening cognition in several hundred healthy, mild cognitive impairment, and Alzheimer's disease patients. This opportunity allowed our team to develop a Machine Learning pipeline that ultimately predicted longitudinal diagnostic decline with over 93% accuracy; a pipeline that has been applied to a small pilot sample of MCI patients predicting Cognitive Training response. I have remained clinically-involved in the neuropsychological assessment of various populations, and collaborate as a licensed neuropsychologist both on a weekly clinical service as well as on a number of NIH-funded U-01, P-01, and R-01 grants. In this regard, my research and clinical experience serves me well as it applies to the present project, as it has provided the foundation for project management, neuropsychological assessment, cognitive training, test administration oversight, battery development, and neuropsychological data interpretation/analysis.

A relevant ongoing project I would like to highlight includes:

NIA R01AG070349
Woods (Site PI)
Role: Co-investigator
02/01/2021-01/31/2026
"Preventing Alzheimer's Disease through Cognitive Training (the PACT trial)."

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2008-2011	Clinical Psychometrist, UF Neuropsychology Clinic, Gainesville, FL
2011-2016	Graduate Assistant, Department of Clinical & Health Psychology, Gainesville, FL
2016-2017	Psychology Intern, West Los Angeles VA Medical Center, Los Angeles, CA
2017-2018	Postdoctoral Clinical-Research Associate, Center for Cognitive Aging and Memory, Gainesville, FL
2018-2019	T32 Postdoctoral Fellow, Center for Cognitive Aging & Memory, Gainesville, FL
2019-2022	Research Assistant Professor, Department of Clinical & Health Psychology, Gainesville, FL
2022-	Assistant Professor, Artificial Intelligence, Department of Clinical & Health Psychology, Gainesville, FL

Other Experience and Professional Memberships

2012-2017	Student Member, APA Division 40 (neuropsychology)
2016-	Ad Hoc Reviewer, The Clinical Neuropsychologist
2018-	Ad Hoc Reviewer, Neuropsychology Review
2019-	Ad Hoc Reviewer, Human Brain Mapping
2019-	Licensed Clinical Psychologist (PY10534)
2020-	Ad Hoc Reviewer, Frontiers in Aging Neuroscience (review count: 3)
2020-	Member, The International Neuropsychological Society
2020-	Editorial Board Member, Frontiers in Aging Neuroscience
2020-	Ad Hoc Reviewer, Human Brain Mapping
2020-2022	Member, American Academy of Neurology (AAN)

C. Contributions to Science

1. Over my tenure as an assistant professor with the Center for Cognitive Aging and Memory, increased focus in my scientific work has been directed toward the use of machine learning prediction of cognitive function, as well as continued use of white matter and neuropsychological predictors in various clinical disorders.
   a. Gullett, J.M., Albizu, A., Fang, R., Loewenstein, D.A., Duara, R., Rosselli, M., Armstrong, M.J., Rundek, T., Hausman, H.K., Dekosky, S.T., Woods, A.J., Cohen, R.A., & The 1Florida ADRC Group. Baseline neuroimaging predicts decline to dementia from amnestic mild cognitive impairment. Frontier's in Aging Neuroscience. 2021;
   b. Gullett JM, O'Shea A, Lamb DG, Porges EC, O'Shea DM, Pasternak O, et al. The association of white matter free water with cognition in older adults. Neuroimage. 2020;
   c. Gullett JM, Chen Z, O'Shea A, Akbar M, Bian J, Rani A, et al. MicroRNA predicts cognitive performance in healthy older adults. Neurobiol Aging. 2020;
   d. Bryant VE, Gullett JM, Porges EC, Cook RL, Bryant KJ, Woods AJ, et al. History of Alcohol Consumption and HIV Status Related to Functional Connectivity Differences in the Brain During Working Memory Performance. Curr HIV Res. 2020;

2. During the two years as postdoctoral fellow prior to starting my assistant professorship with the Center for Cognitive Aging and Memory, my scientific work focused on neuroimaging, clinical, and neuropsychological correlates of normal aging as well as HIV, alcohol use, and breast cancer-related cognitive phenomena.
   a. Gullett JM, Cohen RA, Yang GS, Menzies VS, Fieo RA, Kelly DL, et al. Relationship of fatigue with cognitive performance in women with early-stage breast cancer over 2 years. Psychooncology. 2019;
   b. Kuhn T, Jin Y, Huang C, Kim Y, Nir TM, Gullett JM, et al. The joint effect of aging and HIV infection on microstructure of white matter bundles. Hum Brain Mapp. 2019;
   c. Gullett JM, Lamb DG, Porges E, Woods AJ, Rieke J, Thompson P, et al. The Impact of Alcohol Use on Frontal White Matter in HIV. Alcohol Clin Exp Res. 2018;42(9):1640–9.
   d. Cohen RA, Siegel S, Gullett JM, Porges E, Woods AJ, Huang H, et al. Neural response to working memory demand predicts neurocognitive deficits in HIV. J Neurovirol. 2018;

3. In my early post-baccalaureate and graduate career, I focused my research endeavors on the use of diffusion tensor imaging and structural neuroimaging to investigate clinical phenomena within populations with TBI, PTSD, and temporal lobe epilepsy.

    a. Kuhn T, Gullett JM, Boutzoukas AE, Bohsali A, Mareci TH, FitzGerald DB, et al. Temporal lobe epilepsy affects spatial organization of entorhinal cortex connectivity. Epilepsy Behav. 2018;
    b. Kuhn T, Gullett JM, Nguyen P, Boutzoukas AE, Ford A, Colon-Perez LM, et al. Test-retest reliability of high angular resolution diffusion imaging acquisition within medial temporal lobe connections assessed via tract based spatial statistics, probabilistic tractography and a novel graph theory metric. Brain Imaging Behav. 2016;
    c. Gullett JM, Price CC, Nguyen P, Okun MS, Bauer RM, Bowers D. Reliability of three benton judgment of line orientation short forms in idiopathic parkinsons disease. Clin Neuropsychol. 2013;
    d. Ford A, Colon-Perez L, Triplett WT, Gullett JM, Mareci TH, FitzGerald DB. Imaging white matter in human brainstem. Front Hum Neurosci. 2013;

4. Through my collaborative efforts in other realms, I have also garnered expertise in various scientific topics, including cancer and obesity-related cognitive function, as well as the effect of TBI on neural sleep centers.
    a. Fernando HJ, Cohen RA, Gullett JM, Friedman J, Ayzengart A, Porges E, et al. Neurocognitive Deficits in a Cohort With Class 2 and Class 3 Obesity: Contributions of Type 2 Diabetes and Other Comorbidities. Obesity. 2019;
    b. Cohen RA, Gullett JM, Woods AJ, Porges EC, Starkweather A, Jackson-Cook CK, et al. Cytokine-associated fatigue prior to, during, and post-chemotherapy for breast cancer. J Neuroimmunol. 2019;
    c. Sullan MJ, Bohsali AA, Gullett JM, Goldstein J, Bauer RM, Mareci TH, et al. The Relationship Between Locus Coeruleus Volume and Measures of Sleep and Attentional Control in Veterans with Mild TBI. Clin Neuropsychol (Neuropsychology, Dev Cogn Sect D). 2015;29(3):324.
    d. Sullan M, Bohsali A, Gullett JM, Goldstein J, Bauer R, Mareci T, et al. The Locus Coeruleus and Sleep-Wake Disturbances in Veterans with mTBI. J Sleep med disord. 2014;1(1):1004.

5. Lastly, my interests also led me to explore the white matter connectivity of language centers using tractography in healthy adults, as well as publish a case study detailing a cautionary tale about MRI research with veterans.
    a. Bohsali AA, Triplett W, Sudhyadhom A, Gullett JM, McGregor K, FitzGerald DB, et al. Broca's area - Thalamic connectivity. Brain Lang. 2015;
    b. Ford AA, Triplett W, Sudhyadhom A, Gullett J, McGregor K, FitzGerald DB, et al. Broca's area and its striatal and thalamic connections: A diffusion-MRI tractography study. Front Neuroanat. 2013;
    c. FitzGerald DB, Gullett JM, Levy CE, Crosson BA. Delayed Diagnosis of Intracerebral Foreign Body From the Vietnam War. Mil Med. 2011;

Complete list of published work in my NCBI bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1Z3WHMZO4VfQQ/bibliography/53788754/public/?sort=date&direction=ascending

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: David S. Geldmacher

eRA COMMONS USER NAME (credential, e.g., agency login): DSG8NNIH

POSITION TITLE: Warren Family Endowed Chair in Neurology; Professor of Neurology and Neurobiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Rochester, NY	B.A.	05/1982	Biology, Psychology
SUNY, Health Science Ctr at Syracuse, NY	M.D.	05/1986	Medicine
Mt. Sinai Medical Center; Cleveland, OH	Internship	06/1987	Medicine
Case Western Reserve University, Cleveland, OH	Residency	06/1990	Neurology
University of Florida, Gainesville, FL	Fellowship	06/1991	Behavioral Neurology

A. Personal Statement

I am pleased to contribute effort to the proposal titled "A Single Arm Intervention Study to Evaluate Effects of Personality Traits on Efficacy of Processing Speed Training in Individuals with Subjective Cognitive Decline." My prior work has identified important roles for personality traits in determining the effectiveness of interventions to support caregivers of persons with dementia. Additionally, I served as an investigator on a trial of computerized cognitive training in mild cognitive impairment that suggested participant motivation to persist with training tasks influenced the outcomes. Finally, I have experience working in collaboration across McKnight Centers in the development and analysis of the McKnight Brain Aging Registry project.

I have over 25 years of leadership in clinical care and clinical research programs for people with cognitive disorders. I have led successful clinical research and clinical trials programs in Alzheimer's disease in three different institutions, and regularly participate in national-level steering and publications committees for federally funded and industry sponsored AD trials. At present, I lead the Memory Disorders Clinics at UAB, which serve over 3000 patients annually with memory-related diagnoses; this provides me with real-world exposure to persons with a wide range of cognitive complaints ranging from typical age-related changes in processing speed through sever dementia. As a result, my research has focused on assessing the meaningfulness of treatment outcomes for people with cognitive disorders.

1. Wadley VG*, Bull TP, Zhang Y, Barba C, Bryan RN, Crowe M, Desiderio L, Deutsch G, Erus G, **Geldmacher DS,** Go R, Lassen-Greene CL, Mamaeva OA, Marson DC, McLaughlin M, Nasrallah IM, Owsley C, Passler J, Perry RT, Pilonieta G, Steward KA, Kennedy RE. Cognitive Processing Speed Is Strongly Related to Driving Skills, Financial Abilities, and Other Instrumental Activities of Daily Living in Persons With Mild Cognitive Impairment and Mild Dementia. *J Gerontol A Biol Sci Med Sci.* 2021 Sep 13;76(10):1829-1838. doi: 10.1093/gerona/glaa312. PMID: 33313639; PMCID: PMC8522472.
2. Fritsch T*, McClendon MJ, Wallendal MS, Smyth KA, **Geldmacher DS,** Hyde TF, Leo GJ. Can a Memory Club Help Maintain Cognitive Function? A Pilot Investigation, *Activities, Adaptation & Aging,* 2014; 38:, 29-52, doi: 10.1080/01924788.2014.878873
3. Clark DG*, Kapur P, **Geldmacher DS**, Brockington JC, Harrell L, DeRamus TP, Blanton PD, Lokken K. Nicholas AP, Marson DC. Latent information in fluency lists predicts functional decline in persons at risk for Alzheimer disease. *Cortex* 2014:doi: 10.1016/j.cortex.2013.12.013
4. **Geldmacher DS**, Kirson NY, Birnbaum HG, Eapen S, Kantor E, Cummings AK, Joish VN. Pre-Diagnosis Excess Acute Care Costs in Alzheimer's Patients among a US Medicaid Population. *Appl Health Econ Health Policy.* 2013;11:407-13. doi: 10.1007/s40258-013-0038-9.

B. Positions, Scientific Appointments, and Honors

Positions

2011-present	Professor of Neurology and Neurobiology, Warren Family Endowed Chair in Neurology, and Director, Division of Memory Disorders and Behavioral Neurology, University of Alabama-Birmingham
2002-2011	Associate Professor (with tenure) and Director, Memory Disorders Program, Department of Neurology, University of Virginia, Charlottesville, Virginia
1994-2002	Clinical Director and Director for Clinical Trials, Alzheimer Center, University Hospitals of Cleveland and Case Western Reserve University
1993-2001	Assistant & Associate Professor, Alzheimer Center, Department of Neurology, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, Ohio
1991-1992	Assistant Professor, Department of Neurology, Robert Wood Johnson Medical School, The University Medicine and Dentistry of New Jersey, New Brunswick, NJ

Other Experience and Professional Memberships

2020-current	Invited faculty, Institute on Methods and Protocols for Advancement of Clinical Trials in ADRD (IMPACT-AD), NIA Alzheimer's Clinical Trials Consortium
2018-current	Steering Committee Member, NIA Alzheimer's Clinical Trials Consortium
2017-current	Member, Appeals Advisory Panel (Court Appointed), NFL Concussion Settlement Program
2016-current	Board Certification (Behavioral Neurology and Neuropsychiatry), United Council of Neurologic Subspecialties.
2012-current	Medical Director for Neurology, University of Alabama (UAB) Hospital
2011-current	Medical License, MD32204, Alabama Board of Medical Examiners
2007-2011	Ad hoc Consultant, FDA Peripheral & Central Nervous System Drugs Advisory Committee
2006-current	Induction to membership, American Neurological Association
1995-2002	Steering Committee Member, NIA Alzheimer's Disease Cooperative Study
2012	NIH Special Emphasis Panel: Alzheimer's Disease Cooperative Study
2010	NIH Special Emphasis Panel: Alzheimer's Disease Neuroimaging Initiative
1992	Board Certification (Neurology), American Board of Psychiatry and Neurology (Lifetime)
1988-current	Member, American Academy of Neurology

Honors

2021	Induction to membership, Sigma Xi Scientific Research Honor Society
2015	Election to membership, Alpha Omega Alpha Medical Honors Society
2013	Appointment to Fellow, American Neurological Association
2012	Neurology Department Residency teaching award, UAB Department of Neurology
2008	Election to Fellow, American College of Physicians
2005	Selected for Membership, UVA School of Medicine Academy of Distinguished Educators
2003	Neurology Department Residency teaching award, UVA Department of Neurology
1998-current	"Best Doctors in America" selection

C. Contributions to Science

1. My primary contribution to the science of Alzheimer's disease has been in the assessment of clinical effectiveness for dementia therapies through clinical trials. I have served on protocol design committees, steering committees, NIH Special Emphasis sections and analytic workgroups for multiple trials and consequent database studies. I have received NIH, DoD, and industry funding for investigator-initiated clinical trials. Examples from my work include;
   a. Brown EL*, Ruggiano N, Roberts L, Clarke PJ, Davis DL, Agronin M, **Geldmacher DS**, Hough MS, Muñoz MTH, Framil CV, Yang X. Integration of Health Information Technology and Promotion of Personhood in Family-Centered Dementia Care: Intervention Trial. *Res Gerontol Nurs.* 2021 Sep-Oct;14(5):225-234. doi: 10.3928/19404921-20210825-02. Epub 2021 Sep 1. PMID: 34542347.
   b. Jablonski RA, Winstead V, **Geldmacher DS**. Description of process and content of online dementia coaching for family caregivers of persons with dementia. *Healthcare* (Basel). 2019 Jan 19;7(1). pii: E13. doi: 10.3390/healthcare7010013. PMID: 30669444

c. **Geldmacher DS**, Fritsch T, McClendon MJ, Landreth GE. A randomized pilot clinical trial of the safety of pioglitazone in treatment of patients with Alzheimer disease. *Archives of Neurology.* 2011;68:45-50. doi:10.1001/archneurol.2010.229
d. **Geldmacher DS**, Provenzano G, McRae T, Mastey V, Ieni JR. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. *Journal of the American Geriatrics Society* 2003;51:937-944.

2. Related to the assessment of clinical meaningfulness, I have collaborated on the development of assessment instruments, as well as novel approaches for determining an individual's and family caregiver's needs in the setting of ambulatory care of persons with cognitive imapirments.
   a. Rose KM, Williams IC, Anderson JG, **Geldmacher DS**. Development and Validation of the Family Quality of Life in Dementia Scale. *Gerontologist.* 2020. doi: 10.1093/geront/gnaa022.] PubMed PMID: 32329513.
   b. Ruggiano N, Brown EL, Shaw S, **Geldmacher D,** Clarke P, Hristidis V, Bertram J. The Potential of Information Technology to Navigate Caregiving Systems: Perspectives from Dementia Caregivers. *J Gerontol Soc Work.* 2019;62:432-450. doi: 10.1080/01634372.2018.1546786. PubMed PMID: 30422754.
   c. Love MCN, Pilonieta G, **Geldmacher DS**. Alabama Brief Cognitive Screener: Utility of a New Cognitive Screening Instrument in a Memory Disorders Clinic. *Prim Care Companion CNS Disord.* 2019 Mar 14;21(2). doi: 10.4088/PCC.18m02336. PubMed PMID: 30896091.
   d. Santillan CE*, Fritsch T, Geldmacher DS. Development of a scale to predict decline among mildly demented Alzheimer's disease patients *Journal of the American Geriatrics Society* 2003;51:91-95

3. Previously, my work focused on task characteristics that influence visual exploratory performance in aging and neurologic disease. I developed and implemented a novel means of scoring the commonly used (in behavioral neurology) letter cancellation task. My colleagues and I assessed the utility of the scoring method in different ages, cultures, and mechanisms of neurologic dysfunction.
   a. **Geldmacher DS,** Fritsch T, Riedel TM. Effects of stimulus properties and age on random array letter cancellation tasks. *Aging Neuropsychology and Cognition* 2000;7:194-204
   b. **Geldmacher DS.** Stimulus characteristics determine processing approach on random array letter-cancellation tasks. *Brain and Cognition* 1998; 36:346-354.
   c. **Geldmacher DS**, Hills EC. Effect of stimulus number, target-to-distractor ratio and motor speed on visuospatial search quality following traumatic brain injury. *Brain Injury* 1997; 11(1):59-66
   d. **Geldmacher DS**, Doty L, Heilman KM. Letter cancellation performance in Alzheimer's disease. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology* 1995; 8:259-263.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1Vk2aSA2rkoAo/bibliography/public/

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Woods, Adam

eRA COMMONS USER NAME (credential, e.g., agency login): ajwoods

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Alabama at Birmingham, Birmingham, AL	BS	05/2003	Psychology
George Washington University, Washington, DC	PHD	05/2010	Cognitive Neuroscience
University of Pennsylvania, Philadelphia, PA	Postdoctoral Fellow	06/2013	Cognitive Neuroscience

A. Personal Statement

Dr. Woods is Associate Director of the Center for Cognitive Aging and Memory (CAM) in the McKnight Brain Institute at UF. Dr. Woods is also an Associate Professor and Associate Chair for Research in the Department of Clinical and Health Psychology at UF, with a joint appointment to Neuroscience. He is a cognitive neuroscientist with expertise in cognitive aging and mild cognitive impairment, non-invasive brain stimulation, neuroimaging, and cognitive training for working memory and speed of processing/attention. He is an international leader in the field of non-invasive brain stimulation and neuromodulation, leading the largest transcranial electrical stimulation (tES) and near infrared photobiomodulation trials to date, multiple cognitive training trials, publishing the first comprehensive textbook in the field of tES, and multiple field standards papers. Dr. Woods' research specifically focuses on discovery and application of novel non-invasive interventions for enhancing cognitive function in adults with and without neurodegenerative disease. Dr. Woods has expertise in multi-disciplinary cognitive neuroscience methodologies (MRI/fMRI, electrophysiology, non-invasive brain stimulation), extensive experience with aging-related cognitive disorders, cognitive training applications, and past research with neurological diseases. Over the past ten years, Dr. Woods has established one of the largest and most well-funded neuromodulation laboratories around the world. He is PI of the first and largest phase III RCT for tES using transcranial direct current stimulation (tDCS) and cognitive training, the ACT study (R01AG054077, n=360), the largest phase II near infrared photobiomodulation trial (R01AG064587, n=168), as well as multiple other NIH grants investigating the effects of neuromodulation on the aging brain (RF1AG071469, R01AG070349, etc.). He also serves as co-I on multiple other NIH funded grants focused on neuromodulation of cognitive aging, chronic pain, and mobility using transcranial electrical stimulation (e.g., RF1MH114290, R37AG033906, VA Merit, etc.). Each of these studies attempts to enhance cognitive and brain function through neuromodulation.

Relevant ongoing and recently completed projects I would like to highlight include:

NIA R01AG054077
Woods (PI)
09/01/16-04/31/22
"Augmenting Cognitive Training in Older Adults (ACT)."

NIA RF1AG071469
Woods (MPI)
06/1/21-05/31/25

"Mechanisms, response heterogeneity and dosing from MRI-derived electric field models in tDCS augmented cognitive training"

NIA R01AG064587
Woods (MPI)
08/01/19-04/31/24
"Revitalizing Cognition in Older Adults at Risk for Alzheimer's Disease with Near-Infrared Photobiomodulation"

NIA R01AG070349
Woods (Site PI)
02/01/2021-01/31/2026
"Preventing Alzheimer's Disease through Cognitive Training (the PACT trial)."

Citations:

1. Albizu A, Fang R, Indahlastari A, O'Shea A, Stolte SE, See KB, Boutzoukas EM, Kraft JN, Nissim NR, Woods AJ. Machine learning and individual variability in electric field characteristics predict tDCS treatment response. Brain Stimul. 2020 Oct 10;13(6). PubMed PMID: 33049412; PubMed Central PMCID: PMC7731513
2. Nissim N, O'Shea A, Indahlastari A, Telles R, Richards L, Porges E, Cohen R, Woods AJ. Effects of in-scanner bilateral frontal tDCS on functional connectivity of the working memory network in older adults. Front Aging Neurosci. 2019 Mar 15;11: 51. PubMed PMID: 30930766; PubMed Central PMCID: PMC6428720
3. Woods AJ, Cohen R, Marsiske M, Alexander GE, Czaja SJ, Wu S. Augmenting cognitive training in older adults (The ACT Study): Design and Methods of a Phase III tDCS and cognitive training trial. Contemp Clin Trials. 2017 Dec 5;65:19-32. PubMed PMID: 29313802.
4. Nissim N, Nissim N, O'Shea A, Indahlastari A, Telles R, Richards L, Porges E, Cohen R, Woods AJ. Effects of in-scanner bilateral frontal tDCS on functional connectivity of the working memory network in older adults. Front Aging Neurosci. 2019 Mar 15;11:51. PubMed PMID: 30930766; PubMed Central PMCID: PMC6428720.

B. Positions, Scientific Appointments, and Honors.

Positions and Employment

2010 - 2013	Post-doctoral Fellow, University of Pennsylvania, Philadelphia, PA
2013 -	Assistant Professor, University of Florida, Gainesville, FL
2014 -	Assistant Director, Center for Cognitive Aging and Memory, Gainesville, FL

Other Experience and Professional Memberships

2005 -	Member, Association for Psychological Science
2005 -	Member, International Neuropsychological Society
2010 -	Member, Society for Neuroscience
2014 -	Junior Fellow, World Academy of Arts and Sciences
2015 -	Ad Hoc Reviewer, US Veteran's Administration
2016 -	Ad Hoc Reviewer, National Institutes of Health
2016 -	Member, American Psychological Association

Honors

2006 - 2009	Graduate Research Fellowship, National Science Foundation
2010 - 2013	Post-doctoral Fellowship, Intellectual and Developmental Disabilities Research Center, Children's Hospital of Philadelphia
2014 - 2016	KL2 Scholar, University of Florida Clinical Translational Science Institute
2015 - 2015	Young Investigator Award in Neuromodulation, NYC Neuromodulation 2015
2018-2020	University Preeminence Term Professorship, University of Florida, College of Public Health and Health Professions

2019 Tenure, University of Florida

C. Contribution to Science

Transcranial Electrical Stimulation. Over the past ten years, I have focused my research on the technical and basic science application of non-invasive electrical brain stimulation techniques as novel interventions for enhancement of cognitive function. This work includes both transcranial direct current stimulation and transcranial magnetic stimulation. To further the field, I co-founding a CME certified practical training course in tES that has trained over 1000 researchers and students to safely and consistently apply this method of non-invasive brain stimulation. I have published numerous field standards papers aimed at enhancing replicability and safety for the method and the first textbook in the field, in addition to exploring its impact on a variety of cognitive functions in the brain. I was awarded the 2015 NYC Neuromodulation Young Investigator Award for my scientific and educational contributions to the field. Furthermore, I am also PI of the first Phase III tDCS randomized clinical trial, as well as the largest tDCS study to date. Collectively, this work provides me with a strong foundation in the technical elements and application standards of tES.

a. McLaren ME, Nissim NR, Woods AJ. The effects of medication use in transcranial direct current stimulation: A brief review. Brain Stimul. 2018 Jan - Feb;11(1):52-58. PubMed PMID: 29066167; PubMed Central PMCID: PMC5729094.
b. Indahlastari A, Albizu A, Kraft JN, O'Shea A, Nissim NR, Dunn A, Carballo D, Gordon M, Taank S, Kahn AT, Hernandez C, Zucker WM, Woods AJ. Individualized tDCS Modeling Predicts Functional Connectivity Changes within the Working Memory Network in Older Adults. Brain Stimul. 2021 Sep 1; 14(5):1205-1215. PubMed PMID: 34371212.
c. Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, Mourdoukoutas AP, Kronberg G, Truong D, Boggio P, Brunoni AR, Charvet L, Fregni F, Fritsch B, Gillick B, Hamilton RH, Hampstead BM, Jankord R, Kirton A, Knotkova H, Liebetanz D, Liu A, Loo C, Nitsche MA, Reis J, Richardson JD, Rotenberg A, Turkeltaub PE, Woods AJ. Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. Brain Stimul. 2016 Sep-Oct;9(5):641-61. PubMed PMID: 27372845; PubMed Central PMCID: PMC5007190.
d. Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, Cohen LG, Fregni F, Herrmann CS, Kappenman ES, Knotkova H, Liebetanz D, Miniussi C, Miranda PC, Paulus W, Priori A, Reato D, Stagg C, Wenderoth N, Nitsche MA. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol. 2016 Feb;127(2):1031-1048. PubMed PMID: 26652115; PubMed Central PMCID: PMC4747791.

Neuroimaging and Magnetic Resonance Spectroscopy. My work in neuroimaging and spectroscopy has focused on understanding the brain networks and neurometabolites that underlie cognitive processes and how these processes are altered by age and medical disorders exacerbating aging of the human brain. This work has primarily used structural and functional magnetic resonance imaging and diffusion weighted imaging, but now includes magnetic resonance spectroscopy. Through multimodal neuroimaging, this work aims to identify markers predictive of cognitive decline in older adults, as well as markers of intervention effectiveness. This work has been central to identification of neural intervention targets for tES.

a. Porges EC, Woods AJ, Lamb DG, Williamson JB, Cohen RA, Edden RAE, Harris AD. Impact of tissue correction strategy on GABA-edited MRS findings. Neuroimage. 2017 Nov 15;162:249-256. PubMed PMID: 28882635; PubMed Central PMCID: PMC5705271.
b. O'Shea A, Cohen RA, Porges EC, Nissim NR; Woods AJ. Cognitive Aging and the Hippocampus in Older Adults. Front Aging Neurosci. 2016;8:298. PubMed PMID: 28008314; PubMed Central PMCID: PMC5143675.
c. Porges EC, Woods AJ, Edden RA, Puts NA, Harris AD, Chen H, Garcia AM, Seider TR, Lamb DG, Williamson JB, Cohen RA. Frontal Gamma-Aminobutyric Acid Concentrations Are Associated With Cognitive Performance in Older Adults. Biol Psychiatry Cogn Neurosci Neuroimaging. 2017 Jan;2(1):38-44. PubMed PMID: 28217759; PubMed Central PMCID: PMC5312683.
d. Woods AJ, Hamilton RH, Kranjec A, Minhaus P, Bikson M, Yu J, Chatterjee A. Space, time, and causality in the human brain. Neuroimage. 2014 May 15;92:285-97. PubMed PMID: 24561228; PubMed Central PMCID: PMC4008651.

Working Memory/Executive Function. One area of my work investigates the impact of aging and stroke on working memory and executive function. My recent work in age-related change in working memory/executive

function includes both behavioral and neuroimaging-based identification of therapeutic neural targets for tES. This work spans investigation of early development (age 2-18 years) to effects in later life (ages 60+) and following focal lesions to frontal and parietal brain systems.

a. Hausman HK, Hardcastle C, Albizu A, Kraft JN, Evangelista ND, Boutzoukas EM, Langer K, O'Shea A, Van Etten EJ, Bharadwaj PK, Song H, Smith SG, Porges E, DeKosky ST, Hishaw GA, Wu S, Marsiske M, Cohen R, Alexander GE, Woods AJ. Cingulo-Opercular and Frontoparietal Control Network Connectivity and Executive Functioning in Older Adults. Geroscience. 2021 Dec 23; PubMed PMID: 34950997
b. Evangelista ND, O'Shea A, Kraft JN, Hausman HK, Boutzoukas EM, Nissim NR, Albizu A, Hardcastle C, Van Etten EJ, Bharadwaj PK, Smith SG, Song H, Hishaw GA, DeKosky S, Wu S, Porges E, Alexander GE, Marsiske M, Cohen R, Woods AJ. Independent Contributions of Dorsolateral Prefrontal Structure and Function to Working Memory in Healthy Older Adults. Cereb Cortex. 2021 Feb 5;31(3):1732–1743. PubMed PMID: 33188384; PubMed Central PMCID: PMC7869098
c. Boutzoukas EM, O'Shea A, Albizu A, Evangelista ND, Hausman HK, Kraft JN, Van Etten EJ, Bharadwaj PK, Smith SG, Song H, Porges E, Hishaw GA, DeKosky S, Wu S, Marsiske M, Alexander GE, Cohen R, Woods AJ. Frontal white matter hyperintensities and executive functioning performance in older adults. Front Aging Neurosci. 2021 Jun 28;3:672535. PubMed PMID: 34262445; PubMed Central PMCID: PMC8273864
d. Nissim NR, O'Shea AM, Bryant V, Porges EC, Cohen R, Woods AJ. Frontal Structural Neural Correlates of Working Memory Performance in Older Adults. Front Aging Neurosci. 2016;8:328. PubMed PMID: 28101053; PubMed Central PMCID: PMC5210770.

Attention/Speed of Processing. Over the past ten years, I have studied attentional and processing speed in the brain using a variety of tES, behavioral and imaging research methods in healthy and patient populations to understand the relative contributions of brain systems to attentional and processing speed.

a. Hardcastle C, Hausman HK, Kraft J, Albizu A, Evangelista ND, Boutzoukas EM, O'Shea A, Langer K, Van Etten EJ, Bharadwaj PK, Song H, Smith SG, Porges E, DeKosky ST, Hishaw GA, Wu S, Marsiske M, Cohen R, Alexander GE, Woods AJ. Higher-Order Resting State Network Association with the Useful Field of View Task in Older Adults. Geroscience. 2022 Feb;44(1):131-145. PubMed PMID: 34431043
b. Kraft J, Albizu A, O'Shea A, Hausman HK, Evangelista ND, Boutzoukas E, Hardcastle C, Van Etten, EJ, Bharadwaj PK, Song H, Smith SG, DeKosky S, Hishaw GA, Wu S, Marsiske M, Cohen R, Alexander GE, Porges E, Woods AJ. Functional Neural Correlates of a Useful Field of View (UFOV) Based fMRI Task in Older Adults. Cereb Cortex. 2021 Sep 20. PubMed ID: 34541604
c. Woods AJ, Mennemeier M, Garcia-Rill E, Huitt T, Chelette KC, McCullough G, Munn T, Brown G, Kiser TS. Improvement in arousal, visual neglect, and perception of stimulus intensity following cold pressor stimulation. Neurocase. 2012;18(2):115-22. PubMed PMID: 22013983; PubMed Central PMCID: PMC3266979.
d. Woods AJ, Mennemeier M, Garcia-Rill E, Meythaler J, Mark VW, Jewel GR, Murphy H. Bias in magnitude estimation following left hemisphere injury. Neuropsychologia. 2006;44(8):1406-12. PubMed PMID: 16434066; PubMed Central PMCID: PMC4420160.

Cognitive Aging Interventions. Much of my current and past work focuses on identifying, implementing and assessing non-invasive interventions to facilitate successful cognitive aging and reduce the incidence of dementia later in life. This work has evaluated not only the cognitive and functional consequences of health and pathological aging, but also improvement in these processes through non-pharmacological interventions.

a. Kraft J, O'Shea A, Albizu A, Evangelista N., Hausman, H, Boutzoukas E, Nissim N, Van Etten E, Bharadwaj PK, Song H, Smith SG, Porges E, DeKosky S, Hishaw GA, Wu S, Marsiske M, Cohen R, Alexander GE, & Woods AJ. Structural Neural Correlates of Double Decision Performance in Older Adults. Front Aging Neurosci. 2020 Sep 2;12:278. PubMed PMID: 33117145 PubMed PMCID: PMC7493680
b. Anton SD, Woods AJ, Ashizawa T, Barb D, Buford TW, Carter CS, Clark DJ, Cohen RA, Corbett DB, Cruz-Almeida Y, Dotson V, Ebner N, Efron PA, Fillingim RB, Foster TC, Gundermann DM, Joseph AM, Karabetian C, Leeuwenburgh C, Manini TM, Marsiske M, Mankowski RT, Mutchie HL, Perri MG, Ranka S, Rashidi P, Sandesara B, Scarpace PJ, Sibille KT, Solberg LM, Someya S, Uphold C, Wohlgemuth S, Wu SS, Pahor M. Successful aging: Advancing the science of physical independence in older

adults. Ageing Res Rev. 2015 Nov;24(Pt B):304-27. PubMed PMID: 26462882; PubMed Central PMCID: PMC4661112.

c. Woods AJ, Cohen RA, Pahor M. Cognitive frailty: frontiers and challenges. J Nutr Health Aging. 2013 Sep;17(9):741-3. PubMed PMID: 24154645; PubMed Central PMCID: PMC4471842.

d. Woods AJ, Mark VW, Pitts AC, Mennemeier M. Pervasive cognitive impairment in acute rehabilitation inpatients without brain injury. PM R. 2011 May;3(5):426-32; quiz 432. PubMed PMID: 21570030; PubMed Central PMCID: PMC3275913.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/adam.woods.1/bibliography/45511051/public/

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Kristina Visscher, Ph.D.**

eRA COMMONS USER NAME (credential, e.g., agency login): **VisscherPI**

POSITION TITLE: **Associate Professor, Department of Neurobiology, UAB School of Medicine**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Carleton College, Northfield, MN	BA	1998	Physics
Washington University, St. Louis, MO	Ph.D.	2004	Neuroscience, Advisor - Steve Petersen
Brandeis University, Waltham, MA	Post-Doc	2004-2008	Neuroscience, Psychology, Advisor – Bob Sekuler
Harvard University, Cambridge, MA	Post-Doc	2008-2009	Neuroscience, Advisor – Randy Buckner

A. Personal Statement

The ultimate, long-term goal of my research is to contribute to an understanding of how the brain's processing of information is modified through experience, and how we can use that knowledge to improve patient outcomes. Over the past few years, my lab has focused on the aging brain, and in particular characterizing the brains of healthy agers and effects of cognitive training in older adults. Our lab recently completed the McKnight Brain Aging Registry, a consortium of 4 institutions (UAB, University of Florida, University of Arizona, and University of Miami). As part of this study, we developed a robust and comprehensive neuroimaging sequences (e.g., healthy oldest-old (85+) cortical parcellation) and examined brain networks interactions in cognitively healthy older adults as predictors of cognitive performance, specifically the role of brain networks in supporting overall cognition and processing speed (Sims et al.,2022). Additionally, our past work (e.g., Ross et al., 2019) has examined the effect of the same speed of processing training used in this proposal on brain activity and connectivity in older adults. The current proposal follows up on these ideas in a sample of patients with SCD. I am very excited to work on these new ideas with the team.

B. Positions, Scientific Appointments, and Honors

Professional Experience

2004-2008	Postdoctoral Fellowship, Brandeis University with Bob Sekuler, Psychology Department
2008-2009	Postdoctoral Fellowship, HHMI and Harvard University with Randy Bucker, Psychology Dept
2009-2017	Assistant Professor, Neurobiology, University of Alabama, Birmingham Secondary appointments in Ophthalmology, Psychology, Biomedical Engineering, Vision Sciences, Center for Aging, Civitan International Research Center, and McKnight Brain Institute
2016-present	Co-Director Civitan International Neuroimaging Laboratory, UAB

2017-present Associate Professor Neurobiology, University of Alabama, Birmingham
Secondary appointments in Ophthalmology, Psychology, Biomedical Engineering, Optometry, Center for Aging, Civitan International Research Center, and McKnight Brain Institute

Honors and Awards

1999-2002 NIH Systems Training Grant Fellow, Washington University in St. Louis
2003 Selected for and attended Complex Systems Summer School, Santa Fe Institute for Complex Systems
2004 Spencer T. and Ann W. Olin Fellow for Excellence in Biomedical Research, Washington University
2004-2006 NIH Training Fellow, Neurobiology: Genes, Channels and Behavior, Brandeis University
2006 Selected for and attended Neuroinformatics Summer School, Woods Hole Marine Biological Laboratory
2016 Kavli/National Academy of Sciences Frontiers in Science Fellow
2017 Graduate School Dean's Award for Excellence in Mentorship, UAB
2019 McNulty Civitan Scientist Award
2021 Outstanding Roadmap Scholars Research Mentor Award
2022 UAB President's Diversity Champion Award

C. Contributions to Science

1) Training influences information processing

Background: My lab has been examining in what ways experience shapes vision. We have manipulated 'visual experience' through extensive training sessions in the lab. The four papers highlighted here manipulated visual experience using extensive in-lab computerized training. Aggregated, our data shows that training can influence the efficiency of information processing. Central Findings: In (a) we used pupil diameter metrics to show improved efficiency of attentional resource allocation after training. In a later experiment (d), we used fMRI to show neural data consistent with training improving the efficiency of processing, as measured by decreases in neural activity in response to the stimuli. Our data suggest that improvements in efficiency are achieved through improvements in connection strength among the brain regions involved in performance of the task. In another experiment, in collaboration with another lab, we showed that a different perceptual learning task resulted in behavioral and EEG changes that were consistent with an improvement in efficiency through training (c). We were also able to rule out the possibility that changes in small eye movements called microsaccades give rise to training effects (for 'Speed of Processing' training), paving the way for better understanding of the neural mechanisms of training (b). Influence/Application: Together, this work shows that the effects of common training algorithms arise from processes at a higher level than simply changes in eye movements, and that such training influences efficiency of attentional resource allocation. This sets the stage for future work described in this proposal. Specific Role: I was PI on the projects in (a), (b) and (c), and co-PI on (d).

(a) Burge, W.K., Ross, L.A., Amthor, F.R., Mitchell, W.G., Zotov, A., **Visscher**, K.M. (2013). Processing speed training increases the efficiency of attentional resource allocation in young adults. Frontiers in Human Neuroscience 7:684. PMID: 24151461
(b) Layfield, S., Burge, W., Mitchell, W., Ross, L., Denning, C., Amthor, F., **Visscher**, K.M, (2014). The Effect of Speed of Processing Training on Microsaccade Amplitude. PLoS One 9, e107808. PMID: 25248099
(c) Ross, LA, Webb, CE, Whitaker, C, Hicks, JM, Schmidt, EL, Samimy, S, Dennis, NA, **Visscher**, KM (2018) The effects of useful field of view training on brain activity and connectivity, Journal of Gerontology B Psychological Sciences Society, 2018. Doi: 10.1093/geronb/gby041 PMID: 29757433
(d) Maniglia, M., Jogin, R., **Visscher**, K.M., and Seitz, A.R. (2020). We don't all look the same; detailed examination of peripheral looking strategies after simulated central vision loss. J. Vis. 20, 5.

2) Neural underpinnings of vision in older and vision impaired populations

Background: My long-term goal is to understand how experience alters the brain flexibility, especially in the context of low vision and age-related macular degeneration. To do this, we must understand the vision and and cognitive control systems in aging and low vision. Much of the work in my lab addresses this need, and has

studied and developed methods for better characterizing older and vision impaired populations. Central Findings: In older adults, we showed that two networks of brain regions associated with cognitive control show distinct relationships to different components of executive control (a). This work indicates that, in an older adult population, cortical thinning in specific brain regions can selectively predict task performance in executive function tasks. Importantly, especially for this application, we found that participants with macular degeneration (longstanding central vision loss, who typically use peripheral vision for daily tasks) showed thicker-than-control cortex in the areas associated with peripheral vision, consistent with increased use of peripheral vision leading to increased thickness (b). We have developed explicit methods for characterizing the oculomotor strategies that individuals with low vision use to compensate for their lost central vision (c), and developed precise methods for mapping arbitrary visual images to their cortical representations. Influence/Application: Together this work shows our group has the tools and expertise to examine older, low vision populations, as will be done in this proposal. Specific Role: I was PI on the projects in (a) and (d), and co-PI on (b) and (c).

(a) Schmidt EL, Burge WK, **Visscher** KM, Ross LA (2015) Cortical Thickness in Frontoparietal and Cingulo-opercular Networks Predicts Executive Function Performance in Older Adults. Neuropsychology Oct 12. PMID: 26460586
(b) Burge, W., Griffis, J., Nenert, R., Elkhetali, A., DeCarlo, D., ver Hoef, L., Ross, L., **Visscher**, K., (2016). Cortical thickness in human V1 associated with central vision loss. Scientific Reports, Mar 24, 6:23268 PMID: 27009536
(c) Maniglia, M., **Visscher**, K.M., and Seitz, A.R. (2020). A method to characterize compensatory oculomotor strategies following simulated central vision loss. J. Vis. 20, 15. PMID: 32965480
(d) Defenderfer, M., Demirayak, P., and **Visscher**, K.M. (2021). A method for mapping retinal images in early visual cortical areas. Neuroimage 245, 118737.

3) The brain flexibly shifts activity and connectivity depending on task state.
Background: The brain is always active, and recent conceptual advances in neuroscience have come from the realization that this constant ongoing neural activity and connectivity influences behavior. I have long been interested how ongoing (non-stimulus-driven) activity measured in visual cortical regions influences behavior. Central Findings: My graduate school work applied a technique for examining ongoing neural activity to a range of different tasks, showing, for example, that there are a core set of regions (the dorsal anterior cingulate and anterior insula/frontal operculum) which exhibit these sustained, task-driven signals in a wide range of tasks (a). This work is very highly cited (over 1300 times) in part because it makes clear that there is task state-related flexibility in patterns of activity. Later work in my lab extended this approach to show flexible modulation of sustained signals as well as transient, cue-driven signals in early visual areas, reflecting different control processes acting on sensory signals (c). EEG alpha power over the occipital lobe is also a measure of flexible task state. My lab's work showed that ongoing EEG alpha power is used by the healthy young adult brain to suppress irrelevant, potentially distracting information and that the flexibility of alpha power predicts performance (b). We identified that a set of right frontal regions flexibly shift their functional connectivity to be more strongly functionally connected to the part of cortex that is relevant for the current task, independent of stimuli (d). Importantly, this flexible shift in connectivity patterns relates to task performance. Influence/Application: This work sets the stage for understanding how this flexibility of functional connectivity is modified following experience, which is a goal of the current project. Specific Role: I collected and analyzed data for (a), and was PI on the projects in (b), (c), and (d).

(a) Dosenbach, N.U.F., **Visscher**, K.M., Palmer, E.D., Miezin, F.M., Wenger, K.K., Kang, H.C., Burgund, E.D., Grimes, A.L., Schlaggar, B.L., Petersen, S.E. (2006). A core system for the implementation of task sets. Neuron, 50(5):799-812. PMID: 16731517
(b) Nenert, R, Viswanathan, S, Dubuc, DM, **Visscher**, KM (2012). Modulations of ongoing alpha oscillations predict successful short-term visual memory encoding. Frontiers in Human Neuroscience 6:127. PMID: 22586390.
(c) Elkhetali, AS, Vaden, RJ, Pool, SM, **Visscher**, KM (2015) Early visual cortex reflects initiation and maintenance of task set. NeuroImage, (107, 277-278). PMID 25485712
(d) Elkhetali, A. S., Fleming, L. L., Vaden, R. J., Nenert, R., Mendle, J. E., & **Visscher**, K. M. (2019). Background connectivity between frontal and sensory cortex depends on task state, independent of stimulus modality. NeuroImage, 184, 790–800. PMID: 30237034

4) Cortical Representations of central and peripheral vision show distinct connectivity and activity

Background: As a prerequisite to examine how neural activity in the cortical representations of peripheral vision are altered with experience, my lab has carefully described the activity, connectivity and structure of central vs. peripheral vision in healthy adults. Central Findings: Importantly, their patterns of flexibility with attention are different for central vs. peripheral representations (a). Further, we find that there are reliable differences in the functional connectivity of central vs. peripheral representations, that change based on task demands (b), in particular frontoparietal regions are more strongly connected to central representations than peripheral representations. This pattern is mirrored in structural connections (d). Influence/Application: This work shows that the portions of visual cortex corresponding to central vision are more strongly connected to regions that are important for cognitive control than are portions corresponding to peripheral vision. Specific Role: I am the PI on each of these projects.

(a) Griffis, JC, Elkhetali, AS, Vaden, RJ, **Visscher**, KM (2015) Distinct effects of trial-driven and task set-related control in primary visual cortex. Neuroimage 120, 285–297. PMID 26163806
(b) Griffis JC, Elkhetali AS, Burge WK, Chen RH, **Visscher** KM. (2015) Retinotopic patterns of background connectivity between V1 and fronto-parietal cortex are modulated by task demands. Front Hum Neurosci. Jun 8;9:338. PMID: 26106320

(c) Griffis, J., Elkhetali, A., Burge, W., Chen, R., Bowman, A., Szaflarski, J., & **Visscher**, K. (2017). Retinotopic patterns of functional connectivity between V1 and large-scale brain networks during resting fixation. NeuroImage, 1, 1–13. PMID: 27554527
(d) Sims, S.A., Demirayak, P., Cedotal, S., and **Visscher**, K.M. (2021). Frontal cortical regions associated with attention connect more strongly to central than peripheral V1. Neuroimage 238, 118246. PMID: 3411151

5) Representations of stimuli are influenced by the context of their presentation
Background: My work has examined how current context and memory for previous information influence the representation of stimulus information. Central Findings: In an early study (a) I showed that extensive training influenced the validity of monkeys' memory for visual location: more experience with a stimulus at a particular location in space led to changes in their memory for that location. In (b), we used fMRI to examine how stimulus processing differed between trials where a participant experienced lapses in attention; we found that lapses in attention resulted in a brain-wide a pattern of differential stimulus processing. A postdoctoral fellowship with Bob Sekuler allowed me to immerse myself in quantitative models of short term memory. We showed that auditory short-term memory showed very similar characteristics to visual short term memory (c). Among other similarities, both auditory and visual short term memory fit a 'noisy exemplar' model, in which short term memory for an object is influenced by the other items in memory. Additionally, we found that this influence does not stop on an individual trial, but also depends on items from memory on previous trials (d). Influence/Application: Together this work characterizes how memory representations are modified by context, including other items in memory and task state. Specific Role: I am the first author, who devised the experiments, collected, analyzed data, and wrote the paper for (a,c,d), and was a contributing author helping with devising the experiments and writing the paper in (b).

(a) **Visscher**, K.M., Viets, E., Snyder, L. (2003). Effects of training on memory-guided saccade performance. Vision Research, 43: 2061-71. PMID: 12842159
(b) Weissman, D.H., Roberts, K.C., **Visscher**, K.M., Woldorff, M.G. (2006). Zoning out: The neural bases of momentary lapses in attention. *Nature Neuroscience*, 9(7): 971-8. PMID: 16767087
(c) **Visscher**, K.M., Kaplan, E., Kahana, M.J., Sekuler, R. (2007). Auditory short-term memory behaves like visual short-term memory. PLoS Biology 5(3):e56. PMID: 17311472
(d) **Visscher**, K.M., Kahana, M.J., Sekuler, R. (2009). Trial-to-trial carry-over in auditory short-term memory. Journal of Experimental Psychology: Learning Memory & Cognition 35(1):46-56. PMID: 19210080

Complete List of Published Work: https://www.researchgate.net/profile/Kristina_Visscher

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: A Single Arm Intervention Study to Evaluate Effects of Personality Traits on Efficacy of Processing Speed Training in Individuals with Subjective Cognitive Decline

Principal Investigator(s): Giovanna Pilonieta

Institutions: University of Alabama at Birmhingham & University of Florida

OVERALL IMPACT

Please provide your assessment of the strengths and weaknesses of the application using brief bullet points to reflect the project's likelihood to exert a sustained, powerful impact on the research field(s) involved, using the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact. Please score the application's potential using the following 1 (Highest Impact) to 9 (Lowest Impact) rating scale for each review criteria section:

Impact	High	Medium	Low
Score: 3	1 2 3	4 5 6	7 8 9

Overall Impact 7

This is a single arm clinical trial to determine whether personality traits moderate the effects of Processing Speed Training (PST) on cognitive and functional outcomes in older adults with subjective cognitive impairment. The identification of moderators of the impact of cognitive interventions is a significant public health issue. Members of the investigative team are experts in their respective fields. The environments are ideal for the proposed work. Although this proposal exhibits many strengths, multiple weaknesses were noted. The significance of the chosen intervention is unclear. The PI seems to have no experience running studies. There does not appear to be much in the way of innovation. In terms of approach, the conceptual model to be tested is unclear and there are multiple details missing that would influence interpretability and generalizability of results. This proposal is viewed as having some strengths; however, significant weaknesses in significance, innovation, and approach diminished enthusiasm for this proposal. Because of this, it is received with a low level of enthusiasm.

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance 6

Strengths

- The identification of moderators of the impact of cognitive training is a significant public health issue.

Weaknesses

- The links between personality traits, cognitive abilities, SCD are not very well appreciated for their significance to ADRD.
- The link between personality traits and SCD are well-established so this seems less significant.
- The significance section talks about CCT but almost no explanation is given on why PST was selected.

2. Investigator(s) 4

Strengths

- Giovanna Pilonieta as PI has a breadth of experience in research and particularly statistical analysis.
- Dr. David Geldmacher has significant experience in research related to neurological functioning.
- Dr. Kristina Visscher is a well-trained neuroscientist.
- Dr. Adam Woods is an expert trialist.

Weaknesses

- The PI has very little experience running a study based on provided materials.

3. Innovation 5

Strengths

- The knowledge of how specific personality characteristics may modify the impact of a particular intervention could be innovative.

Weaknesses

- I honestly don't see a lot of innovation here. The methods are not innovative and the conceptual model is not innovative.

4. Approach 8

Strengths

- Leveraging of existing resources is a strength.

Weaknesses

- The approach is surprisingly sparse in terms of details that are important for interpretation of findings.
- It is unclear how SCD will be operationalized based on the definition.
- Race, culture, or socioeconomic status does not appear to be considered at all.
- A Beck Depression Inventory score of 19 is indicative of mild depressive symptoms and these could have a complicating impact on personality measures.
- The neuroimaging approach is not clear.
- A "normal" score for MoCA is inclusion criteria "adjusted for age, sex, and education" but it is not clear what metric is used for this. There are different cut-off score conventions depending on demographics.
- "Adherence and dose exposure for training will be evaluated by usage tracking". How will these metrics be utilized? Not clear based on statistical approach.
- Site is not considered in statistical models.
- The conceptual model to be tested is unclear.

- Why was Posit Science chosen? This is unclear.

5. Environment 1

Strengths

- UAB and UF are truly excellent environments for this proposed work.

Weaknesses

- None noted.

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes:

Strengths

- The separate institutes are excellent.

Weaknesses

- It is unclear how much collaboration the institutes have done together.

2. Potential for clinical translational impact of the intervention on cognitive aging and memory

Strengths

- The identification of moderators of interventions is a significant public health pursuit.

Weaknesses

- Personality disorders are difficult to treat and therefore I am unsure how much translational impact this work will have.

3. Potential for future NIH funding of the research

- I see this as relatively low in term of possible future NIH funding.

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: A single arm intervention study to evaluate effects of personality traits on efficacy of processing speed training in individuals with subjective cognitive decline

Principal Investigator(s): Giovanna Pilonieta

Institutions: UAB, UF (? – research plan is unclear about additional site(s))

OVERALL IMPACT

Please provide your assessment of the strengths and weaknesses of the application using brief bullet points to reflect the project's likelihood to exert a sustained, powerful impact on the research field(s) involved, using the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact. Please score the application's potential using the following 1 (Highest Impact) to 9 (Lowest Impact) rating scale for each review criteria section:

Impact	High	Medium	Low
Score: 6	1 2 3	4 5 6	7 8 9

Overall Impact *Write a brief paragraph summarizing the factors that informed your Overall Impact score.*

The overall focus on non-pharmacologic interventions is both timely and valuable as is the multi-method approach to evaluating outcome. The study team is certainly strong and well suited for the project. The environment is strong. Significant concerns centered around the underdeveloped nature of the proposal. Additional details are needed to support the potential link between personality traits (which are ill-defined and may show overlap with more objective "clinical" measures) and cognitive training. A number of methodlogical gaps were identified that limited enthusiasm and that are described below. Addressing these factors would increase the project's viability and ultimate feasibility for external funding.

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance

Strengths

- Identifying individual level factors associated with cognitive training effects is timely and important
- Identifying mechanistic effects of cognitive training is important

Weaknesses

- Focus on personality traits overlooks a more plausible role of a) awareness of deficits and b) motivation for (or "buy in to") the training program. Justification for study rests on negative findings from prior trials rather than a more clearly developed rationale linking the constructs. Multipel meta-analyses & systematic reviews (including Cochrane reviews) have reported CT effects, which seems to undermine the stated hypotheses.
- Prior data clearly show within-domain improvement but show little to no cross-domain effects. While some data support functional skill improvement, such tasks are not measured, integrated, nor necessarily unique to PST (e.g., prior reports of training specific effects on IADLs from the

ACTIVE trial show a ~4 person difference in conversion to dementia vs. other active interventions – the effect sizes were nearly identical between interventions).

- Unclear how investigators will disentangle "personality" from early "psychiatric" changes that can arise with neurodegenerative disease onset (i.e., concept of mild behavioral impairment).
- Ramifications of the work are unclear in terms of pragmatic next-steps

2. Investigator(s)

Strengths

- Outstanding study team

Weaknesses

- None noted

3. Innovation

Strengths

- Multi-modal investigation of cognitive training effects

Weaknesses

- Several questions could likely be addressed using existing study data (e.g., ACTIVE, ACT, etc).

4. Approach

Strengths

- All procedures are well-known to the study team.
- Robust infrastructure that supports study feasibility.

Weaknesses

- Poor alignment between SCD definition (i.e., MFQ) and CCT approach. The technique matters and CCT often has little to no effect on memory functioning (i.e., cross domain transfer), which undermines the purpose of the study. Selecting CT tasks that more precisely target the constructs of interest would enhance the project.
- Study design is unclear. The brief description suggests a cross-over design but the cross-over condition is not discussed. Long-term effects are not measured (as best I can tell) which seems to undermine stated hypotheses. The budget justification says 20 people will be enrolled while the proposal says 40. Unclear if this is a single or multi-site study (budget justification implies two sites but information should be included in the research plan).
- Selection criteria are suboptimal as "normal" MoCA score is undefined, neuropsych tests use an arbitrary cutoff of -1.5 SD that fails to endorse the acturarial approach suggested by Bondi and colleagues or recognize the impact of high/low baseline functioning, and present a confusing picture in terms of psychiatric history (e.g., major psychiatric conditions are undefined but

seemingly could include those with a history of MDD who are now report only mild symptoms and are on medication).

- Study timeframe is insufficient for evaluating maintenance effects and can only detect improvement. Selection criteria (i.e., individuals do not need to show proessing speed deficits) truncates range of improvement.
- Composite score is unjustified (e.g., no factor analysis) and seems to contain one of the trained tasks (UFOV) as well as CERAD tasks that are also included in UDS-3. Unclear whether change on each outcome measure will also be measured independently, which seems to be the case and raises a host of other questions.
- A growing body of evidence is revealing the limitations of resting-state vs. task-based fMRI. Justification for resting-state is needed, especially when considering the flexible state of networks as it relates to task performance. Other factors known to affect processing speed (e.g., white matter hyperintensities) are not measured or considered.
- Statistical plan is underdeveloped for both neuropsychological tests and fMRI. Stated effect size from prior studies is lower than the predicted outcome. Specific contrasts/analyses are not clear.

5. Environment

Strengths

- Strong environment(s) with all necessary resources

Weaknesses

- Unclear if multiple sites are involved and, if so, how activities will be coordinated and rigor applied.

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes:

Strengths

- Budget justification suggests cross-institute collaboration but it is not noted in the proposal

Weaknesses

- The research plan should clearly state if multiple sites are involved; it does not appear to.

2. Potential for clinical translational impact of the intervention on cognitive aging and memory

Strengths

- Enhanced understanding of CT effects is of value

Weaknesses

- Relationship with ill-defined personality factors is tenuous and may have nominal translational impact.

3. Potential for future NIH funding of the research

- Funding may be challenging given the number of more proximal factors affecting cognitive training and the somewhat ill-defined nature of personality traits.

UNIVERSITY OF MIAMI
SCHOOL of EDUCATION
& HUMAN DEVELOPMENT

LABORATORY OF
NEUROMUSCULAR RESEARCH
AND ACTIVE AGING

June 30, 2022

McKnight Research Foundation (MBRF)
Cognitive Aging and Memory Intervention Core
Inter-institutional Pilot Program

Dear MBRF Foundation members,

We are pleased to submit our proposal, "Cued high-speed multidirectional yoga: Impact on retinal microvascular and cognitive measures" for your review. Our research team includes Drs Signorile, Wang and Jiang from the University of Miami and Dr Ebner from the University of Florida. The proposed YogaCue program includes high-speed intervals to address cardiovascular fitness, and multi-directional responses to visual and auditory cuing, with pattern recognition and retention to address multiple cognitive domains. We will use changes in the retinal microvasculature and capillary function and targeted cognitive testing to assess the success of the YogaCue program.

We suggest:
Dr. Eric Porges, Department of Clinical and Health Psychology, University of Florida, eporges@ufl.edu
Dr. Kristina Visscher, Department of Neurobiology, University of Alabama, kmv@uab.edu
Dr. Ronald Lazar, Department of Neurology, University of Alabama, rlazar@uabmc.edu

as potential reviewers.

We look forward to your review of our proposal and thank you for your consideration.

Sincerely,

Joseph Signorile, PhD
Professor
Department of Kinesiology and Sport Sciences, University of Miami

Cued high-speed multidirectional yoga: Impact on retinal microvascular and cognitive measures

Key Personnel:

University of Miami

Joseph F. Signorile, PhD: Professor and Director
Site: The Laboratory of Neuromuscular Research and Active Aging, Max Orovitz Laboratory Complex, Department of Kinesiology and Sport Sciences

Jianhua Wang, MD: Professor and Director
Site: Advanced Ophthalmic Imaging Laboratory, Bascom Palmer Eye Institute.

Hong Jiang, MD, PhD: Clinical Associate Professor
Site: Advanced Ophthalmic Imaging Laboratory, Bascom Palmer Eye Institute.

University of Florida

Natalie Ebner, PhD, Associate Professor and Director
Site: Social-Cognitive and Affective Development Laboratory, Department of Psychology

Principle Investigator:
Joseph F. Signorile, Ph.D.
Max Orovitz Laboratories
Department of Kinesiology and Sports Sciences
1507 Levante Ave
Coral Gable, FL 33146
jsignorile@miami.edu

RESEARCH PLAN

PROJECT SUMMARY

The number of Americans 65 years of age and older is projected to increase to 88.5 million by 2050.[1,2] Furthermore, cognitive decline is nearly universal with age.[3,4] The rate of decline is modifiable by factors such as education, physical conditioning, and cognitive training. Normal cognitive declines with age are generally in fluid intelligence, specifically, executive function (EF), processing speed, memory, and psychomotor ability.[5,6] Aerobic and anaerobic physical exercise (PE) can positively affect cognitive capacity, increase cerebral blood flow and reverse cerebral small vessel disease.[7-11] Nonetheless, these interventions are often applied too late, or are impractical, given their space and equipment requirements. Further, the tools to evaluate the impact of PE on the cerebral vasculature (E.g. magnetic resonance imaging) are not accessible or cost-efficient for routine clinical use. Yoga is the nation's fastest growing exercise intervention;[12] however, it provides neither the exercise intensity,[13-15] nor cognitive challenge,[16-19] to optimally address cognitive decline. The novel YogaCue program proposed here includes high-speed intervals to address exercise intensity and visual and auditory cuing with pattern recognition and retention to incorporate multiple cognitive domains. Further, this grant will establish imaging of retinal microvasculature and microcirculation, which shares anatomic and physiologic features with the brain, as an accessible and cost-effective clinical tool to evaluate the influence of YogaCue. This is the first step toward our long-term goal of establishing the relationship between the vasculature and circulation of the retina and brain in response to PE. We will compare the effectiveness of YogaCue and standard Hatha yoga using changes in cognition and retinal microvasculature, as well as aerobic and neuromuscular performance. Finally, we will determine the relationships between changes in retinal and cognitive variables and changes in physical performance. Our interdisciplinary approach will: (1) examine the effectiveness of YogaCue as a low-cost, enjoyable, and accessible multimodal prevention tool to improve cognitive, cardiovascular and neuromuscular performance and enhance retinal microvasculature and microcirculation; (2) confirm the use of microvascular and microcirculation changes as markers cognitive change; thereby reciprocally improving care management; (3) involve upcoming researchers, who will gain hands-on experience in cutting edge interventional aging research; thereby inspiring the next generation of researchers in the field.

SPECIFIC AIMS

Aim 1: Determine if YogaCue will improve cognition, aerobic capacity, strength, power, and retinal microvasculature and microcirculation to a greater degree than standard Hatha yoga in cognitively unimpaired older adults. *Rationale and hypothesis:* Since YogaCue includes interval training and cuing for specific movement patterns, we will test the hypothesis that YogaCue improves cognitive, aerobic, and neuromuscular performance, as well as retinal capillary perfusion density, to a greater extent than Hatha yoga in cognitively unimpaired older persons. *Approach*: 40 cognitively unimpaired older adults (≥ 65 years) will be randomized to YogaCue or an active control (Hatha yoga) for 6 months (3x/week). Retinal vascular measures, cognition, and cardiovascular and neuromuscular fitness will be assessed before and after training. **Aim 2: Determine the extent to which changes in retinal microvasculature and microcirculation are related to cognitive function.** *Rationale and hypothesis:* We have previously demonstrated that high-velocity circuit training (HVCT), a specialized form of interval training, can improve retinal microvascular structure,[20], vessel density[21], capillary function[22] and tissue perfusion[23], as well as cognitive function[20,21,24,25] Therefore, this aim tests the hypothesis that changes in cognitive function due to YogaCue relate to retinal vascular changes. *Approach:* Correlations among cognitive tests and retinal vascular variables will be determined. **Aim 3 (Exploratory): Determine relative contributions of neuromuscular and cardiovascular fitness changes to retinal microvascular, microcirculation, and cognitive changes.** *Rationale:* Given that retinal microvascular structure and function change with neuromuscular training,[26-28] cardiovascular training,[29-31] and to a greater extent, the combination of the two, [32] and that better results have been demonstrated using combined cognitive and PE interventions than PE or cognitive training alone;[17-19] [33-37] this aim tests the degree to which changes in cognitive function and retinal vascular variables are associated with changes in neuromuscular and cardiovascular improvements. *Approach:* Stepwise regression will be used to assess contributions of neuromuscular and cardiovascular changes to changes in cognitive and retinal variables.

RESEARCH STRATEGY

Significance

There is a critical need to develop and monitor interventions that reduce levels of age-related cognitive decline. PE can ameliorate declines in working memory, cognitive flexibility, and inhibitory control of EF;[38] however, the most effective exercise prescription remains undetermined.[39] Overground and treadmill walking have produced cardiorespiratory improvements[30] and improved EF, attention, memory, and cognitive flexibility.[29,31] Further, resistance training programs targeting strength and hypertrophy have produced positive changes in cognition.[26-28] While aerobic training is often considered optimal,[40,41] high-intensity interval training has proven more effective in improving cognition and depression than moderate intensity continuous exercise in multiple populations; [42,43] and high-intensity intervals provide an effective stimulus for increasing brain-derived neurotrophic factor (BDNF).[44,45] In

fact, a muscle-brain endocrine loop, with skeletal muscle as the secretory organ, has been established in animal and human models due to aerobic exercises;[46-51] while metabolites from the anaerobic component of intervals can pass the blood-brain barrier, improving metabolic health, neurogenesis, cognitive function and brain health.[52,53] High-intensity intervals are also more effective than steady-state exercise in promoting cerebral angiogenesis allowing increased delivery of oxygen, glucose and neurotropic factors to promote and support brain plasticity.[10,11] Research also supports concurrent (endurance and resistance training) or multicomponent training (aerobic, strength, balance etc.) over training targeting a single fitness variable.[39,54] **Our preliminary results indicate that HVCT can maximize cardiovascular benefits, increase strength and power, and improve EF in older adults**,[32,55] and improve memory and processing speed in persons with severe mental illness.[56] Muscle mass maintenance is correlated with decreased risk of ADRD,[26] and age-related decreases in leg power can predict cognitive decline.[57] Also, high-speed power training increases cognitive function to a greater degree than low-speed strength training.[58] Unfortunately, (1) these training programs are equipment-dependent, reducing their accessibility; and, (2) low-cost, clinically accessible tools for monitoring the impact of exercise on cerebral vascular markers of cognitive change are currently unavailable. **Yoga, which is quickly becoming a favorite non-medical therapy,[12] can improve satisfaction levels in older female practitioners,[59] and has modest equipment and space requirements; h**owever, traditional yoga provides limited cognitive overload and does not include the aerobic and power training components, critical to improving memory. Unlike traditional yoga, our novel YogaCue program includes high-speed intervals, to increase upper and lower body power,[60] and oxygen consumption;[15] while requiring multi-directional responses to congruent and incongruent visual and auditory goal-based cuing, as well as pattern recognition and retention, to address multiple cognitive domains.[17] Finally, as a multi-domain training program, YogaCue should produce better results than PE or cognitive training alone.[16,18,19] In addition, easily accessible clinical markers must be established to monitor neurovascular responses to this, or any, PE program.[24,61] **Neurovascular responses to YogaCue can be directly monitored through visualization of the retinal microvasculature; as the brain and retinal vasculature share anatomic and physiologic features**.[62,63] The transparent ocular media allow studying of the retinal microvasculature and microcirculation in vivo; and changes in these variables reflect changes in the brain.[64] Indeed, normal aging alters the retinal microvasculature[65,66] as does ADRD.[67-69] As in the brain, alterations in retinal microvasculature may precede large vessel changes; therefore, the retinal microvascular system offers a unique opportunity to address the critical needs to monitor YogaCue's effects on cognitive function and the cerebral microvasculature.

Innovation

Our proposal is innovative, as it examines the efficacy of our unique multicomponent YogaCue program in improving cognitive function and cerebral blood flow, as measured through retinal microvascular changes. This provides: (1) a low-cost, accessible intervention for improving age-related cognitive decline and delaying, if not preventing, ADRD; (2) a clinically-accessible tool to quantify cerebral vascular changes due to PE; and, (3) an improvement in care management through their reciprocal use. Further, the Max Orovitz (MO) laboratory provides a unique setting for developing and administering YogaCue and evaluating fitness and cognition. We have been developing programs to target the specific needs of older persons for 25 years, with 7 years of experience modifying yoga practices to improve functional performances in elders with and without neuromuscular disease.[70-74] The doctoral student (KC), who will serve as the project coordinator and teach YogaCue classes, has over 5 years of experience teaching yoga, holds a Master's degree in Exercise Science, and intends to pursue the topic of PE as an intervention for age-related cognitive decline following matriculation. The laboratory has sufficient space for teaching YogaCue and possesses the computerized equipment and assessment techniques to measure the variables necessary to test our hypotheses.

C.2. The combination of novel modalities for non-invasive imaging of retinal microvasculature, microcirculation, and microstructure at the UM Bascom-Palmer Advanced Ophthalmic Imaging laboratory, directed by Drs Wang and Jiang. Bascom-Palmer Vision Laboratory A incorporates advanced ophthalmic imaging modalities that will provide unique measures of retinal blood flow,[25] tissue perfusion,[25] capillary density;[24] and recently developed retinal capillary function.[22] Our approach makes innovative use of a suite of advanced ophthalmic imaging devices, including: 1) OCTA for evaluating retinal capillary perfusion density (CPD) in different vascular plexuses using fractal analysis and normalization using corresponding tissue volume;[65] 2) retinal microstructure, including tissue volumes of intraretinal layers.[65,75] 3) retinal microcirculation (retinal blood flow and tissue perfusion),[25] and 4) retinal capillary function (see method).[22] Using these advanced imaging modalities and approaches to evaluate the neuro-vascular system at the micrometer level enables us to collect critical data to test our hypotheses and set the stage for our long-term goal of establishing the relation between retinal and brain vasculature and circulation in response to PE.

C.3. Our interdisciplinary approach, involving ophthalmology, kinesiology, cognitive science, and engineering, directly addresses the critical need for accessible interventions and assessment techniques to address ADRD.

Approach

Forty cognitively unimpaired older adults (≥ 65 years) will be randomly assigned to perform YogaCue or an active

control (standard yoga) for 6 months (three 1-hour sessions/week). Cognition, retinal vascular measures, and fitness levels will be assessed before and after 6 months. YogaCue is based on our high-speed interval power yoga program, which incorporates rapid vinyasa sequences, and has been proven safe and effective with Parkinson's patients of the same age (71.2 ±6.5 y) as the proposed population.[72,73] We have shown that this program increases muscle activation patterns,[60] energy expenditures and oxygen utilization patterns[15] to a significantly greater extent than traditional yoga, and meets or exceeds the criteria of moderate-intensity aerobic exercise.[15,76] This is considerably important given the impact of aerobic exercise on cognitive decline and deterioration of brain structures due to oxidative stress, free radicals and mitochondrial instability, and subsequent lower ATP production.[77,78] Further, YogaCue combines the instructor's auditory and visual cues with mats embossed with four colored lines indicating different movement patterns (yoga flows) to construct an enriched environment (see Figure 1). Enriched environments, whether provided through computer-gaming[75] or physical environment,[16] positively affect cognition. Finally, as a multi-domain training program, YogaCue should produce better results than PE or cognitive training alone.[17-19,33-37] Recently, we have shown that high-velocity circuit resistance training (HVCT), an intervention which provides similar moderate aerobic overload to YogaCue, is effective in improving aerobic fitness, and cognitive measures in older individuals.[23,25]

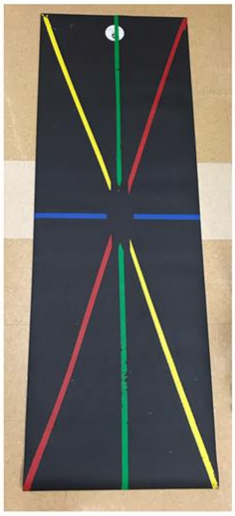

Figure 1. Yoga Mat with embossed lines to allow color cuing for changes in YogaCue pose sequences (Flows).

The YogaCue Program: YogaCue combines sequences of flows (pose progressions) and visual and auditory cuing, to challenge subjects' abilities to: remember the links between cues and flows (working memory); respond correctly to changing cues (adaptable thinking); and, react correctly to congruent and incongruent cues. Also, subjects will need to develop muscle utilization patterns in response to visual, auditory, and mixed cuing, targeting psychomotor ability and fluid intelligence. YogaCue will employ monthly changes to target different cognitive domains; and cognitive load will increase across the program to ensure sufficient overload for continued progress. As the study progresses, pose durations will decrease, while the transition speeds will increase to provide greater aerobic and neuromuscular overload. Participants will be encouraged to conceptualize an informal game-based environment to maximize gains and reduce anxiety. We have used this to increase adherence in computer gaming,[79] yoga,[60,70-72,74] and functional training interventions.[71,73,80-82] YogaCue, *Month 1* will focus on familiarization with flows, concentrating on proper alignment, and reducing injury risk. The instructor will call out the flow number before flow begins. The flow order will not change throughout the month to allow familiarization. For *Month 2*, weeks 1 and 2, each flow will be linked a color on the yoga mat (Flow 1, Flow 2, Flow 3, Flow 4). The instructor will say the color associated with a flow. The sequence will be the same as Month 1 to facilitate associations between flows and colors. This addresses the memory, similar to Part B of the Hopkins Verbal Learning Test. During weeks 3 and 4 of Month 2, signs with the colors: green, red, blue, and yellow will be substituted for auditory cues, and the presentation order will remain constant. *Month 2* requires switching from recalling auditory to visual cues, challenging cognitive flexibility and EF, as measured in the Dimensional Change Card Sort test. Episodic memory (recognizing past events: Picture Sequence test) is also required to recall which flow to perform based on colors previously seen and heard. *Month 3* requires participants to remember the colors associated with each flow and perform the flows in a *randomized orde*r. For weeks 1 and 2 of Month 3, the instructor will announce a color, and the associated flow will be performed until all four flows are performed. During weeks 3 and 4 the color signs will be substituted for verbal cues. *Month 4* will be a recovery phase. Weeks 1 and 2 will use slow flow, deep stretch classes emphasizing body awareness and slow breathing. Weeks 3 and 4 of Month 4 will re-introduce the original yoga protocol using verbal and visual cues, respectively. *Month 5* will incorporate the auditory cues as used during the first two weeks; but a gong will now precede the verbal cue indicating a color (flow) change, and therefore, a different flow. The colors yellow-red and blue-green will be paired together. When the instructor hits the gong and says "Blue," the subject should perform the complementary flow in the pair, or the green flow (flow 1); while on the verbal cue "Green" the subject should perform the blue flow. These same conceptual patterns will be used for the red-yellow pair. This part of the protocol trains EF and complex attentional processes/inhibition, since the subject must suppress the response of performing the flow related to the color that is stated, and perform the flow indicated by its colored pair (similar to performance probed in the Stroop task, which requires subjects to attend to relevant and ignore irrelevant cues). During weeks three and four of Month 5, the instructor may or may not use the gong or bell prior to vocalizing a color. During *Month 6* all cues learned during the previous months will be utilized by the instructor. Additionally, the flows will be continuous, rendering the ability to process cognitive tasks quickly to maintain the speed of the class as an integral part of the yoga flows. This capacity is associated with the Pattern Comparisons Processing Speed test, which requires the subject to quickly and correctly compare pictures to determine if they are the same. This final month of YogaCue also incorporates participants' abilities to process visual, auditory, and working memory and to execute the appropriate yoga flow, similar to the List Sorting Working Memory Test which gives auditory and visual cues for the participant to sort in a specific order. Further, the five categories of

psychomotor skill associated with Dave's taxonomy[83,84] (Imitation, Manipulation, Precision, Articulation, and Naturalization) will each be targeted throughout the YogaCue workout as new cues are introduced and responses are learned and perfected.

Cognitive Testing. Since the greatest neurocognitive changes seen with aging are in fluid, rather than crystallized, intelligence,[5,62] our testing battery will focus on fluid cognition changes with training. The neurocognitive battery will consist of well-established measures that show high sensitivity in detecting early cognitive impairment in older persons and consist of tests to evaluate EF, processing speed, memory, and psychomotor ability and will include. the Hopkins Verbal Learning Test,[85,86] the Trail Making Test (TMT) part A and B,[87] and the composite score from the Fluid Cognition Composite Score (FCCS) from the NIH Toolbox Cognitive Function Battery,[88] which includes Dimensional Change Card Sort,[89] Flanker,[90] Picture Sequence Memory,[91] List Sorting,[92] and Pattern Comparison measures.[93]. The battery will be administered both at baseline and after YogaCue training.

Ocular imaging and measurements: Ocular imaging will be performed at baseline and 6M. Retinal blood flow (RBF) will be measured using a retinal function imager (RFI). Retinal capillary density (RCD, expressed as fractal dimension, Dbox) and intraretinal layer thicknesses and volumes will be measured by optical coherence tomography angiography (OCTA). Retinal tissue perfusion (RTP) will be calculated as the RBF divided by the corresponding tissue volume. Volumetric vessel density (VVD) will be calculated as RCD divided by corresponding tissue volume. Retinal capillary function (RCF), representing the ability of blood transfer per unit of capillary, will be calculated as RBF divided by corresponding RCD.[22]

The retinal blood flow measurement using an RFI (model 3000, Optical Imaging, Rehovot, Israel) has been reported.[65,66,94] Using a recording of high-speed fundus photos with repeated flashing, the retinal blood flow velocity is recorded and measured. The measurement is based on tracking the motion of erythrocytes in a series of fundus photos. First, the blood flow velocity is obtained. Second, blood flow volume in arterioles and venules is measured in the vessel segments crossing a circle with a diameter of 2.5mm centered on the fovea.[65,67,95] The sum of blood flow in all arterioles or venules crossing the 2.5mm circle is calculated separately. Since the blood flow in the arterioles and venules has been found to be approximately equivalent,[68] the averaged blood flow from the arterioles and venules represents blood flow supply.

Optovue OCTA device (AngioVue, Optovue Inc., Fremont, CA) will be used to measure CPD. The system has been widely used to image retinal microvasculature in a non-invasive way. The OCTA system runs at a scan speed of 70,000 A-scans per second, and an area 3 x 3 mm center on the fovea will be scanned. The total retinal vascular network (RVN) data will be exported. After that, the RVN Angio image will be processed using the custom software described previously.[65,96] In brief, the image is processed using a series of image processing procedures to remove background noise and generate binary images. After removing the large vessels with a diameter ≥ 25 μm, the remaining small vessels (mainly capillaries) are analyzed using a fractal analysis software program (Benoit Pro 2.0, TruSoft International, Inc., St. Petersburg, FL, USA). The avascular zone in the fovea has been estimated in a diameter of 0.6 mm.[97] Box counting method will be used in fractal analysis to yield CPD as expressed as Dbox in the annulus from 0.6 to 2.5. [65,96] RCF is defined as the ratio of RBF and CPD with the unit of nl/s/Dbox, meaning in the given time (per second), the ability of the capillary bed (per Dbox) to transfer the amount of blood flow volume (i.e., nl). The AngioVue OCTA system does not provide the ability to segment the layers in the macular area of a diameter of 2.5 mm centered on the fovea. Therefore, the dataset of the OCT scans can be exported from the OCT device and input into the Orion software program (Orion, Voxeleron LLC, Pleasanton, CA, USA) for segmenting intraretinal layers and obtaining tissue volumes of these segmented layers.[65,67,95,98]

An ophthalmic examination will be conducted to confirm eligibility. These examinations included best-corrected visual acuity, intraocular pressure (IOP), and a slit-lamp examination of anterior and posterior segments. Exclusion criteria included the presence of diagnosed dementia or MCI, refractive error greater than ± 6 diopters (D), obvious ocular media opacity, macular degeneration, and glaucoma. Other exclusion criteria were cardiovascular diseases or systemic diseases such as a history of stroke, coagulopathy, uncontrolled hypertension, and diabetes. After pupil dilation, all metrics of both eyes will be taken at baseline and 6M.

Aerobic capacity testing: Aerobic capacity will be tested before and after the 6-month training period. The Max Orovitz Laboratory has been assessing training-induced changes in oxygen consumption in older persons for over a decade.[15,99-104] Although graded treadmill tests with ergospirometry[15,99-104] were the most common; field tests were often used when population size is large[32,105] or when assessing at-risk populations.[56,106] Currently, we are employing the formula of Ross et al., validated in 1,083 cardiopulmonary disease patients, with the six-minute walk test (6MWT) to assess oxygen consumption.[107] Further, a regression model developed in 156 community-dwelling elders showed that 6MWT distance could be used to classify seniors by physical capacity.[108] The 6MWT was validated against treadmill walking duration to 85% predicted maximal heart rate in 37 older community-dwelling individuals by Rikli and Jones,[109] who also reported day-to-day reliability to be excellent (R = .91-.94). Kervio et al.[110] confirmed 6MWT validity and reliability as a measure of cardiovascular function in older adults, but noted that two practice trials were required to reduce any learning effect. The method of Rikli and Jones will be employed.[109] Subjects will attend a

practice day and perform two foreshortened familiarization trials prior to the testing session.

Neuromuscular performance testing. Subjects will perform all tests on Keiser A420 computerized pneumatic resistance machines (Keiser Corp., Fresno, CA, USA). On day 1, leg press (LP) and chess press (CP) strength (1-retetiotion maximum: 1RM) will be tested using the protocol recommended by the National Strength and Conditioning Association[111], which we have used in multiple studies employing older persons without incident[73,82,112,113]. Participants will return for power testing no sooner than two days after the first testing session. They will complete LP and CP power testing at 40%, 50%, 60%, 70%, 80% and 90% of their 1RM according to the protocol of Potiaumpai et al[114] used regularly in our laboratory without any negative events.[32,73,115,116] The reliability for CP and LP in our laboratory using a healthy naïve sample was recently reported at 0.974 and 0.972, respectively.[112]

Statistical Analyses

A 2 (time) x 2 (group) analysis of covariance (ANCOVA), with MoCA score as a covariate, will be used to test for significant differences between the HSCT group and CON across time. Significant main effects and interactions will be further examined using Tukey's post hoc tests. Further, an intent-to-treat analysis will be performed. Finally, generalized linear regression will be used to examine the relationships of the vascular measurements to cardiovascular, neuromuscular and cognitive measures with control of confounding factors.

D. **Multisite MBI Collaborations.** Our research strategy takes advantage of the expertise in exercise programming previously demonstrated in Dr Signorile' s laboratory, the advanced ophthalmic imaging devices, methods, and analyses available through the ophthalmic imaging lab, directed by Drs Jiang and Wang, and the cognitive evaluation tools, which will be employed by Dr Signorile's team under the guidance of Dr Ebner. Dr. Signorile's team will also conduct all fitness testing. All teams have extensive experience in conducting human studies and clinical trials. Drs. Jiang and Wang have conducted many clinical studies and trials in patients with dementia, multiple sclerosis, and diabetic retinopathy, including the current NIH study (R01 NS111115, MPI: Wang & Detre) and Florida Department Health funded AD study (FDH 20A05, PI: Jiang). Dr. Signorile's team completed numerous human studies with older adults and patients with movement disorders and is conducting an ongoing NIH study R01AG053163 (PI: Czaja). In addition, Drs Signorile, Jiang and Wang are currently conducting a pilot study funded by University of Miami Provost Pilot Study Award (UM PRA 2022-2555, PIs: Signorile, Jiang and Wang) investigating retinal vascular responses to HSCT. In addition, this project will involve researchers in training (i.e., doctoral student, post-doc and research follow) who will experience cutting-edge research approaches. Therefore, the next generation of researchers in the field will be inspired and trained. In Dr Signorile's laboratory, Ms Kylie Courtney, a doctoral student and yoga instructor has been integral in the design of the YogaCue program and will be responsible for its implementation, and interpretation of results from all physical performance-based testing. In the advanced ophthalmic imaging lab, Dr. Simms is a research fellow who will experience these cutting-edge ocular imaging modalities on these novel biomarkers in response to the PE program. Dr. Simms will also experience image analysis as well. Dr Didem Pehlivanoglo is a post-doctoral student in Dr Ebner's Laboratory with experience in cognitive and affective neuroscience as it relates to aging.

E. TIMELINE AND FUTURE DIRECTIONS: Training will incorporate 2 sequential 6-month training periods during which 20 subjects each will be trained. Given our previous research, we expect our protocol to be approved by the internal review boards within one month of funding, the first cohort to begin testing by Month 4 and training to start by month 5. Training will last through Month 10, and testing will occur during Month 11. Recruitment for the second wave will occur during months 9-11, allowing testing for the second cohort by Month 12, with training from Month 13 through Month 18 and final testing during Month 19, allowing data analysis, statistical analysis and production of the final report and at least one manuscript through the Months 20-24. Through the rigorous hypothesis-driven experiments, the outcomes will provide an exercise-based intervention that incorporates one of the most popular training modalities in the world, yoga, modified to provide the cardiovascular and cognitive overloads necessary to produce positive cognitive changes and delay or prevent the onset of ADRD. Further, the outcomes of the study will provide critical information on whether retinal microvasculature and microcirculation are biomarkers of the efficacy of YogaCue, and potentially other PE programs that target cognitive change, thereby providing an effective and clinically-accessible diagnostic tool for tracking changes in the cerebral vasculature related to PE. We project that, given the proven expertise of our team, this pilot will lead to future funding. We also are providing, through their funding in this grant, the groundwork for our research assistants to establish themselves in cognitive aging and memory intervention.

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BUDGET AND BUDGET JUSTIFICATION

Site	Year 1	Year 2
University of Miami		
Personnel	$47,088	$49,501
Supplies	$4,950	$3,200
	$52,038	**$51,701**
University of Florida		
Personnel	**$7,959**	**$8,041**
Total Budget	**$59,997**	**$59,742**

Personnel:

University of Miami

Joseph Signorile, PhD, PI, Professor (No salary requested) will oversee the YogaCue training, cognitive testing and physical performance testing at his laboratory. He will train the doctoral student, who will serve as the clinical coordinator, and will supervise day-to-day training and required testing. He will be responsible for overseeing all data entry and maintenance of the physical performance and cognition databases. He will also oversee the physical plant of the laboratory and assure that all equipment is in working order and properly calibrated. He will interpret all results related to physical performance testing and provide both safety information and IRB information specific to YogaCue training and performance testing. He will conduct bi-weekly group meetings where the team will discuss ongoing progress and challenges and will have daily interactions with the doctoral student.

Jianhua Wang, MD, PhD, PI, Professor (No salary requested). Given his expertise in bioengineering and optics of ophthalmic imaging as well as clinical applications of advanced ophthalmic imaging, Dr. Wang will oversee the study execution of ocular imaging at the Bascom Palmer Eye Institute. He will be responsible for lab operations, system maintenance and imaging all subjects. He will supervise Dr Simms and be responsible for the interpretation of all ophthalmic data.

Hong Jiang, MD, PhD, PI, Clinical Associate Professor (No salary requested). Dr. Jiang will oversee all clinical aspects of the study at the University of Miami and participate actively in the clinical development and refinement aspects of the clinical protocol, subject recruitment, clinical examination and testing as well as data analysis and interpretation related to retinal vascular biomarkers and manuscript preparation. In addition, she will provide an overall perspective to the study and oversee safety issues of the study. She will meet any clinical administrative requirements including compliance with the IRB. She will moderate weekly group meetings at which the team will discuss ongoing progress and challenges.

Kyle Courtney, Graduate Student (Dr. Signorile lab), (66% salary requested) was integral in the design of the YogaCue and, as a certified yoga instructor, will oversee all training and testing. She will also supervise the proper entering of data and monitor the training progress of the subjects in the YogaCue training program using the dedicated computer system and heat rate monitor data, respectively. She will also be responsible for assuring that all equipment is available for training each week. She will ensure proper performance of all exercises and provide the necessary changes in poses associated with each wave of the program.

Dr. Simms, Research Associate/Study Coordinator (Dr. Jiang/Dr. Wang lab) (32% salary requested). The research associate/study coordinator will be responsible for the day-to-day frontline management of the clinical aspects of study implementation. She will manage and maintain Institutional Review Board submissions. She will generate and maintain a potential participant list including review of medical records. She will schedule and confirm study participant appointments and maximize patient retention. She will generate protocol-specific source documents and ensure appropriate collection materials are available for each study visit. The study coordinator will also image study participants using ophthalmic devices and process images to obtain measurement results. She will be involved in data organization and data quality control.

University of Florida

Natalie Ebner, PhD, PI, Associate Professor (No salary requested) will assist in the content and compilation of the cognitive test battery in Year 1. This task will include assistance with literature searches and task material implementation for data collection at University of Miami. In Year 2, Dr. Ebner and the postdoc will assist in the

analysis of the de-identified cognitive data shared by the University of Miami by running statistical models to address the research aims.

Didem Pehlivanoglo, Postdoc (13% salary requested). will, under Dr. Ebner's supervision, play a key role in the content and compilation of the cognitive test battery (Year 1) and in the analysis of the de-identified cognitive data (in Year 2). The postdoc will also be involved in preparation of publications and dissemination of the results.

Equipment:
Yoga mats. Ten yoga mats are requested to supplement our existing ten mats allowing class sizes of up to 20 or more persons if subjects have their own mats.
Yoga Blocks. Ten yoga blocks are requested for subjects to use as aids, especially during the initial two months of training and potentially beyond for some participants. This will supplement our exiting ten blocks
Yoga Straps. Ten yoga straps are requested for assistants to use as aids and to ensure subject safety, especially during the initial two months of training and potentially beyond for some participants.
Yoga Bolsters. Five bolsters are requested to supplement the 15 existing bolsters in the laboratory.
Bluetooth Speaker. The speaker will be used in conjunction with the yoga instructor's existing iPhone playlist.

Supplies:
Lab Consumables Funds are requested for lab consumables and miscellaneous clinical supplies and include RFI bulbs and flashlights. In addition, a computer, software and study specific computer forms will be needed.

Other Expenses:
Patient Compensation
$75 per study patient visits (2).This will be reimbursement for their time and traveling expenses to the University of Miami Medical campus.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Signorile, Joseph

eRA COMMONS USER NAME (credential, e.g., agency login): signorile01

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Rutgers University, Newark, NJ	BA	06/1976	English Literature
Kean University, Union, NJ	OTH	06/1978	Physical Education
University of Florida, Gainesville, FL	MPE	06/1982	Exercise Physiology
Texas A&M University, College Station, TX	PHD	09/1990	Exercise Physiology

A. Personal Statement

I am a Professor of Exercise Physiology in the Department of Kinesiology and Sport Sciences and Director of the Laboratory of Neuromuscular Research and Active Aging. I also have a joint appointment at the Center for Aging in the Department of Psychiatry at the Miller School of Medicine. I received his BS from Rutgers University, Masters from the University of Florida and Ph.D. from Texas A&M. I recently ended a nine-year joint appointment at the Miami Veteran's Administration Hospital. I have been a pioneer in applying the diagnosis/ prescription model for tailored exercise to improve function and reduce falls in older persons and continue to work on new technologies for improving independence. Within the context of prescriptive exercise, my laboratory was one of the first to use power training to address physical declines in older persons and individuals with Parkinson's disease. I have also developed several assessment tools to quantify the physical progression of aging, and most recently the assessment of executive function, through the development of a walking executive function test called the WRIT. Much of my latest work has concentrated on the impact of circuit training on cardiovascular performance and cognition and I am currently collaborating with researchers from the McKnight Foundation, Department of Neurology and Department of Ophthalmology in developing retinal scans to assess changes in cognition using through exercise training. I released my definitive book on aging exercise prescription entitled Bending the Aging Curve in 2011, which has been translated into Cantonese, Korean and Italian. My expertise in the area of yoga-based interventions and aging and research background make me well suited for this project.

1. Zhang J, Strand K, Totillo M, Chen Q, Signorile JF, Jiang H, Wang J. Improvement of retinal tissue perfusion after circuit resistance training in healthy older adults. Exp Gerontol. 2021 Dec 29;146:111210. PubMed PMID: 33385483.
2. Cherup NP, Strand KL, Lucchi L, Wooten SV, Luca C, Signorile JF. Yoga meditation enhances proprioception and balance in individuals diagnosed with Parkinson's disease. Percept Mot Ski. 2021 Feb;128(1):304-23 PMID: 32746736
3. Fang M, Strand K, Zhang J, Totillo M, Chen Q, Signorile JF, Jiang H, Wang J. Characterization of retinal microvasculature and its relations to cognitive function in older people after circuit resistance training. Exp Gerontol. 2020 Dec;142:111114. PubMed PMID: 33132156; PubMed Central PMCID: PMC7704902.
4. Cherup N, Roberson K, Potiaumpai M, Widdowson K, Jaghab AM, Chowdhari S, Armitage C, Seeley A, Signorile J. Improvements in cognition and associations with measures of aerobic fitness and muscular power following structured exercise. Exp Gerontol. 2018 Oct 2;112:76-87. PubMed PMID: 30223046.

B. Positions and Honors

Positions and Employment

1982 - 1986	Instructor, University of Florida, Gainesville, FL
1986 - 1989	Research Assistant, Texas A&M University, College Station, TX
1989 - 1995	Assistant Professor, University of Miami, Coral Gables, FL
1994 - 2004	Senior Researcher, Stein Gerontological Institute, Miami, FL
1995 - 1996	Adjunct Faculty, University of Miami Center on Aging, Miami, FL
1995 - 2005	Associate Professor, University of Miami, Miami, FL
2001 - 2012	Research Health Specialist, Vetrans Affairs Medical Center GRECC, Miami, FL
2005 -	Professor, University of Miami, Coral Gables, FL
2011 -	Director, Laboratory of Neuromuscular Research and Active Aging, Coral Gables, FL

Other Experience and Professional Memberships

Honors

1993	Elected Member, New York Academy of Science
1996	Appointed to Graduate Faculty, University of Miami
2016	Appointed Editorial Staff, *Journal of Strength and Conditioning Research*
2017	Editorial Excellence Award, *Journal of Strength and Conditioning Research*
2020	Appointed Editorial Staff, *Experimental Gerontology*

C. Contribution to Science

1. I was one of the first researchers to recognize that the functional declines and histological changes that occur with aging reflected loss of velocity rather than simple strength, thereby dictating power or high-speed training as a viable intervention. As evidenced below, we have evolved this research to include interventions that target cognition and cardiovascular changes.
   b. Fang, M., Strand, K., Zhang, J., Totillo, M., Signorile, J.F., Galvin, J.E., Wang, J., Jiang, H. Retinal vessel density correlates with cognitive function in older adults., Exp Gerontol., 2021 Jun 3;111433. PubMed PMID: 34091000.
   c. Roberson KB, Potiaumpai M, Widdowson K, Jaghab AM, Chowdhari S, Armitage C, Seeley A, Jacobs KA, Signorile JF. Effects of high-velocity circuit resistance and treadmill training on cardiometabolic risk, blood markers, and quality of life in older adults. Appl Physiol Nutr Metab. 2018 Aug;43(8):822-832. PubMed PMID: 29539268.
   d. Strassnig M, **Signorile JF**, Potiaumpai M, Romero MA, Czaja S, Gonzalez C, Harvey PD. High velocity circuit resistance training improves cognition, psychiatric symptoms and neuromuscular performance in patients with persistent mental illness. *Psychiatry Res.* 2015; 30;229(1-2):295-30. PubMed PMID: 26187340.

2. Given the popularity of yoga as an exercise intervention, our laboratory has applied our expertise in modifying exercise interventions to target the specific needs of the individual. Our modifications have included the incorporation of high-speed training into traditional yoga programs to develop interventions that target neuromuscular power and present the practitioner with a yoga-based high-speed interval program. Additionally, we have incorporated both action observation and mental imagery into programs we developed for our older participants and those with Parkinson's disease.

   a. Wooten SV, Signorile JF, Desai SS, Paine AK, Mooney K. Yoga meditation (YoMed) and its effect on proprioception and balance function in elders who have fallen: A randomized control study. Complement Ther Med. 2018 Feb;36:129-136. PubMed PMID: 29458919.
   b. Potiaumpai M, Martins MC, Wong C, Desai T, Rodriguez R, Mooney K, Signorile JF. Difference in muscle activation patterns during high-speed versus standard-speed yoga: A randomized sequence crossover study. Complement Ther Med. 2017 Feb;30:24-29. PubMed PMID: 28137523.

c. Potiaumpai M, Martins MC, Rodriguez R, Mooney K, Signorile JF. Differences in energy expenditure during high-speed versus standard-speed yoga: A randomized sequence crossover trial. Complement Ther Med. 2016 Dec;29:169-174. PubMed PMID: 27912943.

d. Ni M, Mooney K, Signorile JF. Controlled pilot study of the effects of power yoga in Parkinson's disease. Complement Ther Med. 2016 Apr;25:126-31. PubMed PMID: 27062960.

e. Ni, M., Signorile, J.F., Mooney, K., Balachandran, A., Potiaumpai, M., Luca, C., Moore, J.G., Kuenze, C.M., Eltoukhy, M., Perry, A.C. Comparative impact of power training and high-speed yoga on motor function in patients with Parkinson's disease. Arch Phys Med Rehabil. 2016, Mar;97(3):345-354. PubMed PMID: 26546987.

3. Since training must be properly applied and progressed to maximize gains, my associates and I have also completed a number of studies that examined optimal training methodology and progression.
   a. Buskard ANL, Jacobs KA, Eltoukhy MM, Strand KL, Villanueva L, Desai PP, Signorile JF. Optimal approach to load progressions during strength training in older adults. Med Sci Sports Exerc. 2019 Nov;51(11):2224-2233. PubMed PMID: 31107348.
   b. Strand KL, Lucchi L, Copo TG, Cherup NP, Signorile JF. Optimal loads for power in older men and women using plate-loaded resistance machines. Exp Gerontol. 2019 Sep;124:110638. PubMed PMID: 31202881.
   c. Buskard A, Zalma B, Cherup N, Armitage C, Dent C, Signorile JF. Effects of linear periodization versus daily undulating periodization on neuromuscular performance and activities of daily living in an elderly population. Exp Gerontol. 2018 Nov;113:199-208. PubMed PMID: 30316811.
   d. Ni M, Signorile JF. High-speed resistance training modifies load-velocity and load-power relationships in Parkinson's disease. J Strength Cond Res. 2017 Oct;31(10):2866-2875. PubMed PMID: 27893480.

4. To truly apply the diagnosis prescription model to exercise, effective tools must be available for assessing need across the broad spectrum of performance and functional variables associated with successful aging. Therefore, the trajectory of our training studies was logically mirrored by our team's development of unique diagnostic tools allowing quantification of specific needs as evidenced by the articles below.

   a. Castillo DC, Strand KL, Oh J, Eltoukhy M, Totillo MC, Signorile JF. The development of a regression model to predict object transfer power in older adults. J Strength Cond Res. 2020 Nov;34(11):3086-3093. PubMed PMID: 33105358.
   b. Leyva A, Balachandran A, Britton JC, Eltoukhy M, Kuenze C, Myers ND, Signorile JF. The development and examination of a new walking executive function test for people over 50 years of age. Physiol Behav. 2017 Mar 15;171:100-109. PubMed PMID: 28063787.
   c. Smith WN, Del Rossi G, Adams JB, Abderlarahman KZ, Asfour SA, Roos BA, Signorile JF. Simple equations to predict concentric lower-body muscle power in older adults using the 30-second chair-rise test: a pilot study. Clin Interv Aging. 2010 Aug 9;5:173-80. PubMed PMID: 20711436; PubMed Central PMCID: PMC2920197.
   d. Signorile JF, Sandler D, Kempner L, Stanziano D, Ma F, Roos BA. The ramp power test: a power assessment during a functional task for older individuals. J Gerontol A Biol Sci Med Sci. 2007 Nov;62(11):1266-73. PubMed PMID: 18000147.

Complete List of Published Work in My Bibliography
https://www.ncbi.nlm.nih.gov/myncbi/1tKFuqvrvoekM/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Active Grants

UM PRA 2022-2555, University of Miami Provost's Research Award for FY2022 Signorile (PI)

06/01/2021-05/31/2022
Circuit Resistance Training and Retinal Vascular Changes in Older Persons (pilot study)
This internal award from the Provost's office for research will collect preliminary data on Retinal Vascular Changes in Older Persons.
Role: PI

1R01AG053163-01 Czaja (PI), Signorile (Co-Investigator) 07/01/2016 - 06/30/2021
A Personalized Health Behavior System to Promote Well-Being in Older Adults: R01.
The objectives of this study are to examine the usability and efficacy, for diverse older adults, of a new tablet-based dynamic system that will provide: (1) personalized behavior-change programs for improved diet and increased physical activity and (2) online social interaction and support from small teams pursuing similar goals.
Role: Co-I

MD012610-01A1 Jimanez (PI); Signorile (Co-Investigator) 05/09/2019 – 01/31/2024

Health Promotion in the Prevention of Anxiety and Depression: The Happy Older Latinos are Active (HOLA Study: RO1.
Given the prevalence and morbidity of depression in later life, the inadequacies of current treatment approaches for averting years living with disability, the inequities in access to the mental health care delivery system, and the workforce shortages to meet the mental health needs of older Latinos, development and testing of innovative strategies to prevent depression and anxiety are of great public health significance and have the potential to change practice. The study will compare the effectiveness of HOLA and healthy lifestyles education in reducing risk factors for major depression and generalized anxiety disorder among older Latinos with subthreshold depression or anxiety; compare the impact of HOLA and healthy lifestyles education in reducing the 2-year incidence and recurrence of major depression and generalized anxiety disorder among older Latinos with subthreshold depression or anxiety; and, compare the effectiveness of HOLA and healthy lifestyles education in improving health-related outcomes among older Latinos with minor or subthreshold depression or anxiety among older Latinos with minor or subthreshold depression or anxiety.
Role: Co-I

Completed Research Support (past 5 years):

CG-DNEDU-OB-122RM Levis (PI), Signorile (Co-Investigator) 07/01/2016 - 12/31/2018
The Effects of Cannabinoids on Traumatic Brain Injury (Scythian Biosciences Inc.): This study will evaluate the efficacy of using cannabinoids for the traumatic brain injury. Assessments will be diverse and include cognition, behavior, psychosocial outcomes, sleep, pain, and cardiovascular dysregulation.
Role: Co-I

PF-PLA-1710 Signorile, J (PI), Eltoukhy, M (Co-PI) 09/01/2107 – 08/31/2018
Parkinson's Disease Foundation: PAIR Leadership Grant.
Assessment of changes in gait patterns during cognitive and visual dual-tasking using the Xbox Kinect System.
The objective of this study is to examine changes in gait of Parkinson's patients due to cognitive and visual-cognitive dual-tasking using the Kinect sensor.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Wang, Jianhua

eRA COMMONS USER NAME (credential, e.g., agency login): jianhuawang

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Zhejiang Medical University, Hangzhou, Zhejiang	MD	07/1988	Medicine
University of Waterloo, Waterloo, ON	MS	06/2000	Vision Science
University of Waterloo, Waterloo, ON	PHD	07/2003	Vision Science

A. Personal Statement

I have a broad background in vision research and electronic engineering, especially in advanced ophthalmic imaging and human studies. As an assistant professor at the University of Rochester, I have learned optics and prototyped time-domain optical coherence tomography (OCT) devices through the join work with OCT experts. After I moved to Miami, I have been working with other researchers and optics engineers to develop many other prototypes of spectral-domain OCT devices. They are ultra-high resolution OCT, ultra-long scan depth OCT, dual-channel OCT, magnetomotive OCT, and CMOS camera-based ultra-high-speed OCT. In recent 10 years, I have worked on vascular imaging of the eye and developed the methods and hardware to image microvasculature and microcirculation in the retina and ocular surface. Working with a group of clinicians, I focus on microvasculature and microcirculation in the retina as a window of the cerebral vasculature in aging, dementia, and multiple sclerosis. As the PI or co-Investigator on many previous industrial- and NIH-funded grants, I worked out the proposed research and published more than 190 papers in top journals. Currently, I am the co-director of scientific experimental imaging laboratory at the Bascom Palmer Eye Institute and meanwhile managing my own advanced ophthalmic imaging lab. In summary, I have a good record of successful research projects in the area of ophthalmic imaging and clinical research. My expertise and experience make me well equipped and qualified for working on this proposed project.

On-going relevant projects that I would like to highlight include:

R01NS111115A1, NIH/NINDS Wang and Detre (MPI) 08/15/19-08/15/24
Novel Biomarkers of Small Vessel Contributions to Vascular Cognitive Impairment and Dementia (VCID)
Role: CPI

Food UM 01, Global Healthcare Focus LLC Wang, Jianhua (PI) 01/01/17-03/31/23
Food supplement Ocufolin on retinal blood flow velocity in patients with vascular retinopathy
Role: PI

20A05, Florida Department of Health Jiang (PI) 04/14/20-06/30/23
Retinal biomarkers for monitoring vascular contributions to Alzheimer's disease
Role: Co-Investigator

MBI-Pilot-2022 UBA/UM, McKnight Brain Institute Lazar, Ronald (PI) 06/01/21-05/31/23
Improving Age-Related Cognitive Decline with Exercise in Hypertensive Older Adults: A Pilot Study to Investigate A Retinal Microvascular Biomarker and the Role of IGF-1
Role: CPI

UM PRA 2022-2555, University of Miami Provost's Research Award Signorile Joseph (PI) 06/01/21-05/31/22
Circuit Resistance Training and Retinal Vascular Changes in Older Persons (pilot study)
Role: CPI

Citations

1. Fang M, Strand K, Zhang J, Totillo M, Signorile JF, Galvin JE, **Wang J**, Jiang H. Retinal vessel density correlates with cognitive function in older adults. Exp Gerontol. 2021 Jun 6;152:111433. PubMed PMID: 34091000; NIHMSID: NIHMS1712579.
2. Wang H, Hu H, Gregori G, Zhang J, Jiang H, **Wang J**. The Effect of Software Versions on the Measurement of Retinal Vascular Densities Using Optical Coherence Tomography Angiography. Curr Eye Res. 2021 Mar;46(3):341-349. PubMed Central PMCID: PMC7878200.
3. Lin Y, Jiang H, Liu Y, Rosa Gameiro G, Gregori G, Dong C, Rundek T, **Wang J**. Age-Related Alterations in Retinal Tissue Perfusion and Volumetric Vessel Density. Invest Ophthalmol Vis Sci. 2019 Feb 1;60(2):685-693. PubMed Central PMCID: PMC6383727.
4. Jiang H, Wei Y, Shi Y, Wright CB, Sun X, Gregori G, Zheng F, Vanner EA, Lam BL, Rundek T, **Wang J**. Altered Macular Microvasculature in Mild Cognitive Impairment and Alzheimer Disease. J Neuroophthalmol. 2018 Sep;38(3):292-298. PubMed Central PMCID: PMC5902666.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020 -	Professor, Bascom Palmer Eye Institute, Department of Electrical and Computer Engineering, University of Miami, Miami, FL
2012 - 2020	Associate Professor (Tenured), Bascom Palmer Eye Institute, Department of Electrical and Computer Engineering, University of Miami, Miami, FL
2010 - 2012	Associate Professor, Bascom Palmer Eye Institute, Department of Electrical and Computer Engineering, University of Miami, Miami, FL
2009 -	Scientific Co-director of Experimental Imaging Laboratory, Bascom Palmer Eye Institute, University of Miami, Miami, FL
2008 - 2012	Assistant Professor, Department of Electrical and Computer Engineering, University of Miami, Miami, FL
2006 - 2010	Assistant Professor, Bascom Palmer Eye Institute, University of Miami, Miami, FL
2003 - 2006	Research Assistant Professor, University of Rochester, Department of Ophthalmology, Rochester, NY
2001 - 2001	Research Associate, University of Waterloo, Waterloo, ON
1996 - 1999	Professional Affairs Manager, Johnson & Johnson Vision Products, China, Shanghai
1991 - 1995	Ophthalmologist, Department of Ophthalmology, Hangzhou First Hospital, Hangzhou
1988 - 1990	Resident, Department of Ophthalmology, Hangzhou First Hospital, Hangzhou

Honors

2004	Pearson Medal for Creative Research, University of Waterloo
2003	Best Paper in Session, American Society of Cataract & Refractive Surgery
2003	Travel award, International Society of Contact Lens Research
2001	Travel award, International Society of Contact Lens Research
2000	Irvin M. & Beatrice Borish Student Travel Fellowship Award, American Academy of Optometry

C. Contribution to Science

1. Through my more than 25 years of career development, I significantly contribute to the development of optical coherence tomography prototypes for clinical research, especially in the field of anterior segment imaging. Worked with OCT experts, high-speed time-domain OCT was developed for imaging tear film and

tear dynamics in contact lens wearers and patients with dry eye syndrome. Collaborated with clinicians and engineers, ultra-high-resolution OCT devices for imaging the anterior segments were developed for imaging the tear film, epithelium, and ocular tumor by conducting clinical research.

a. Shao Y, Tao A, Jiang H, Mao X, Zhong J, Shen M, Lu F, Xu Z, Karp CL, **Wang J**. Age-related changes in the anterior segment biometry during accommodation. Invest Ophthalmol Vis Sci. 2015 Jun;56(6):3522-30. PubMed Central PMCID: PMC4464043.
b. Zhu D, Shen M, Jiang H, Li M, Wang MR, Wang Y, Ge L, Qu J, **Wang J**. Broadband superluminescent diode-based ultrahigh resolution optical coherence tomography for ophthalmic imaging. J Biomed Opt. 2011 Dec;16(12):126006. PubMed Central PMCID: PMC3247935.
c. Chen Q, **Wang J**, Shen M, Cui L, Cai C, Li M, Li K, Lu F. Tear menisci and ocular discomfort during daily contact lens wear in symptomatic wearers. Invest Ophthalmol Vis Sci. 2011 Apr 6;52(5):2175-80. PubMed PMID: 21051728.
d. Palakuru JR, **Wang J**, Aquavella JV. Effect of blinking on tear dynamics. Invest Ophthalmol Vis Sci. 2007 Jul;48(7):3032-7. PubMed PMID: 17591869.

2. Worked with optics experts, I contributed significantly to long scan depth OCT for imaging the full eyes in studying accommodation and full eye biometry. A unique system consists of two spectral domain OCT devices equipped with wavefront sensor was developed.

a. Du C, Shen M, Li M, Zhu D, Wang MR, **Wang J**. Anterior segment biometry during accommodation imaged with ultralong scan depth optical coherence tomography. Ophthalmology. 2012 Dec;119(12):2479-85. PubMed Central PMCID: PMC3505244.
b. He JC, **Wang J**. Measurement of wavefront aberrations and lens deformation in the accommodated eye with optical coherence tomography-equipped wavefront system. Opt Express. 2014 Apr 21;22(8):9764-73. PubMed Central PMCID: PMC4083049.
c. Shao Y, Tao A, Jiang H, Mao X, Zhong J, Shen M, Lu F, Xu Z, Karp CL, **Wang J**. Age-related changes in the anterior segment biometry during accommodation. Invest Ophthalmol Vis Sci. 2015 Jun;56(6):3522-30. PubMed Central PMCID: PMC4464043.

3. I contribute significantly to image microvasculature on the ocular surface and retina. A system called functional slit-lamp biomicroscope (FSLB) was developed and a patent of single-shot for generating conjunctival microvascular network map was filled. This novel system enables easy imaging of the conjunctival microvascular network and small vessel blood flow velocity, which was used to study microvascular response to contact lens wear and changes in dry eye. Worked with vascular experts in neuro-ophthalmology, we developed automatic segmentation of retinal microvascular network obtained using Retinal Function Imager (RFI) for studying retinal microvascular changes in multiple sclerosis, AD, diabetics, and cerebral small vessel diseases. In addition, we developed ultra-high resolution OCT for imaging the retina, and our segmentation software can segment 9 retinal sub-layers. The recent development of segmentation software enables automatic segmentation of all intraretinal maps of retinal sub-layers. Furthermore, I adapted the RFI for the first time for imaging the conjunctiva by designing an optical adapter.

a. Fang M, Strand K, Zhang J, Totillo M, Signorile JF, Galvin JE, **Wang J**, Jiang H. Retinal vessel density correlates with cognitive function in older adults. Exp Gerontol. 2021 Jun 6;152:111433. PubMed PMID: 34091000; NIHMSID: NIHMS1712579.
b. Lin Y, Jiang H, Liu Y, Rosa Gameiro G, Gregori G, Dong C, Rundek T, **Wang J**. Age-Related Alterations in Retinal Tissue Perfusion and Volumetric Vessel Density. Invest Ophthalmol Vis Sci. 2019 Feb 1;60(2):685-693. PubMed Central PMCID: PMC6383727.
c. Jiang H, Wei Y, Shi Y, Wright CB, Sun X, Gregori G, Zheng F, Vanner EA, Lam BL, Rundek T, **Wang J**. Altered Macular Microvasculature in Mild Cognitive Impairment and Alzheimer Disease. J Neuroophthalmol. 2018 Sep;38(3):292-298. PubMed Central PMCID: PMC5902666.
d. Shao Y, Jiang H, Wei Y, Shi Y, Shi C, Wright CB, Sun X, Vanner EA, Rodriguez AD, Lam BL, Rundek T, Baumel BS, Gameiro GR, Dong C, **Wang J**. Visualization of Focal Thinning of the Ganglion Cell-

Inner Plexiform Layer in Patients with Mild Cognitive Impairment and Alzheimer's Disease. J Alzheimers Dis. 2018;64(4):1261-1273. PubMed PMID: 30040712.

4. I am also the first person who applied molecular imaging in ophthalmic research by using multimodal imaging modalities. Working with biologists, I developed a strategy to use novel spectroscopic and magnetomotive OCT approaches for in vivo detecting cochlin (a protein) in glaucomatous mice. This approached significantly improves our ability to detect and quantify proteins that are predictors of susceptibility (and/or progression or efficacy of treatments) in specific local tissue prior to clinical detection. The breakthrough will be immensely helpful to control various disease states.

    a. **Wang J**, Wang MR, Jiang H, Shen M, Cui L, Bhattacharya SK. Detection of magnetic particles in live DBA/2J mouse eyes using magnetomotive optical coherence tomography. Eye Contact Lens. 2010 Nov;36(6):346-51. PubMed Central PMCID: PMC3401487.
    b. Goel M, Sienkiewicz AE, Picciani R, **Wang J**, Lee RK, Bhattacharya SK. Cochlin, intraocular pressure regulation and mechanosensing. PLoS One. 2012;7(4):e34309. PubMed Central PMCID: PMC3319572.
    c. **Wang J**, Aljohani A, Carreon T, Gregori G, Bhattacharya SK. In vivo quantification of cochlin in glaucomatous DBA/2J mice using optical coherence tomography. Sci Rep. 2015 Jun 5;5:11092. PubMed Central PMCID: PMC4457137.

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https://www.ncbi.nlm.nih.gov/myncbi/jianhua.wang.1/bibliography/public/

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Jiang, Hong

eRA COMMONS USER NAME (credential, e.g., agency login): hongjiang

POSITION TITLE: Clinical Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Zhejiang Medical University, Hangzhou, Zhejiang	MD	07/1988	Medicine
Zhejiang Medical University, Hangzhou, Zhejiang	MS	07/1993	Neurology
University of Hong Kong, Hong Kong	PHD	07/2001	Neuroscience
Zhejiang Medical University, Hangzhou, Zhejiang	Other training	07/1990	Internship (Internal Medicine)
University of Rochester, Rochester, New York	Postdoctoral Fellow	07/2005	Neuroscience
Rochester General Hospital, Rochester, New York	Other training	07/2006	Intership (Internal Medicine)
Jackson Memorial Hospital/University of Miami, Miami, FL	Resident	07/2010	Neurology
Bascom Palmer Eye Institute, University of Miami, Miami, FL	Fellow	07/2011	Neuro-Ophthalmology

A. Personal Statement

I am an Associate Professor of Ophthalmology and Neurology, and my research is focused on ocular biomarkers of central nervous system disorders, such as dementia. As a neurology-trained neuro-ophthalmologist, I have a broad background in both basic and clinical research. I have participated in various clinical trials related to dementia. Working with the exceptional and experienced scientists and engineering team at the Bascom Palmer Eye Institute, I have been involved in advanced structural and functional ophthalmic imaging for more than ten years. My work has been reflected in my recent publications as the corresponding author in the field of functional imaging of the retina and conjunctiva. As PI or co-investigator on severa university-, Florida state- and NIH-funded grants, I laid the groundwork for the proposed research by involving the development of topographical thicknesses mapping of the retinal sublayers and novel quantification of the retinal microvasculature in vivo. Recently, my team also worked with the researcher with expertise in deep learning. We were able to apply deep learning in the analysis of retinal thickness maps and capillary networks acquired using optical coherence tomography angiography. In summary, my expertise and experience make me well equipped and qualified for working on this proposed project.

On-going relevant projects that I would like to highlight include:

20A05, Florida Department of Health Jiang, Hong (PI) 04/14/20-06/30/23
Retinal biomarkers for monitoring vascular contributions to Alzheimer’s disease
Role: PI

UM PRA 2022-2555, University of Miami Provost's Research Award Signorile, Joseph (PI)
06/01/21-05/31/22
Circuit Resistance Training and Retinal Vascular Changes in Older Persons (pilot study)
Role: CPI

R01NS111115A1, NIH/NINDS Wang and Detre (MPI) 08/15/19-08/15/24
Novel Biomarkers of Small Vessel Contributions to Vascular Cognitive Impairment and Dementia (VCID)
Role: Co-Investigator

Food UM 01, Global Healthcare Focus LLC Jianhua Wang (PI) 01/01/17-05/31/23
Food supplement Ocufolin on retinal blood flow velocity in patients with vascular retinopathy
Role: Co-Investigator

Citations:

1. **Jiang H**, Wang J, Levin BE, Baumel BS, Camargo CJ, Signorile JF, Rundek T. Retinal Microvascular Alterations as the Biomarkers for Alzheimer Disease: Are We There Yet?. J Neuroophthalmol. 2021 Jun 1;41(2):251-260. PubMed Central PMCID: PMC8079547.
2. Zhang J, Strand K, Totillo M, Chen Q, Signorile JF, **Jiang H**, Wang J. Improvement of retinal tissue perfusion after circuit resistance training in healthy older adults. Exp Gerontol. 2021 Apr;146:111210. PubMed PMID: 33385483.
3. Fang M, Strand K, Zhang J, Totillo M, Chen Q, Signorile JF, **Jiang H**, Wang J. Characterization of retinal microvasculature and its relations to cognitive function in older people after circuit resistance training. Exp Gerontol. 2020 Dec;142:111114. PubMed Central PMCID: PMC7704902.
4. **Jiang H**, Wei Y, Shi Y, Wright CB, Sun X, Gregori G, Zheng F, Vanner EA, Lam BL, Rundek T, Wang J. Altered Macular Microvasculature in Mild Cognitive Impairment and Alzheimer Disease. J Neuroophthalmol. 2018 Sep;38(3):292-298. PubMed Central PMCID: PMC5902666.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2019 -	Clinical Associate Professor, Neuro-ophthalmology & Neurology, Bascom Palmer Eye Institute & Dept. of Neurology, University of Miami, MIAMI, FL
2012 - 2019	Clinical Assistant Professor, Neuro-ophthalmology & Neurology, Bascom Palmer Eye Institute & Dept. of Neurology, University of Miami, Miami, FL
2011 - 2012	Clinical Instructor, Neuro-ophthalmology and Neurology, Bascom Palmer Eye Institute, University of Miami, Miami, FL
1990 - 1997	Neurologist, Second Affiliated Hospital of Zhejiang Medical University, Hangzhou

Honors

2019	The J. Lawton Smith Award 2019, NANOS
2011	ARVO Travel Grant, National Eye Institute
2008	Travel Award, Florida Society of Neurology
2000	Young Investigator Award for Best Oral Presentation, Queen Mary Hospital
2000	Travel and Conference Award , Dr. Lo Kwee Seong Education Foundation
1999	Travel Grant, International Federation of Parkinson’s disease Foundations
1997	Lady Ivy Wu Fellowship , University of Hong Kong

C. Contribution to Science

1. I have initiated the development of automatic segmentation of retinal microvascular network obtained using Retinal Function Imager (RFI) and Optic Coherence Tomography Angiography (OCTA) for studying retinal microvascular changes in multiple sclerosis, Alzheimer's disease, diabetics, and cerebral small vessel diseases. Our team applied novel fractal analysis of retinal capillary network acquired using optical coherence tomography angiography (OCTA). We are the first group that analyzes retinal microvasculature which is normalized by the tissue volume, called volumetric vessel density (VVD). In addition, we are also the first group to calculate retinal tissue perfusion based on retinal blood flow acquired using RFI.

a. **Jiang H**, Wang J, Levin BE, Baumel BS, Camargo CJ, Signorile JF, Rundek T. Retinal Microvascular Alterations as the Biomarkers for Alzheimer Disease: Are We There Yet?. J Neuroophthalmol. 2021 Jun 1;41(2):251-260. PubMed Central PMCID: PMC8079547.
b. Zhang J, Strand K, Totillo M, Chen Q, Signorile JF, **Jiang H**, Wang J. Improvement of retinal tissue perfusion after circuit resistance training in healthy older adults. Exp Gerontol. 2021 Apr;146:111210. PubMed PMID: 33385483.
c. Lin Y, **Jiang H**, Liu Y, Rosa Gameiro G, Gregori G, Dong C, Rundek T, Wang J. Age-Related Alterations in Retinal Tissue Perfusion and Volumetric Vessel Density. Invest Ophthalmol Vis Sci. 2019 Feb 1;60(2):685-693. PubMed Central PMCID: PMC6383727.
d. **Jiang H**, Delgado S, Liu C, Rammohan KW, DeBuc DC, Lam BL, Wang J. In Vivo Characterization of Retinal Microvascular Network in Multiple Sclerosis. Ophthalmology. 2016 Feb;123(2):437-438. PubMed Central PMCID: PMC4724448.

2. To image microvasculature on the conjunctiva in studying cerebral small vessel diseases, a system called functional slit-lamp biomicroscope (FSLB) was developed and a patent of single-shot for generating conjunctival microvascular network map was filled. This novel system enables easily imaging of the conjunctival microvascular network and small vessel blood flow velocity.

a. Xu Z, **Jiang H**, Tao A, Wu S, Yan W, Yuan J, Liu C, DeBuc DC, Wang J. Measurement variability of the bulbar conjunctival microvasculature in healthy subjects using functional slit lamp biomicroscopy (FSLB). Microvasc Res. 2015 Sep;101:15-9. PubMed Central PMCID: PMC4537817.
b. Wang L, Yuan J, **Jiang H**, Yan W, Cintrón-Colón HR, Perez VL, DeBuc DC, Feuer WJ, Wang J. Vessel Sampling and Blood Flow Velocity Distribution With Vessel Diameter for Characterizing the Human Bulbar Conjunctival Microvasculature. Eye Contact Lens. 2016 Mar;42(2):135-40. PubMed Central PMCID: PMC4591084.
c. **Jiang H**, Zhong J, DeBuc DC, Tao A, Xu Z, Lam BL, Liu C, Wang J. Functional slit lamp biomicroscopy for imaging bulbar conjunctival microvasculature in contact lens wearers. Microvasc Res. 2014 Mar;92:62-71. PubMed Central PMCID: PMC3960300.
d. **Jiang H**, Ye Y, DeBuc DC, Lam BL, Rundek T, Tao A, Shao Y, Wang J. Human conjunctival microvasculature assessed with a retinal function imager (RFI). Microvasc Res. 2013 Jan;85:134-7. PubMed Central PMCID: PMC3534915.

3. To study retinal degeneration in neurological diseases such as multiple sclerosis, I have contributed to the development of slit-lamp-based ultra-high resolution OCT for imaging the retina. Our segmentation software can segment 9 retinal sub-layers. The recent development of segmentation software enables automatic segmentation of 6 maps of retinal sub-layers.

a. **Jiang H**, Delgado S, Tan J, Liu C, Rammohan KW, DeBuc DC, Lam BL, Feuer WJ, Wang J. Impaired retinal microcirculation in multiple sclerosis. Mult Scler. 2016 Dec;22(14):1812-1820. PubMed Central PMCID: PMC4993688.
b. **Jiang H**, Delgado S, Liu C, Rammohan KW, DeBuc DC, Lam BL, Wang J. In Vivo Characterization of Retinal Microvascular Network in Multiple Sclerosis. Ophthalmology. 2016 Feb;123(2):437-438. PubMed Central PMCID: PMC4724448.
c. Wang Y, **Jiang H**, Shen M, Lam BL, DeBuc DC, Ye Y, Li M, Tao A, Shao Y, Wang J. Quantitative analysis of the intraretinal layers and optic nerve head using ultra-high resolution optical coherence tomography. J Biomed Opt. 2012 Jun;17(6):066013. PubMed Central PMCID: PMC3381522.
d. **Jiang H**, Abukhalil F, Shen M, Gregori G, Lam BL, Wang Y, Wang J. Slit-lamp-adapted ultra-high resolution OCT for imaging the posterior segment of the eye. Ophthalmic Surg Lasers Imaging. 2012 Jan-Feb;43(1):76-81. PubMed PMID: 22251848.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1buofoatUF5Q8/bibliography/public/

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Ebner, Natalie C

eRA COMMONS USER NAME (credential, e.g., agency login): NATALIE.EBNER

POSITION TITLE: Professor of Psychology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Free University Berlin, Berlin	BA	04/1998	Psychology
Free University Berlin, Berlin	MA	03/2001	Psychology
Free University Berlin, Berlin	PHD	05/2005	Psychology
Max Planck Institute for Human Development, Berlin	Postdoctoral	06/2007	Psychology
Yale University, Connecticut	Postdoctoral	07/2011	Psychology

A. Personal Statement

I have a broad background in cognitive and socioemotional experimental research across the adult lifespan and in aging. I use a multi-methods approach in my research that includes self-report, cognitive-behavioral measures, neuroimaging techniques, and hormone/neuropeptide markers. As a pre- and postdoctoral fellow at the Free University Berlin and the Max Planck Institute for Human Development, I supervised behavioral research on emotion-cognition interactions across adulthood. As a postdoctoral fellow, and later as Associate Research Scientist at Yale University and as faculty at University of Florida (UF), I have expanded my research to examine neuropsychological changes associated with cognition-emotion interactions and decision making. Methods applied to these studies include neuroimaging and eye-tracking as well as pharmacological (i.e., intranasal oxytocin administration) and real-life (i.e., simulated phishing) interventions. In addition to my primary appointment in the Department of Psychology at UF, I hold a joint appointment as faculty in the Florida Institute for Cyber Security Research. I am also affiliated with the Center for Cognitive Aging and Memory, the Institute on Aging (adjunct faculty), the McKnight Brain Institute, the Pain Research and Intervention Center of Excellence, and the Substance Abuse Training Center in Public Health on campus. I have received multiple awards, such as the Young Research Scientist Award from the German Psychological Association, the International Max Planck Research School on the Life Course Outstanding Alumni Award, the UF College of Liberal Arts and Sciences International Educator of the Year Award, the UF Research Foundation Professorship Award, and, very recently, the UF College of Liberal Arts and Sciences Faculty Achievement Award. Since 2015, I have been a Kavli Fellow of the National Academy of Sciences. My body of work is documented in over 100 publications. Over the last 10 years, my research has been funded by NIH, NSF, and other agencies and I have gained extensive expertise in supervision of graduate and postdoctoral trainees and in working with junior faculty and postdocs. In this proposal I will supervise the implementation and administration of the cognitive test battery and will be actively involved in related task implementation/staff training, data analysis, and results interpretation. I will work jointly with the other members of this well-crafted team on results dissemination in the form of peer-reviewed publications and conference/workshop presentations, as well as grant reporting.

<u>Ongoing projects that I would like to highlight include:</u>
NIH/NIA R01AG072658
Ebner/Lighthall/Wilson (MPI)
03/01/22-04/30/27

Characterizing and Modulating Neurocognitive Processes of Learning to Trust and Distrust in Aging

NIH/NIA R01AG057764
Ebner/Spreng (MPI)
09/01/2018-06/30/2023
Uncovering and Surveilling Financial Deception Risk in Aging

NIH/NIA R01AG059809
Cruz-Almeida/**Ebner** (MPI)
08/01/2018-04/30/2023
Mechanisms of Oxytocin's Analgesia in Older Adults

Representative Publications:

a. **Ebner NC**, Johnson MR, Rieckmann A, Durbin KA, Johnson MK, Fischer H. Processing own-age vs. other-age faces: neuro-behavioral correlates and effects of emotion. Neuroimage. 2013 Sep;78:363-71. PubMed Central PMCID: PMC3684564
b. Rana M, Varan AQ, Davoudi A, Cohen RA, Sitaram R, **Ebner NC**. Real-time fMRI in neuroscience research and its use in studying the aging brain. Front Aging Neurosci. 2016 Oct;8:239. PubMed Central PMCID: PMC5067937
c. Horta M, Ziaei M, Lin T, Porges EC, Fischer H, Feifel D, Spreng RN, **Ebner NC**. Oxytocin alters patterns of brain activity and amygdalar connectivity by age during dynamic facial emotion identification. Neurobio. Aging 2019 June; 78: 42-51. PubMed Central PMCID: PMC6545147
d. Frazier I, Lighthall NR, Horta M, Perez E, Ebner NC. CISDA: Changes in integration for social decisions in aging. Wiley Interdiscip Rev: Cogn Sci. 2019 May;10(3):e1490. PubMed Central PMCID: PMC8202094

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-Present	Member, Study Section SPIP, National Institutes of Health
2021-Present	Editorial Board: Brain Aging
2020-Present	Professor, University of Florida, Department of Psychology
2020-Present	Affiliate Faculty, Center for Addiction Research & Education, University of Florida
2020	Ad-hoc Reviewer, Review Panel BBBP, National Institutes of Health
2019	Member, Steering Committee of National Academies of Sciences and National Institutes of Health Workshop
2018-Present	Affiliate Faculty, Pain Research and Intervention Center of Excellence (PRICE), Clinical and Translational Science Institute (CTSI), College of Medicine, University of Florida
2018-Present	Editorial Board: Journal of Experimental Psychology: General
2018-2020	Editorial Board: Cognition and Emotion
2018	Early Career Reviewer (ECR), Review Panel MESH, National Institute of Health
2018	Ad-hoc Reviewer, Review Panel SPIP, National Institutes of Health
2018	Ad-hoc Reviewer, Review Panel BBBP, National Institutes of Health
2018-Present	Editorial Board: Psychology and Aging
2018	Ad-hoc Reviewer, Austrian Science Foundation
2018	Ad-hoc Reviewer, Canada Research Chair
2017-2020	Associate Professor (with tenure), University of Florida, Department of Psychology
2017-2019	Member, Organizing Committee of the Indonesian-American Kavli Frontiers of Science Symposium
2016-Present	Ad-hoc Reviewer, National Science Foundation
2016-Present	Affiliate Faculty, Florida Institute for Cybersecurity Research (FICS), University of Florida
2013-Present	Affiliate Faculty, Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP) University of Florida
2013-2015	Junior Scholar in Claude D. Pepper Older Americans Independence Center Institute on Aging, Department of Aging & Geriatric Research, College of Medicine, University of Florida
2012-Present	Ad-hoc Reviewer, Swiss National Science Foundation
2012-2019	Editorial Board: Frontiers in Psychology: Emotion Science
2011-2017	Assistant Professor, University of Florida, Department of Psychology

2010-2011	Associate Research Scientist, Yale University, Department of Psychology
2007-2010	Postdoctoral Fellow, Yale University, Department of Psychology
2005-2007	Postdoctoral Fellow, Max Planck Institute for Human Development
2001-2005	Predoctoral Fellow, Free University Berlin & Max Planck Institute for Human Development

Honors

2020	UF College of Liberal Arts and Sciences Faculty Achievement Award
2019	UF Research Foundation Professorship Award
2016	UF College of Liberal Arts and Sciences International Educator of the Year Award
2016	UF Excellence Award -- Assistant Professors
2015	Kavli Fellow National Academy of Sciences
2014	International Max Planck Research School on the Life Course (LIFE) Outstanding Alumni Award, APA Board of Educational Affairs Award to Advance Interdisciplinary Education and Training in Psychology
2006	Heinz-Heckhausen-Jungwissenschaftlerpreis (Young Research Scientist Award), German Psychological Association

C. Contributions to Science

1. Own-Age Bias in Attention, Memory, and Emotion Perception

One line of my research builds on the fact that our environment is complex, and our cognitive system is limited, thus not all stimuli can be fully and simultaneously analyzed. There is evidence that emotional and self-relevant information is preferentially processed, possibly due to the highly practiced and elaborate knowledge structures associated with it as well as the greater personal and social costs of inattention or inaccurate memory. My research findings open new insights into how faces of different ages are processed and how they bias attention and memory. I show that this bias is affected by the emotional content of the faces and impacts memory for person-related information (e.g., personal goals and agendas). My results challenge and inform interpretations of face and emotion processing and age-related differences therein as older participants may be at a disadvantage relative to young participants when stimuli are faces of only young individuals. In our more recent work, we further demonstrate that brain regions involved in attentional biases can be trained via real-time functional magnetic imaging neurofeedback, including in older adults and individuals with Parkinson's disease or at risk for Alzheimer's disease. My findings are not only important from a developmental perspective, but they also place constraints on general theories of attention and memory and have various important implications for social interactions, emotional regulation, self-perceptions, psychological well-being, and health in adulthood and aging.

Representative Publications:

a. **Ebner NC**, He Y, Fichtenholtz HM, McCarthy G, Johnson MK. Electrophysiological correlates of processing faces of younger and older individuals. Soc Cogn Affect Neurosci. 2011 Sep;6(4):526-35. PubMed Central PMCID: PMC3150862.
b. **Ebner NC**, Johnson MR, Rieckmann A, Durbin KA, Johnson MK, Fischer H. Processing own-age vs. other-age faces: neuro-behavioral correlates and effects of emotion. Neuroimage. 2013 Sep;78:363-71. PubMed Central PMCID: PMC3684564.
c. Rana M, Varan AQ, Davoudi A, Cohen RA, Sitaram R, **Ebner NC**. Real-time fMRI in neuroscience research and its use in studying the aging brain. Front Aging Neurosci. 2016 Oct;8:239. PubMed Central PMCID: PMC5067937.
d. Strickland-Hughes CM, Dillon KE, West RL, **Ebner, NC**. Own-age bias in face-name associations: Evidence from memory and visual attention in younger and older adults. Cognition. 2020 Mar. PubMed PMID: 32192981

2. Decision Making and Aging

My lab aims at identifying adult age differences in cognitive, affective, and social influences on decision making, including in the applied contexts of health and computer security. We have shown that young and older adults differ in their use of future-time travel for healthy decision making. In addition, we have developed an infrastructure that allows us to determine internet users' susceptibility to cyberattacks (e.g., phishing emails) in the natural setting of the participants' homes. This research has found evidence of a particular vulnerability

in older compared to young internet users, combined with very low susceptibility awareness in the elderly. We have also developed a conceptual framework for social decision making in aging, as well as novel deception-related and social decision paradigms, which we submit to empirical testing in ongoing research (e.g., on phishing and misinformation/fake news).

Representative Publications:

a. Lin T, Capecci D, Ellis D, Rocha H, Dommaraju S, Oliveira DS, **Ebner NC**. Susceptibility to spear-phishing emails: Effects of internet user demographics and email content. ACM Transactions on Computer-Human Interaction, 2019 Jul; 26(5):1-28 PubMed Central PMCID: PMC7274040
b. **Ebner NC**, Ellis DM, Lin T, Rocha HA, Yang H, Dommaraju S, Soliman A, Woodard DL, Turner GR, Spreng RN, Oliveira DS. Uncovering susceptibility risk to online deception in aging. J Gerontol B Psychol Sci Soc Sci. 2020 Feb 14;75(3):522-533. PubMed PMID: 29669133
c. Grilli, MD, McVeigh, KS, Hakim, ZM, Wank, AA, Getz, SJ, Levin, BE, **Ebner, NC**, Wilson, RC. Is this phishing? Older age is associated with greater difficulty discriminating between safe and malicious emails. J Gerontol B Psychol Sci Soc Sci. 2021, 76:1711-1715. PubMed PMID PMCID: PMC8557838
d. Hakim, ZM, **Ebner, NC**, Oliveira, DS, Getz, SJ, Levin, BL, Lin, T, Lloyd, K, Lai, VT, Grilli, MD, Wilson, RC. Evaluating the cognitive mechanisms of phishing detection with PEST, an ecologically valid lab-based measure of phishing susceptibility. Behavior Research Methods, 2021. PubMed Central PMCID: PMC8188181

3. Oxytocin and Socioemotional Aging

As summarized in recent theoretical papers, oxytocin is a neuropeptide with beneficial effects in social and emotional domains, mostly studied in healthy young adults, schizophrenia, and autism. Our group is the first to comprehensively study acute and chronic oxytocin effects in the context of emotional, motivational, and social-cognitive aging. We have developed a theoretical framework that allows us to examine the extent to which the neuropeptide oxytocin is associated with improved functioning in aging, considering gene-brain-behavior relationships using behavioral, (epi)genetic, pharmacological, and neuroimaging techniques. In this line of work, we have generated supportive evidence of good tolerability and benefits of oxytocin intranasal intervention on various functions in aging (e.g., affect, social decision making, resting brain activity)

Representative Publications:

a. **Ebner NC**, Chen H, Porges, E, Lin T, Fischer H, Feifel D, Cohen RA. Oxytocin's effect on resting-state functional connectivity varies by age and sex. Psychoneuroendocrinology. 2016 Jul;69: 50-59. PubMed Central PMCID: PMC4942126
b. **Ebner NC**, Horta M, Lin T, Feifel D, Fischer H, Cohen RA. Oxytocin modulates meta-mood as a function of age and sex. Front Aging Neurosci. 2015 Sep;7:175. PubMed Central PMCID: PMC4565056.
c. Plasencia G, Luedicke JM, Nazarloo HP, Carter CS, **Ebner NC**. Plasma oxytocin and vasopressin levels in young and older men and women: Functional relationships with attachment and cognition. Psychoneuroendocrinology. 2019 Dec. PubMed Central PMCID: PMC6943921
d. Horta M, Kaylor K, Feifel D, **Ebner NC**. Chronic oxytocin administration as a tool for investigation and treatment: A cross-disciplinary systematic review. Neurosci & Biobehav Rev. 2020 Jan; 108: 1-23. PubMed Central PMCID: PMC6949379.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/natalie.ebner.1/bibliography/public/

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: Cued high-speed multidirectional yoga: Impact on retinal microvascular and cognitive measures

Principal Investigator(s): Signorile et al

Institutions: UM, UF

OVERALL IMPACT

Please provide your assessment of the strengths and weaknesses of the application using brief bullet points to reflect the project's likelihood to exert a sustained, powerful impact on the research field(s) involved, using the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact. Please score the application's potential using the following 1 (Highest Impact) to 9 (Lowest Impact) rating scale for each review criteria section:

Impact	High	Medium	Low
Score: 3	1 2 3	4 5 6	7 8 9

Overall Impact *Write a brief paragraph summarizing the factors that informed your Overall Impact score.*

- Aim 1 determines whether yogacue will improve outcomes more than standard yoga. The potential significance is moderate, as it's an efficacy study for a specific intervention – both are likely to have overlapping outcomes.
- Aim 2 is to determine the extent to which changes in retinal microvasculature are related to cognitive function. These researchers have already shown that HVCT improves several retinal measures; they aim to replicate this result in this new group of participants.
- Aim 3 is to determine the relative contributions of neuromuscular and cardiovascular fitness changes to retinal measures and cognitive changes. They will use stepwise regression to relate neuromuscular and cardiovascular changes to cofnitive and retinal variables
- Overall the project has a high probability of future funding.
- If successful, it would lead to an exciting new approach for combined cognitive/exercise training. It is woefully underpowered, but this is inevitable, given it is a pilot. Perhaps more individual-subject approaches could address the underpoweredness (multiple assessments, or mid-training assessment).

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance 3

Strengths

- Interventions that reduce age related cognitive decline are essential.

- Further evidence toward using retinal vasculature as an outcome measure that relates to cognitive and vascular health would help evidence toward using this relatively cheap marker as an endpoint in clinical trials, or an assessment for individual patients.
-

Weaknesses

- If one of the interventions is shown to be an improvement relative to the other, further work would be needed to identify what aspect resulted in the improvement.

2. Investigator(s) 1

Strengths

- The team is extensive and has all the necessary expertise.
- Students will be trained in this study, bringing more expertise to the field and to McKnight centers.

Weaknesses

- none

3. Innovation 2

Strengths

- Having a multi-component program to target both cerebral blood flow and cognitive function is innovative.
- Using OCTA as an outcome measure is innovative
-

Weaknesses

- OCTA has been used before in similar studies, and the applicants note that it has been used as an outcome measure to assess cardiovascular health.

4. Approach 5

Strengths

- Smart to emphasize fluid cognition in cognitive testing.
- The combination of trainings within the YogaCue paradigm seems lika potentially productive effect.
- Using retinal microvasculature as an outcome measure is a strength of the proposal.

Weaknesses

- 20 people in each group is small. While this is a pilot, the worry is that such small sample sizes can lead to two problems: inflated effect sizes, as well as false positive errors.
- Worries about power to detect an effect exist for some of the outcome variables. Aims 2 and 3 seem to use only the participants randomized to YogaCue, and involve regression analyses. 20

participants in a regression analysis requires a very large association to be 'significant' and has a large probability of false positives.

- It appears that Hatha yoga interventions and YogaCue interventions will be performed in groups, 6 months apart? This would mean that there will be an additional confound of time in all comparisons between the conditions. This was not entirely clear from the write up, but I fully hope it was designed so that the timing is counterbalanced across conditions.

5. Environment 1

Strengths

- The labs seem to have expertise in this domain, and will be well able to complete the project as stated.

Weaknesses

-

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes: 1

Strengths

- Excellent collaboration.

Weaknesses

-

2. Potential for clinical translational impact of the intervention on cognitive aging and memory 1

Strengths

- Potentially combines benefits of high intensity training with those of yoga and some cognitive training regimens.

Weaknesses

- The study assesses whether this particular yoga intervention is better than another, but it isn't clear what factors are important in the change. In the case of a 'positive' result, further work would be needed to know if it is the high intensity component, or the cognitive training component, or something else that is driving the difference. Knowing this would be necessary to identify other interventions that would be effective. However, if YogaCue ends up being the magic intervention that beats every other intervention, in every population, then this is irrelevant.

3. Potential for future NIH funding of the research 2

- High. Though future funding would likely depend on the ability to identify and propose mechanisms behind the improvement in YogaCue condition relative to Hatha yoga. It would be more impactful to identify a generalizable condition or factor that improves outcomes, rather than a single task.

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title:

Principal Investigator(s):

Institutions:

OVERALL IMPACT

Please provide your assessment of the strengths and weaknesses of the application using brief bullet points to reflect the project's likelihood to exert a sustained, powerful impact on the research field(s) involved, using the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact. Please score the application's potential using the following 1 (Highest Impact) to 9 (Lowest Impact) rating scale for each review criteria section:

Impact	High	Medium	Low
Score	1 2 3	4 5 6	7 8 9

Overall Impact: 3

Write a brief paragraph summarizing the factors that informed your Overall Impact score.

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance score: 2

Strengths

- The data from this pilot RCT could provide important preliminary evidence for the acceptability and early evidence of efficacy of a low cost, Yoga-based, dcognitive intervention.
- The demonstration of a multimodal method combining cognitive training and physical exercise would provide new scientific support for integrating physiological and cognitive components in an intervention.
- Retinal biomarkers as surrogates for the CNS hold the potential to be informative non-invasive tools to measure the impact of interventions.

Weaknesses

- The absence of measures of compliance and acceptability will make difficult the interpretation of study outcomes.
- There are few data to show that physical exercise improves cognition among individuals without baseline cognitive impairment. The inclusion/exclusion criteria leave open the possibility of enrolling those who will not benefit cognitively from intervention.

2. Investigator(s): 2

Strengths

- The investigative team is a strength in this project.

Weaknesses

-

3. Innovation: 3

Strengths

- The use of Yoga to combine physical and cognitive interventions is innovative.

Weaknesses

- The retinal biomarkers have apparently been already been shown to be correlated with cognitive decline from Alzheimer's disease, exercise and with cognitive interventions.

4. Approach: 4

Strengths

- **The design using the YogaCue and conventional yoga in the setting of an RCT is a strength.**
- **The pre/post correlation of cognition with the retinal biomarkers is also a strength**

Weaknesses

- There are no pre-stated measures or criteria for compliance, adherence and acceptability. A failure of any of these factors will render the other outcomes difficulty to interpret.
- There are no inclusion criteria other than age, leaving open the confounders of enrolling individuals with normal cognition, other reasons for cognitive impairment, the effects of concomitant medication, depression, and pulmonary conditions. It is not clear why diabetes is an exclusion if a neuropathy is not present.
- There is no statement whether there will be selective blinding of study outcomes by those assessing cognitive, exercise and retinal changes.
- The final section labeled "Timeline and Future Directions" does not state possible next steps that would be incorporated in a federal application.

5. Environment: 1

Strengths

- The environment is excellent.

Weaknesses

-

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes:
Strengths • The collaborating institutions are UMiami and UFlorida. Most of the work will be done in Miami, but Dr. Ebner from Florida has an important role regarding the cognitive components of this project **Weaknesses** •

2. Potential for clinical translational impact of the intervention on cognitive aging and memory:
Strengths • There is high potential for clinical translation of this intervention **Weaknesses** •

3. Potential for future NIH funding of the research:
• There is high potential for future NIH funding.

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: Cued high-speed multidirectional yoga: Impact on retinal microvascular and cognitive measures

Principal Investigator(s): Signorile et al

Institutions: UM, UF

OVERALL IMPACT

Please provide your assessment of the strengths and weaknesses of the application using brief bullet points to reflect the project's likelihood to exert a sustained, powerful impact on the research field(s) involved, using the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact. Please score the application's potential using the following 1 (Highest Impact) to 9 (Lowest Impact) rating scale for each review criteria section:

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- Aim 1 determines whether yogacue will improve outcomes more than standard yoga. The potential significance is moderate, as it's an efficacy study for a specific intervention – both are likely to have overlapping outcomes.
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- Overall the project has a high probability of future funding.
- If successful, it would lead to an exciting new approach for combined cognitive/exercise training. It is woefully underpowered, but this is inevitable, given it is a pilot. Perhaps more individual-subject approaches could address the underpoweredness (multiple assessments, or mid-training assessment).

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance 3

Strengths

- Interventions that reduce age related cognitive decline are essential.

- Further evidence toward using retinal vasculature as an outcome measure that relates to cognitive and vascular health would help evidence toward using this relatively cheap marker as an endpoint in clinical trials, or an assessment for individual patients.
-

Weaknesses

- If one of the interventions is shown to be an improvement relative to the other, further work would be needed to identify what aspect resulted in the improvement.

2. Investigator(s) 1

Strengths

- The team is extensive and has all the necessary expertise.
- Students will be trained in this study, bringing more expertise to the field and to McKnight centers.

Weaknesses

- none

3. Innovation 2

Strengths

- Having a multi-component program to target both cerebral blood flow and cognitive function is innovative.
- Using OCTA as an outcome measure is innovative
-

Weaknesses

- OCTA has been used before in similar studies, and the applicants note that it has been used as an outcome measure to assess cardiovascular health.

4. Approach 5

Strengths

- Smart to emphasize fluid cognition in cognitive testing.
- The combination of trainings within the YogaCue paradigm seems lika potentially productive effect.
- Using retinal microvasculature as an outcome measure is a strength of the proposal.

Weaknesses

- 20 people in each group is small. While this is a pilot, the worry is that such small sample sizes can lead to two problems: inflated effect sizes, as well as false positive errors.
- Worries about power to detect an effect exist for some of the outcome variables. Aims 2 and 3 seem to use only the participants randomized to YogaCue, and involve regression analyses. 20

participants in a regression analysis requires a very large association to be 'significant' and has a large probability of false positives.

- It appears that Hatha yoga interventions and YogaCue interventions will be performed in groups, 6 months apart? This would mean that there will be an additional confound of time in all comparisons between the conditions. This was not entirely clear from the write up, but I fully hope it was designed so that the timing is counterbalanced across conditions.

5. Environment 1

Strengths

- The labs seem to have expertise in this domain, and will be well able to complete the project as stated.

Weaknesses

-

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes: 1

Strengths

- Excellent collaboration.

Weaknesses

-

2. Potential for clinical translational impact of the intervention on cognitive aging and memory 1

Strengths

- Potentially combines benefits of high intensity training with those of yoga and some cognitive training regimens.

Weaknesses

- The study assesses whether this particular yoga intervention is better than another, but it isn't clear what factors are important in the change. In the case of a 'positive' result, further work would be needed to know if it is the high intensity component, or the cognitive training component, or something else that is driving the difference. Knowing this would be necessary to identify other interventions that would be effective. However, if YogaCue ends up being the magic intervention that beats every other intervention, in every population, then this is irrelevant.

3. Potential for future NIH funding of the research 2

- High. Though future funding would likely depend on the ability to identify and propose mechanisms behind the improvement in YogaCue condition relative to Hatha yoga. It would be more impactful to identify a generalizable condition or factor that improves outcomes, rather than a single task.

McKnight Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss

Funded by the McKnight Brain Research Foundation through the American Brain Foundation and the American Academy of Neurology

Application Deadline: September 14, 2023

This award aims to support young investigators in clinical studies relevant to age-related cognitive decline and memory loss. The award also recognizes the importance of rigorous training in clinical research and encourages young investigators to seek opportunities to establish future careers in the area of human cognitive aging. **Please note: the focus should NOT be solely on a neurodegenerative dementia (e.g. Alzheimer's disease); however, proposals that focus on combined study of cognitive aging and neurodegenerative cognitive changes may be considered.**

The award will consist of a commitment of $65,000 per year for two years, plus a $10,000 per year stipend to support education and research-related costs for a total of $150,000. Supplementation of the award with other grants is permissible, but to be eligible to apply for this award, the other grant source(s) cannot exceed $75,000 annually.

The American Academy of Neurology is firmly committed to embracing the diversity among our members, applicants, and reviewers and affirms the importance of equity and inclusiveness within the AAN research program.

HOW TO APPLY

1. Visit AAN.com/view/ResearchProgram
2. Go to "2022 McKnight Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss"
3. Select "Apply now"

Please only submit one application - applicants are not allowed to submit applications for more than one award. Your application will also be considered for all relevant clinical research scholarship awards.

Visit the Frequently Asked Questions portion of the website for more information.

IMPORTANT DATES

September 14, 2023: Application deadline – Note that this is the deadline for all documents, including those from the mentor and chair. Applications will be declined if this information is not submitted by September 14.
January 2024: Notification of recipients
July 1, 2024: Funding begins

ELIGIBILITY

1. For the purpose of this scholarship, research is defined as "patient-oriented research conducted with human participants, or translational research specifically designed to develop treatments or enhance identification of age-related cognitive decline and memory changes. These epidemiologic or behavioral studies, clinical trials, studies of disease mechanisms, the development of new technologies, and health outcomes research." Disease-related studies not directly involving humans are also encouraged if the primary goal is the development of therapies, diagnostic tests, or other tools to prevent or mitigate neurological diseases.
2. Recipient must be interested in an academic career in neurological research who has completed residency or a PhD no more than 5 years prior to the beginning of this award (July 1, 2024). If you have completed both residency and a PhD, your eligibility is based on when you completed residency. If you completed a fellowship of any kind after residency, your eligibility is still based on the date you finished residency.
3. The proposed program of training and research must be performed entirely within an institution in the United States accredited by the relevant accrediting authority.

A successful application should include the following:

- Well-developed hypothesis: The hypothesis is testable and presented in clear language.
- Detailed statistical plan: Statistical methods are well-designed and detailed.
- Strong mentorship: There is clear demonstration of strong mentorship to support the project.
- Feasible primary outcomes: Each aim is feasible, focused, and logical.
- Innovation: Project concept is original, novel, and will advance the applicant's long-term career goals.
- Well-defined training plan: There is a clear and gap-based career development plan.

EVALUATION AND SELECTION

Applications are evaluated by reviewers based on the following criteria:

- Quality and originality of the research plan
- Applicant's ability and promise as a clinician-scientist based on prior record of achievement and career plan, and NIH Biosketch
- Quality and nature of the training to be provided and the mentor-specific, departmental, and institutional training environment
- Innovation of the research plan approach
- Project significance: the ability to progress the field or solve an important problem

REQUIRED ATTACHMENTS FOR APPLICATION

1. PDF of Three-page Research Plan, including brief statements of aims, background, contemplated approaches to methodology and any supporting preliminary data/figures. References do not count toward the page limit. The research plan should be written by the applicant and should represent their original work. However, the applicant is expected and encouraged to develop this plan based on discussion with the proposed mentor.
2. PDF of Applicant's NIH Biosketch. See this link for the most recent NIH Biosketch template

Once the above information is fully completed and **submitted** by the applicant:

3. The **chair** will receive an email with a link asking them to check a box confirming that the applicant's clinical service responsibilities will be restricted to no more than 30 percent of the applicant's time and include a list of applicant's non-research related service. The chair will NOT be asked to submit a letter.
4. The **mentor** will receive an email with a link to submit a letter of reference detailing their support of and commitment to the applicant's proposed research and training plan. The letter should be 1,000 words or less and specifically indicate the mentor's role in the development and preparation of the applicant's research plan including:
    - How the proposed research fits into the mentor's research program
    - Expertise and experience in the area of research proposed and the nature of the mentor's proposed time commitment to the applicant's supervision and training
    - Mentor's prior experience in the supervision, training, and successful mentoring of clinician scientists
    - Potential for applicant's future research career and comparison of applicant to other trainees
    - Institution's commitment to 70 percent protected research time
5. The **mentor** will also be required to upload a NIH Biosketch.

ANNUAL AND FINAL PROGRESS REPORTS

An annual progress report is due in May of the first year. Renewal of the award in year two is contingent upon presentation of a satisfactory progress report. Additionally, a final research report and a final expenditure report are due within 60 days following the close of the grant term. The final expenditure report must be prepared by the institution's financial office.

CONTACT INFORMATION:

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