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

Friday, January 29, 2021
4:30 pm ET – 5:30 pm ET

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

Members:	Dr. Madhav Thambisetty, Committee Chair; Dr. Patricia Boyle; Dr. Robert Krikorian; Dr. Richard Isaacson; Dr. Sue Pekarske; and Dr. Mike Dockery, MBRF Chair
Also Attending:	Ms. Amy Porter, Ms. Melanie Cianciotto

AGENDA

4:30 pm ET	1.	Call to Order/Roll Call	Dr. Thambisetty
	2.	Current Grants/Programs	Dr. Thambisetty
ACTION		a. Review of Pilot Grant Applications and Reviewers' Comments b. McKnight Clinical Translational Research Scholarship Program Report (American Brain Foundation/AAN) • 2021 Scholars and their Project Proposals • Full List of all Scholars and Mentors • Discussion - Draft Agreement for 2022-2027 Program Renewal 1) ABF Response to Advertising and Application Request 2) ABF Response to Review Request	
	3.	Report on Outreach to Possible Partners for the MBRF Mid-Career Research Award in Cognitive Aging and Memory Loss	Dr.Thambisetty
5:30 pm ET	4.	Adjourn	Dr. Thambisetty
ACTION			All

To: The McKnight Brain Research Foundation Board of Trustees

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

Date: December 11, 2020

Re: McKnight Research Foundation (MBRF) Cognitive Aging and Memory Intervention Core Pilot Grants: 2020-2022 Cycle

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

A Review of the Process and the Impact of COVID-19

We began formulating the guidelines of the RFP for the current cycle in mid-February 2020, which was discussed at the Leadership Council call on 3/4/2020. Two weeks later, the academic community went on lockdown because of COVID-19, and all research ceased at the four MBI's. With little information on the expected duration of the lockdown, we nevertheless issued the RFP on 4/4/2020, with the Letter of Intent due on 5/1/2020 and a full proposal due on 7/1/2020. Receiving only two LOI's felt the result the pandemic, we extended the due date to 6/1/2020 and full proposals were expected by 8/1/2020. In the end, we received four LOI's, all of which resulted in requests for a full proposal.

We received all four full proposals by the due date. Because Dr Lazar had submitted one of the grant applications, Dr Levin assumed the role of getting two internal reviewers for each proposal in order to firewall all PIs from the review process. Because of COVID-19, it was much more difficult than anticipated to get reviewers, largely because clinical researchers were struggling to make up for the approximately three-month period when data could not be collected on their funded projects. In the end, we received the final review this week, and we are forwarding the four applications, the eight 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 eight reviews.

2. Scores

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

		Scores	
Applicant	**Reviewer 1**	**Reviewer 2**	**Mean Score**
Lazar (UAB)	2	3	2.5
Hernandez (UAB)	3	4	3.5
Gomes-Osman (Miami)	5	2	3.5
Kaur (Miami)	4	4	4

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 therefore recommend to the Trustees pilot funding for the Lazar and Hernandez proposals. Lazar (UAB and Miami) seeks to use a 10-week, remotely monitored, high intensity training intervention on a stationary cycle in older adults with hypertension. The project would explore associations between retinal microvascular density, growth factors, and cognitive function, and the response of hypertension to this intervention. There was a tie in the mean scores of Hernandez (UAB and Florida) and Gomes-Osman (Miami and Florida), but the former was chosen largely because of the numerous moderate weaknesses Identified by Reviewer 1 with the latter. In addition, Dr. Hernandez is a junior investigator and her study addresses gut-brain interactions in a translational rodent model in the context of cognitive aging. Both studies recommended for support by the MBRF were judged as having high potential for future NIH funding. 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, both Drs. Lazar and Levin would be pleased to meet with the Trustees during their consideration of these recommendations.

Respectively submitted,

Bonnie Levin, PhD

Ronald M. Lazar, PhD

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: Harnassing Optimal Mechanisms of Exercise for Cognitive Gains (HOME-Cog)

Principal Investigator(s): Joyce Gomes-Osman, PT, PhD, and Eric Porges, Ph.D.

Institutions: University of Miami and 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	1 2 3	4 5 6	7 8 9

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

This is creative and highly innovative proposal which attempts to address mechanisms underlying potential exercise induced cognitive and physical changes. Intervention is person specific aerobic exercise regimen, 3 X a week for 50 minutes, over the course of an 8 week period. Mechanisms of potential LTP/neuroplasticity induced by this exercise are being examined using TACS (transcranial alternating current stimulation) combined with EEG. Primary outcomes are changes in TACS/EEG (gamma), heart rate variability, and cognition. The strength of this proposal relates to innovative approach and an at home interventoin. The weakness is study design and methodology. No justification of sample size or clearcut inclusion/exclusion criteria or screening. Why age 55? In one place the N is listed at 30 and another as 40. Rationale for selection of designated cognitive tests under developed and those that are selected (except perhaps CANTAB RT) are likely not sufficiently sensitive to detect differences.. Given likelihood of strong practice effects, unclear whether single arm study is best design. Overall, a novel project with significant methodologic issues that detract from its potential.

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

- Potential for clarifying mechanism of action of exercise induced cognitive changes

Weaknesses

- Weaknesses relate to methodology.

2. Investigator(s)

Strengths

- Strong team including Drs. Gomes-Osman (PI) and Dr. Porges at UF, and Dr. Pascual Leone;

Weaknesses

- In addition to above, 8 other investigators listed. Other than Dr. Pascual Leon, lack of specificity regarding the roles of these investigators. No biosketches provided

3. Innovation

Strengths

- Highly innovative application of the TACS/EEG method to examine potential changes induced by exercise intervention

Weaknesses

-

4. Approach

Strengths

- Novel at home indices for measuring brain brased changes. Very creative

Weaknesses

- No justification for sample size. In one place the N is listed as 40 and another 30. Which is it and why?
- Need better clarification of participant inclusion-exclusion criteria. Only mentioned that folks had to be age 55+
- Cognitive aim is weakest. Selection of cognitive measures is not ideal. Need more 'power measures'. CANTAB is ok, but need better exec function and memory measures. (i.e., Digit Span listed as the only exec function measure, a list learning from RBABS for mememory. RBANS better suited for lower functioning population.
- Due to single arm design one cannot disentangle practice effects on cognition. I appreciate that there will be correlational analyses, but wonder if it might make sense to include at 10 folks without the aerobic intervention. Particularly since there is some ambiguity re garding sample size.
- The person specific aerobic regimen has strengths and weaknesses. Is there data suggesting that some individual exercise protocols are more effective than others vis a vis the primary dv in aim 2.

5. Environment

Strengths

- Infrastructure at both UM and UF is superb

Weaknesses

-

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes

Strengths

- Strong collaborative relationship between the UM group headed by Dr. Gomes- and the UF group led by Dr. Porges

Weaknesses

- None

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

Strengths

- Superb, assuming that methodologic issues can be addressed

Weaknesses

- Methodologic weakness detracts significantly

3. Potential for future NIH funding of the research

- Very innovative, but need to clean up methodologic issues

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: Harnessing Optimal Mechanisms of Exercise for Cognitive Gains (HOME-Cog)

Principal Investigator(s): Joyce Gomes-Osman

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

Overall Impact: 2

This proposal is the first step in a study that seeks to identify biomarkers associated with exercise-related cognitive improvement. The potential benefits if this study is succesful are large. Succesful identification of biomarkers that correlate with, and even predict, individual differences in the cognitive benefits of exercise could have enormous clinical relevance in identifying those who will benefit from exercise, as well as determining the optimal amount of exercise they should do.

In addition, in response to the COVID crisis, all measurements in the study – including the measurement of physiological measures such as HRV and tACS/EEG – will be run inside participants' homes. This is highly novel and, if successful, will demonstrate the feasibility of this approach that could be used in a wide range of other studies.

I note some minor weaknesses in Approach – lack of power calculation, possible concerns about safety – that would need to be addressed in more detail in an R01.

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

- Exercise has been associated with improvements in cognition, but there are big individual differences in size of this effect. This study sets out to better understand these individual differences by looking for biomarkers that correlate with cognitive improvement
- If successful, this will enable researchers to determine who is likely to benefit from exercise and who is not, and prescribe the optimal dose of exercise to those who will benefit

Weaknesses

-

2. Investigator(s)

Strengths

- The PI has assembled an impressive team that appears to have all relevant skills and experience

Weaknesses

-

3. Innovation

Strengths

- Directly measuring changes in neuroplasticity using tACS/EEG is new
- Relating changes in HRV to cognitive changes induced by exercise is new
- Doing all of this in participants' homes is extremely novel and, if successful, may open up all kinds of possibilities for tACS and EEG studies to be run remotely

Weaknesses

-

4. Approach

Strengths

- Running the study remotely is clearly a strength in the current COVID situation and, if successful, will also open up a new way of conducting psychophysiological studies.
- Including participants in late-midlife is a strength

Weaknesses

- The remote study could also be a weakness. Will participants be able to place the electrodes correctly? Will participants be less engaged, and less likely to complete, a long remote study?
- The remote nature of the work also has implications for the safety of the study. While tACS side effects are rare under lab conditions, and indeed tACS systems can be purchased for home use, what would happen if there were an adverse event remotely? I suspect NIH would require a Data Safety Monitoring Board for this study and this is something the investigators might consider setting up.
- Lack of power calculation for determining sample size

5. Environment

Strengths

- Both Universities have considerable strength in aging and MBI at both locations strengthens the collaboration between sites

Weaknesses

-

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes

Strengths

- Researchers at both sites will play a role in different parts of the project.
- Areas of collaboration are clearly defined as are the areas where each location / investigator will take the lead

Weaknesses

-

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

Strengths

- If successful, this study will establish the feasibility of running these kinds of experiments in participants' homes. Such an advance could completely change the way in which these kinds of studies are run and lead to new and larger scale interventions of this sort

Weaknesses

-

3. Potential for future NIH funding of the research

- Strong

UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM

UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE

July 31, 2020

Dear McKnight Research Foundation (MBRF) Cognitive Aging and Memory Intervention Core Committee Members,

Please find enclosed the submission of the grant proposal entitled: Harnessing Optimal Mechanisms of Exercise for Cognitive Gains (HOME-Cog). The current proposal outlines a collaborative project between the between the Evelyn F. McKnight Brain Institutes (MBI) at University of Miami and University of Florida that aims to inform the knowledge gap on the mechanistic action of exercise on the brain by characterizing important mechanisms of neuroplasticity and cardiovascular capacity, proposed to underlie cognitive response to exercise.

Investigators on this grant application:

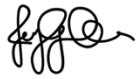
1. Joyce Gomes-Osman, PT, PhD (Principal Investigator), Assistant Professor, Departments of Physical Therapy and Neurology, University of Miami
2. Katalina McInerney, PhD (Co-Investigator), Assistant Professor, Department of Neurology, Division of Neuropsychology, University of Miami
3. Mitchell Slugh, PhD, (Co-Investigator), Instructor, Department of Neurology, Division of Neuropsychology, University of Miami
4. Tatjana Rundek, MD, PhD (Co-Investigator), Professor of Neurology and Public Health Sciences, Department of Neurology, University of Miami
5. Bonnie Levin, PhD (Co-Investigator), Bernard and Alexandria Schoninger Professor of Neurology, Director, Division of Neuropsychology, University of Miami
6. David Loewenstein, PhD (Co-Investigator), Professor of Psychiatry & Behavioral Sciences and Neurology
7. Alvaro Pascual-Leone, MD, PhD (Co-Investigator), Professor of Neurology, Harvard Medical School
8. Eric Porges, PhD, Assistant Professor Center for Cognitive Aging & Memory (CAM) Department of Clinical and Health Psychology, University of Florida
9. Joseph Gullett, Research Assistant Professor Center for Cognitive Aging & Memory (CAM) Department of Clinical and Health Psychology, University of Florida
10. Adam Woods, PhD, Associate Professor, Department of Clinical and Health Psychology, College of Public, Health and Health Professions, University of Florida
11. Ronald Cohen, PhD, Professor and Director, Clinical Translational Research in Cognitive Aging and Memory, University of Florida

Proposed Reviewers for this application:

1. Dylan J Edwards, PhD, Director, Moss Rehabilitation Research Institute, EdwardDy@einstein.edu
2. Ronald M Lazar, PhD, Professor of Neurology and Evelyn F. McKnight Endowed Chair in Memory and Learning, University of Alabama, rlazar@uabmc.edu

Thank you for your consideration. Please feel free to contact me should you need any further information.

Sincerely,



Joyce Gomes-Osman, PT, PhD
Assistant Professor, Departments of Physical Therapy and Neurology
Director, Neuromotor Plasticity Laboratory
University of Miami Miller School of Medicine

Department of Physical Therapy
5915 Ponce De Leon Boulevard, 5th floor, Coral Gables, FL 33146
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Grant Proposal Title:
Harnessing Optimal Mechanisms of Exercise for Cognitive Gains (HOME-Cog).

Key and Senior Personnel:

1. Joyce Gomes-Osman, PT, PhD (Principal Investigator), Assistant Professor, Departments of Physical Therapy and Neurology, University of Miami
2. Katalina McInerney, PhD (Co-Investigator), Assistant Professor, Department of Neurology, Division of Neuropsychology, University of Miami
3. Mitchell Slugh, PhD, (Co-Investigator), Instructor, Department of Neurology, Division of Neuropsychology, University of Miami
4. Tatjana Rundek, MD, PhD (Co-Investigator), Professor of Neurology and Public Health Sciences, Department of Neurology, University of Miami
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9. Joseph Gullett, PhD (Co-Investigator), Research Assistant Professor Center for Cognitive Aging & Memory (CAM) Department of Clinical and Health Psychology, University of Florida
10. Adam Woods, PhD (Co-Investigator), Associate Professor, Department of Clinical and Health Psychology, College of Public, Health and Health Professions, University of Florida
11. Ronald Cohen, PhD (Co-Investigator), Professor and Director, Clinical Translational Research in Cognitive Aging and Memory, University of Florida

Project/Performance Sites

This study will be conducted at the Evelyn F. McKnight Brain Institutes at University of Miami and University of Florida.

Principal Investigator: Joyce Gomes-Osman, PT, PhD
Institution and Mailing Address: University of Miami Department of Physical Therapy, 5915 Ponce de Leon Blvd, 5th floor, Coral Gables, 33146. Email: j.gomes@miami.edu, Tel: 1-305-284-2632, FAX: 1-305-284-6128

A.SUMMARY

Extensive evidence supports a link between aerobic exercise and cognitive improvements in aging adults. A major limitation with existing research is that some individuals show robust cognitive benefits from exercise, while others show less pronounced improvements. Our incomplete understanding of the mechanisms that influence this variability and the low adherence to exercise are critical knowledge gaps and major barriers for achieving optimal efficacy of exercise for brain health in aging. The goal of this McKnight Pilot Grant project is to inform the knowledge gap on the mechanistic action of exercise on the brain by characterizing important mechanisms of neuroplasticity and cardiovascular capacity proposed to underlie cognitive response to exercise. We will deliver an 8-week, home-based aerobic exercise intervention remotely to 30 sedentary healthy adults 55+ years of age. We will employ and test an innovative home-based, non-invasive assessment of neuroplasticity using transcranial alternating current stimulation (tACS). We will assess cardiovascular capacity using heart rate variability, and cognitive function using a neuropsychological test battery, also using remote procedures. The current proposal outlines a collaborative project between the between the Evelyn F. McKnight Brain Institutes (MBI) at University of Miami and University of Florida. Finally, the results of this study will inform an extended proposal to rigorously investigate mechanisms driving cognitive gains associated with different exercise doses and modalities in the form of an R01 submitted by the end of this award.

B.SPECIFIC AIMS

Maintenance of cognitive health is critical to healthy aging. Individuals with poor cognitive function are more likely to lose independence and have reduced quality of life. Pharmacological approaches to treating cognitive decline in mid to later life have been limited.[1] In contrast, interventions that increase levels of physical activity have been effective at improving cognitive function in aging adults.[2–4]

Aerobic exercise with its cardiorespiratory gains contributes to cognition by optimizing cerebrovascular function, ultimately leading to more efficient neural processing.[5] At the brain level, neuroplasticity is an important mechanism and driver of aerobic exercise-induced cognitive improvements. Neuroplasticity is broadly defined as a change in neural structure and function in response to experience or environmental stimuli. A critical component of neuroplasticity in response to exercise is long-lasting synaptic potentiation. Direct electrical recordings of hippocampal neurons show synaptic enhancement (i.e., long-term potentiation or LTP)[6] after exercise that correlates with improved cognitive outcomes.[7–13] In our prior studies where we utilized Transcranial Magnetic Stimulation (TMS) as a probe, we demonstrated a substantial LTP-like neuroplasticity response to exercise that was relevant for exercise-induced cognitive gains.[14] We have also established the feasibility of using TMS neuroplasticity response as an outcome measure of exercise-induced improvements in cognitive function in adults over the age of 55 years after 8 weeks of aerobic exercise.[15]

An important limitation of existing research is that adhering to supervised in-person exercise can be challenging for many aging adults. Given the increasing use of ubiquitous mobile technologies by aging adults, a remotely delivered exercise research program may facilitate recruitment and retention, address barriers to exercise participation, and accelerate the translation of our findings to a broader audience. Home-based interventions are especially relevant in light of the COVID-19 pandemic and current social distancing practices.

Importantly, unlike TMS that requires in-person visits, it is possible to conduct a remote and non-invasive neuroplasticity assessment by using tACS combined with electroencephalography (EEG). TACS/EEG is uniquely suited for a home-based intervention as it can be delivered with a device designed for home use that is placed at the participant's home. Utilizing established procedures using a secure video platform, the participant is instructed on how to appropriately place the EEG cap, and the study investigators conduct the assessment via remote neurophysiological monitoring. Small electrodes placed on the scalp deliver a short burst of tACS, which induces a controlled perturbation in the brain that is measured by EEG changes.

Variability in exercise-induced cognitive improvements remains the most significant barrier to achieving optimal efficacy of exercise for brain health in aging. Some individuals show robust cognitive benefits from exercise, while others show less pronounced improvements. Advancing understanding of differences in cognitive response to exercise will require concurrent examination of neuroplasticity and cardiovascular changes after exercise. The variation in time between consecutive heartbeat intervals or heart rate variability (HRV) is a robust measure of cardiovascular capacity that is relevant to aging and can be measured remotely. HRV reflects the dynamic mechanisms of autonomic heart rate regulation,[16] and independently captures and predicts age-related cardiovascular changes[16–18] that correlate with age-related cognitive decline.[19–21] Importantly, HRV is modifiable and increased after exercise.[22–25] Brain-heart pathways linking cardiac autonomic responses measured by HRV and neuroplasticity measured with non-invasive brain stimulation are reported,[26,27] but no studies have investigated these relationships in response to exercise in aging.

We will conduct a single-arm intervention pilot trial estimating the degree to which an 8-week home-based moderate-to-vigorous aerobic exercise will be feasible, and induce within-participant change in post-tACS gamma EEG power (neuroplasticity), HRV (cardiovascular) and cognitive performance (neurocognitive battery). The trial will enroll 40 adults of age 55 years or greater within 2 years. Our specific aims are to:

Aim 1. Conduct a pilot trial to examine the feasibility of a home-based, remotely delivered trial consisting of 8 weeks of moderate-to-vigorous intensity aerobic exercise. We predict that this study will be feasible, defined by successful recruitment of 40 participants within 2 years, with at least 80% adherence.

Aim 2: Determine if 8 weeks of home-based, moderate-to-vigorous aerobic exercise induces changes in: a) tACS/EEG neuroplasticity response; and b) HRV. We hypothesize that both, post-tACS gamma EEG power and HRV will increase after 8 weeks of exercise.

Aim 3: Determine whether a) 8 weeks of home-based, moderate-to-vigorous aerobic exercise improves cognition; and whether b) cognitive response to exercise is modified by tACS/EEG neuroplasticity, and HRV gains. We hypothesize that cognitive function will improve after exercise and that this effect will be modified by post-tACS gamma EEG power and HRV.

The results of this study will demonstrate the potential use of tACS/EEG as a biomarker of cognitive responses to exercise and will inform a larger R01 application to investigate the mechanisms driving cognitive gains associated with different exercise doses and modalities.

C. RESEARCH STRATEGY

Significance

1. Exercise is demonstrated to effectively maintain and improve cognition in aging adults. Cognitive health is critical for healthy longevity because it is highly linked to one's functional independence in carrying out important aspects of life, such as living independently and managing healthcare and finances. While cognition begins to decline upon reaching older age, there are documented changes in the structure and function of the nervous system that begin in late middle age.[28] Taken together, these findings indicate that effective strategies for maintaining and improving cognitive health are critically needed and should be introduced earlier, preferably before reaching 'older adulthood' at 65 years of age.

There is currently no effective pharmacological agent for treating age-related cognitive decline. Exercise, however, is demonstrated to effectively promote cognitive brain health in aging adults. At least 50 meta-analyses collectively suggest modest, but significant improvements in cognitive abilities following long-term exercise interventions (i.e., those that last at least 4 weeks).[3,4,29–35] Syntheses of systematic review and meta-analyses have reached the same conclusion.[36,37] Professional and scientific organizations such as the US Department of Health,[38] the American College of Sports Medicine[39] and the Institute of Medicine[40] have independently recognized that being physically active is an important part of cognitive health promotion in aging individuals.

2. Low adherence to exercise is a major obstacle that can be addressed by home-based interventions. Despite the widely disseminated benefits to physical function and cognition associated with maintaining a regular exercise regimen, less than 40% of individuals 65 and older in the US are considered active, and 20% of these individuals do not regularly participate in any physical activity.[41] In-person interventions are the most widely available option for engagement in physical exercise, but many older adults find it challenging to adhere to such interventions. Results from our own work of a large-scale systematic review of 98 randomized controlled exercise trials demonstrated that only 35.7% individuals reported adherence to exercise above 80%.[2] Physical exercise interventions need to be tailored to the older adult population to improve recruitment and retention in research studies, and to increase the possibility that older adults will incorporate physical activities as part of their daily lives.[42,43] Home-based exercise interventions address relevant barriers to participation to in-person interventions.[44,45] The use of mobile platforms that many older adults own and are comfortable operating eliminates commute time and assistance with transportation.[46] Home-based interventions are particularly relevant in current times, when many older adults may be less enthusiastic about leaving their homes. As telehealth services are more widely available, remote exercise interventions are a viable and safe option for older adults to become more active.[46–49] Finally, home-based interventions are less prone to be impacted by restrictions to in-person procedures that are present during the COVID-19 pandemic.

3. Variability in cognitive response to exercise is a major barrier for progress in this field. Despite established effectiveness, the great variability in the cognitive response to exercise, results in a lack of clarity with respect to which regimens are required to achieve specific and consistent results. For example, the optimal and necessary exercise doses and regimens required to achieve maximal cognitive benefits are

unknown. What is needed to advance science in this field is to examine why exercise is more or less effective for different individuals. To answer this question, we need measures or biomarkers that capture the effects of exercise at the brain level, and better knowledge of mechanisms that could explain variations in cognitive response to exercise. The main goal of this proposal is to gain a greater understanding of important mechanisms that contribute to variability in cognitive response to aerobic exercise, namely neuroplasticity and cardiovascular capacity.

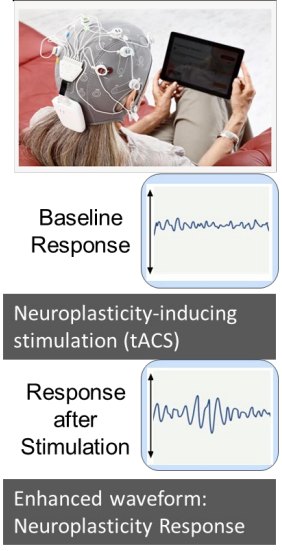
Innovation

1. Evaluating mechanisms of neuroplasticity to capture the effects of exercise in the brain is novel. Neuroplasticity changes in the brain underlie exercise-induced cognitive improvements. At the brain level, synaptic neuroplasticity is a mediator found to be necessary and sufficient for exercise-induced improvements in cognition. In experimental models, aerobic exercise leads to enhanced synaptic activity in hippocampal neurons (i.e., long-term potentiation or LTP) that is correlated with cognitive gains in visuospatial abilities.[8,9] In experimental animal models of impaired LTP, aerobic exercise 'rescues' synaptic neuroplastic ability, which is associated with cognitive gains.[10–13]

We presently lack measures of synaptic neuroplasticity for clinical use that could act as surrogate markers of the effect of exercise in the brain. We will employ a neurophysiological measure that enables insights into synaptic neuroplasticity in humans utilizing non-invasive brain stimulation, and relate changes in this measure to changes in cardiovascular capacity and cognitive performance that occur in response to aerobic exercise.

We will use tACS, which is a specific form of transcranial electrical stimulation (tES) combined with EEG to measure neuroplasticity. tES has many applications, but is mostly known and used for its ability to modulate activity of cortical areas (i.e., neuromodulation), which is harnessed for clinical applications like the treatment of depression.[50,51] We will employ neuromodulation in an innovative application: We will use tACS as a probe to measure neuroplasticity instead of using it as a treatment. The tACS/EEG neuroplasticity measure is illustrated in Figure 1. The TACS/EEG device, designed for home use, is placed at the participant's home. Utilizing established remote visit procedures, the participant is instructed on how to appropriately place the EEG cap, and study investigators conduct the assessment via remote neurophysiological monitoring in real-time. The practical application of tACS is simple: a low intensity (1-2 mA) alternating electrical current in the range of gamma frequencies (40-60Hz) is applied to the scalp overlying cortical areas of interest, while the cathodes are placed on the forehead. We will target the primary cortex and prefrontal cortices, separately.[52,53] This weak electric current induces a controlled perturbation of the brain that is assessed by EEG as a local response, and a distributed adaptation of the brain to the local, controlled perturbation.

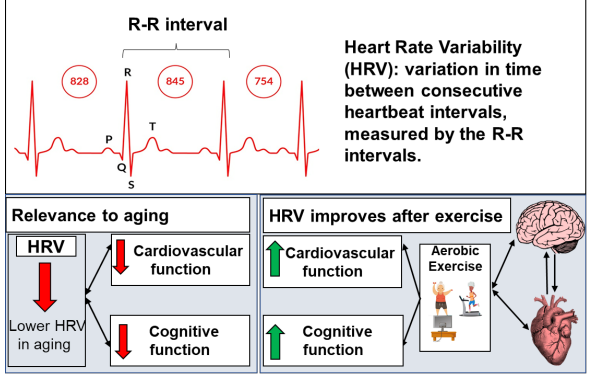
Fig 1. tACS/EEG neuroplasticity



Following the delivery of tACS to the targeted cortical area, the amplitude of EEG signals are transiently increased for up to a period of approximately an hour,[54] after which they return to baseline levels. The time course of EEG changes parallels the increases in synaptic efficacy during LTP.[55] Both mechanisms are highly dependent on NMDA[56] and GABAergic receptor activity.[57] The degree of potentiation of gamma power post-tACS is considered an index of neuroplasticity that is correlated with cognitive abstract reasoning abilities.[52,53,58] tACS is safe and well established in clinical neurophysiology across different ages, including aging individuals.[59,60] Our findings will demonstrate the potential use of tACS/EEG to capture a biomarker of neuroplasticity to study the cognitive responses to exercise.

2. Relating Heart rate variability and neuroplasticity changes after exercise is novel. HRV (Figure 2) is defined as the variation in time between consecutive heartbeat intervals. HRV, and specifically High Frequency HRV is a robust biomarker of the cardiovascular effects of exercise in aging, reflecting central, neural modulation of cardiac activity by the parasympathetic branch of autonomic nervous system.[61,62] Consistent findings report that HRV is a valid, reliable, and independent risk factor for cardiovascular disease mortality,[17,63] and cognitive impairment in aging.[64] Regular exercise improves HRV through cardiovascular and autonomic adaptations.[23,65] A recent meta-analysis and meta-regression showed that aerobic training is the most effective exercise to enhance HRV in aging adults.[25] Importantly, exercise-induced increase in HVR correlates with improved executive function.[24,66] Dr. Porges' lab at UF has investigated HRV in healthy

Fig 2. Heart Rate Variability



adults and neuropsychiatric populations.[67,68] This proposal creates a unique opportunity for us to work together to bridge a major knowledge gap on critical mechanisms underlying exercise-induced cognitive gains in aging individuals by relating changes in HRV and tACS/EEG neuroplasticity after exercise.

Approach

IRB approval already exists for this study. This is an open trial involving an 8-week exercise intervention. We will recruit a total of 30 adults aged 55 years or older from the University of Miami Community. Eligible individuals will sign a remotely delivered informed consent as per University Policy.

Inclusion Criteria: a) age ≥ 55years; b) no clinically detectable cognitive impairment (Montreal Cognitive Assessment or MoCA score ≥ 24); c) low activity level as defined by the International Physical Activity Questionnaire; d) primary language is English. Exclusion criteria: a) any unstable medical condition; b) medical contraindication to physical exercise; c) lack of familiarity with mobile devices (iPad).

Study Kit: Upon signing informed consent, participants will be mailed a Study Kit, containing devices that will be used during the assessments and exercise intervention. These include: 1) a sphygmomanometer (Omron, Inc.), 2) a heart rate monitor (Polar Inc.), 3) a pulse oximeter (Diagnostix™), 4) a physical activity monitor (ActiGraph LLC), and 5) an iPad and 6) a pre-paid shipping label. At the end of the study, participants will mail back the study kit using the pre-paid shipping label.

Study Design: Participants will undergo a remotely delivered pre-intervention assessment battery consisting of assessments of cognitive testing, tACS/EEG neuroplasticity and cardiovascular capacity, and will begin exercising. After the 8-week exercise program, they will repeat the cognitive, tACS/EEG neuroplasticity and cardiovascular capacity assessments. Participants will be compensated a total of $120 for study participation.

Home-based Exercise Intervention: Exercise sessions follow standard physical therapy protocols with existing safety procedures that were adapted to a virtual setting. Dr. Gomes-Osman is a licensed Physical Therapist and will oversee the exercise procedures. Home-based exercise sessions will be monitored remotely using a secure, video platform through Zoom. We will follow a standard set of exercises that will be individually adapted to each participant's available resources and personal situations. For instance, individuals whom have access to exercise equipment will be able to use them, and others who do not will be given an exercise plan that that will not require any equipment (containing exercises such as squats and marching in place). Participants will engage in 3 weekly 50-minute sessions (totaling 150 weekly minutes) of moderate-to-vigorous intensity aerobic exercise for a total of 8 weeks (relative to their age-predicted maximal heart rate determined at 220-age[69] (54-65% on weeks 1-4 and 65-90% on weeks 5-8). We will assess perceived effort using the 20-point Borg scale.

Remote Assessment Measures: All assessment measures will be performed at baseline and after the 8-week exercise intervention. All visits will be monitored remotely using a secure, video platform through Zoom and will be conducted by the study team members of Dr. Gomes-Osman's Laboratory, with appropriate oversight.

Neuroplasticity: We will employ established tACS/EEG procedures to measure neuroplasticity.[70,71] Dr. Alvaro Pascual-Leone, one of the foremost international authorities in neurophysiological methods will oversee the implementation of the neuroplasticity assessments, and Dr. Gomes-Osman has 11 years' research experience using non-invasive brain stimulation. We will utilize the non-invasive brain stimulation/EEG hybrid STARSTIM®-Home system (Neuroelectrics, Inc) and will record EEG before (5 mins), during (3 mins) and after (5 mins) tACS stimulation. Participants will be instructed on how to appropriately place the EEG cap, and will receive tACS stimulation (3min, 40-60Hz, 1-2mA) targeting the motor and prefrontal cortices through remote neurophysiologic monitoring by the study team. We will use published methods of artifact removal and event detection algorithms to extract the magnitude and duration of post-tACS gamma EEG power changes from the EEG signals.[70,71]

Cognitive performance: We will use a neuropsychological test battery that has been adapted for a remote delivery by our Neurocognitive Divisions. Executive function will be assessed using the Digit Span subtest of the Wechsler Adult Intelligence Scale;[72] list learning (among other constructs) will be assessed with the repeatable neuropsychological battery (RBANS); verbal fluency and semantic retrieval will be assessed using phonemic and category fluency tests; the Geriatric Depression Scale will assess depressive symptoms;[73] and the Patient-Reported Outcomes Measurement Information System (PROMIS) will assess quality of life outcomes.[74] We will employ adjunct assessments using the Cambridge Neuropsychological Test Automated Battery (CANTAB) to assess speed of processing.[75]

Submaximal aerobic capacity and HRV: HRV will be assessed at rest and during 1-minute Sit-to-Stand Test[76] using the ActiGraph GT9X Link, paired with a wireless heart rate monitor (POLAR Inc.) that generates beat to beat intervals (R-R interval), an approach demonstrated to be comparable to in ECG for HRV measurement.[77] Data will be then transferred to a computer using the CentrePoint system. All R-R data will be manually reviewed by trained team members. HRV measures will include time and frequency domains, and spectral and nonlinear indices,[16,78] calculated offline using Kubios and Cardioedit/Cardiobatch software.[79,80] Dr. Porges' Lab (UF MBI)

have extensive expertise in the collection and analyses of HRV,[67,68] and thus, will oversee the HRV implementation and conduct analyses.

Management of Safety Concerns: A careful exercise safety plan exists for this study and includes a rigorous screening for safety to exercise, and procedures for safe administration of remote exercise visits according to University of Miami Policy (standard telehealth procedures). Dr. Gomes-Osman is a licensed Physical Therapist and will oversee the exercise procedures. Dr. David R. Gater, MD, PhD, Chair of PM&R, will be available for consults regarding medical clearance of participants. There are no known serious risks associated with tACS/EEG. Subjects may rarely experience scalp irritation from the electrode placement. We will collect all subjective complaints during and after tACS/EEG, and potential adverse events. As mentioned, Dr. Alvaro Pascual-Leone will provide the guidance on tACS/EEG safety and interpretation.

Data Analysis Plan: Baseline characteristics will be summarized as means ± standard deviation or medians (interquartile ranges) for continuous variables and as frequency (%) for categorical variables. Normality for the distributions of continuous variables will be visually assessed and statistically tested. If the normality assumption is questionable, Box-Cox transformation will be used to reduce the skewness in the indicated analyses or non-parametric tests will be used. All statistical tests will be conducted against a 2-sided alternative hypothesis, employing a significance level of 0.05. We will quantify exercise adherence to the home-based intervention as the percentage of exercise sessions attended by 40 participants within 2 years, and we will examine whether adherence was achieved by successful recruitment and completion of with at least 80% adherence using a binominal test **(Specific Aim 1)**. In the univariate analysis, we will compare the changes in tACS/EEG neuroplasticity **(Specific Aim 2a)** and HRV **(Specific Aim 2b)** from pre-intervention to post-intervention using paired t-test. In the multivariable analyses, we will adjust for baseline characteristics (age, sex, race-ethnicity, education) using mixed effect modeling to quantify improvements in cognitive performance after exercise **(Specific Aim 3a)**, and to determine an association between changes in cognitive performance and changes in tACS/EEG neuroplasticity and HRV **(Specific Aim 3b).** We will use serial modification models by including and excluding tACS/EEG neuroplasticity and HRV terms to evaluate whether the relationships between changes in cognitive performance after exercise are affected by these two mechanisms. Dr. Chuanhui Dong, Associate Professor of Neurology, and Lead Biostatistician for the McKnight Brain Institute will conduct the statistical analyses for the proposed study.

Limitations/Additional mechanisms contributing to cognitive gains post-exercise: Other health mechanisms beyond those considered in the present application can influence the cognitive response to exercise. We will collect depressive symptoms and quality of life before/after exercise, allowing us to gain preliminary insights into how they might influence cognitive gains after exercise. High cardiovascular[81] and inflammatory burden[82] impairs neuroplasticity and cognitive gains, and we will also examine such mechanisms in our future studies.

D. MULTISITE MBI COLLABORATIONS

This study will harness and strengthen existing collaborations between the Evelyn F. McKnight Brain Institutes at University of Miami and University of Florida. In addition to MBIs resources, the infrastructure for this trial will be provided by Dr. Gomes-Osman's KL2 award that evaluates an 8-week in-person exercise intervention and in-person neurophysiological assessments on neuroplasticity using TMS. These established procedures have been adapted to and tested for a remote format for the current study. The recruitment, assessments, and implementation of the home-based exercise will be performed by UM MBI (Dr. Gomes-Osman Lab). Dr. Porges' Lab (UF MBI) have extensive expertise in the collection and analyses of HRV[67,68] and therefore will assist to plan, develop and conduct the HRV analyses. Drs. McInerney and Slugh (UM MBI) and Gullett (UF MBI) will develop and oversee the neuropsychological assessments. Drs. Rundek, Loewenstein and Levin (UM), Cohen and Woods (UF) will provide guidance, advice, and support. The trial will also expand the collaborative efforts of UM and UF MBIs to the Marcus Institute for Aging Research in Boston, Harvard Medical School (Dr. Alvaro Pascual-Leone, who will guide the implementation and analysis of the tACS/EEG).

E. TIMELINE AND FUTURE DIRECTIONS

A timeline of research activities is seen in Table 1. The results of this study will contribute to the framework of 'precision brain health' for aging adults by advancing understanding of critical and modifiable markers (neuroplasticity, cardiovascular) implicated in variability in cognitive response to exercise. Importantly, we will submit an R01 in year 2 of this award to further investigate such mechanisms using different exercise doses.

Table 1: Research Activities	Year 1	Year 2
Execution of **Aim 1, Aim 2** and **Aim 3**		
Presentations and Publications		
R01 Submission		

F. RERENCE LIST

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BUDGET YEARS PERFORMANCE PERIOD: 2020 – 2022

Please note: Only Requesting support for items in table below, shown in bold font.

Budget Category	Budget Item	Amount ($)	Justification (See details below)
Personnel:			
1. Joyce Gomes-Osman, PT, PhD	75% Yearly Salary Support	-	Principal Investigator. No salary support requested
2. Eric Porges, PhD	**4% Yearly Salary Support (4,000 per year for 2 years)**	**8,000**	**Co-investigator.**
3. TBA Research Assistant	**50% Yearly Salary Support (21,225 per year for 2 years)**	**42,450**	**TBA Research Assistant.**
	Total Requested Personnel	***50,720***	
Supplies:			
1. Physical Activity Monitors	**GT9x Link activity monitors (10 x $250); Charger for activity monitor (10 x $40); and Straps (10 x $22)**	**3,120**	**Study Kit Component. Physical Activity monitoring of participant during intervention.**
2. Access to Centre Point Software	**Software License ($1500 per year for 2 years)**	**3,400**	**Necessary for the remote monitoring with the Physical Activity Monitors**
3. Blood Pressure Monitor	**Wireless Upper Arm Blood Pressure Monitor BP7350 7 Series® + AC Adapter (10 units x $62)**	**620**	**Study Kit Component. Safely monitoring of participant during assessment and intervention.**
4. Fingertip Pulse Oximeter	**Fingertip Pulse Oximeter ADC Diagnostix 2100 (10 units x $80)**	**800**	**Study Kit Component. Safely monitoring of participant during assessment and intervention.**
5. Heart rate monitor	**Polar H10, Polar Electro (10 units x $90)**	**900**	**Study Kit Component. Safely monitoring of participant during assessment and intervention.**
6.iPad and internet connection	**Apple iPad 10.2" 7th Generation, Wi-fi + Cellular 128gb (10 units x $531), T-Mobile unlimited cellular data (10 units x $55 x 24 months)**	**18,510**	**Study Kit Component. Required to conduct remote assessments and exercise visits.**
7. Non-invasive brain stimulation/EEG hybrid system	**STARTSTIM®-Home system (2 units x $10,000)**	**30,000**	**Study Kit Component. Brain plasticity assessment.**
8. Access to the Cambridge Neuropsychological Test Automated Battery (CANTAB)	**(All CANTAB tests up to 100 tests)**	**3,060**	**Adjunct assessment to the neuropsychological test battery.**
	Total Requested supplies	**60,410**	
Other Expenses:			
9. Shipping costs	**Estimated cost (USPS large Priority Mail with insurance $59 x 2 shipments per participant x 30 participants)**	**3,540**	**Costs related with shipping the study kit.**
10. Research Participation Compensation	**$120 per participant for 30 participants**	**3,600**	**Expenses to compensate participants for their time.**
11. Publication Costs	**$1,000 per year for 2 years**	**2,000**	**To publish our research findings on the proposed project.**
	Total Requested 'other expenses'	***9,140***	
	Total Requested Support for Years 1 and 2	**120,000**	

Personnel Justification

Joyce Gomes-Osman, PT, PhD; Principal Investigator (no salary support requested)
Dr. Joyce Gomes-Osman is an Assistant Professor of Physical Therapy and Neurology at the University of Miami, Miller School of Medicine (UM). Her long-term research goal is to develop exercise interventions that can be individually tailored to promote cognitive brain health in aging adults. Dr. Gomes-Osman proposes an open trial to develop, implement and characterize the effects of an 8-week remotely delivered exercise intervention on cognitive performance, a transcranial alternating current stimulation (tACS) measure of neuroplasticity and cardiovascular capacity as measured by heart rate variability (HRV) in sedentary adults aged 55+. Dr. Gomes-Osman has salary support of 75% covered by her CTSI-NIH KL2 grant until December 2020, and will continue to be supported by the Department of Physical Therapy at the University of Miami thereafter, thus, not requiring further salary support to conduct the proposed project. Dr. Gomes-Osman has Department support for 2 graduate research assistants for 20 weekly hours, in her Neuromotor Plasticity Laboratory. **Base Salary** $74,855**, Fringe Benefits** $19,387

Eric Porges, PhD; Co-investigator
Dr. Eric Porges is an Assistant Professor Center for Cognitive Aging & Memory (CAM) Department of Clinical and Health Psychology University of Florida, Gainesville. Dr. Porges' Research Interests encompass Mechanisms of Aging and Healthy Development across the Life Span, Neuroimaging Methods applied to cognition, including GABA Magnetic Resonance Spectroscopy and Vagal Nerve Stimulation. Importantly, Dr. Porges has expertise HRV measurements and thus he will oversee the collection analysis and interpretation of HRV in the proposed project. **Base Salary** $78,329**, Fringe Benefits** $21,671

Research Assistant (TBA)
Research assistant will give support to the lab activities described in the proposed application. 50% salary support in Years 1-2. Duties and responsibilities in the laboratory include, collecting data, recruiting participants, analyzing lab results, managing data, engaging in and assisting with manuscript preparation for the publishing of scientific findings. **Base Salary** $31,736**, Fringe Benefits** $10,714.

Katalina McInerney, PhD (Co-Investigator), Assistant Professor, Department of Neurology, Division of Neuropsychology, University of Miami (no salary support requested)

Mitchell Slugh, PhD, (Co-Investigator), Instructor, Department of Neurology, Division of Neuropsychology, University of Miami (no salary support requested)

Tatjana Rundek, MD, PhD (Co-Investigator), Professor of Neurology and Public Health Sciences, Department of Neurology, University of Miami (no salary support requested)

Bonnie Levin, PhD (Co-Investigator), Bernard and Alexandria Schoninger Professor of Neurology, Director, Division of Neuropsychology, University of Miami (no salary support requested)

David Loewenstein, PhD (Co-Investigator), Professor of Psychiatry & Behavioral Sciences and Neurology (no salary support requested)

Alvaro Pascual-Leone, MD, PhD (Co-Investigator), Professor of Neurology, Harvard Medical School (no salary support requested)

Joseph Gullett, PhD (Co-Investigator), Research Assistant Professor Center for Cognitive Aging & Memory (CAM) Department of Clinical and Health Psychology, University of Florida (no salary support requested)

Adam Woods, PhD (Co-Investigator), Associate Professor, Department of Clinical and Health Psychology, College of Public, Health and Health Professions, University of Florida (no salary support requested)

Ronald Cohen, PhD (Co-Investigator), Professor and Director, Clinical Translational Research in Cognitive Aging and Memory, University of Florida (no salary support requested)

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: *Reuniting the Brain and Body to Understand Cognitive Aging: The Nexus of Geroscience and Neuroscience*.

Principal Investigator(s): Abigail Hernandez, PhD (UAB)

Christy S. Carter, PhD (UAB) Thomas W. Buford, PhD (UAB) Jennifer Bizon, PhD (UF)

Sara Burke, PhD (UF)

Institutions: University of Alabama at Birmingham (host institution), 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 *Write a brief paragraph summarizing the factors that informed your Overall Impact score.*

This is an very good application from an outstanding group of collaborators that proposes to study gut-brain interactions in the context of cognitive aging. The ultimate goal is to determine if novel therapeutic strategies targeting the gut can improve age-related cognitive decline in a validated rodent model of aging. Overall, this study is likely to have a moderate - high impact in the field of cognitive aging. In their approach, Aims 1 and 2 will leverage banked tissue from probiotic and ketogenic diet treated animal groups and will analyze brain inflammation and E/I signaling. This is an excellent use of resources and will provide new data as to the effects of probiotics and ketogenic diet on key proteins and cytokine expression in important areas of the brain involved in cognitive aging. Aim 3, will develop an 8 day chronic vagal stimulation model and measure changes in brain inflammation in HPC and PFC, tryptophan metabolism and dysbiosis. This Aim has not been as well described as it could have been and failed to address the multiple mechansims and affects that cervical vagal stimulation may have including changes in blood pressure, heart rate and other circulating hormones that may contribute to their observed effects on brain inflammation and tryptophan metabolism. It is unclear how stimulation of both vagal efferent and afferents will mimic or be attributed to the changes in just the "gut-briain" axis as is presumed in the application. These limitations diminished sonewhwat the overall impact.

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

- This study is of high significance and address an important yet, to date, understudied, area of cogntivie aging. Human studies report advanced age is associated with gut dysbiosis which was subsequently associated with cognitive impairment. These investigators will leverage their current NIH funding in geroscience and cogntivive againg to advance important new knowledge in the gut-brian axis and how it affects cognitive aging in their rodent model.

Weaknesses

- none

2. Investigator(s)

Strengths

- Outstanding group of investigators brining together expertise in the required fields to ensure project success.

Weaknesses

-

3. Innovation

Strengths

- High Innovation. This project will focus on the gut microbiome as a target "organ" of intervention for addressing age-related cognitive dysfunction is innovative, as few studies have considered this approach despite evidence of microbiota involvement in other nervous system disorders with cognitive dysfunction and its role in inflammation.
-

Weaknesses

- none

4. Approach

Strengths

- The team has, for the most part, adapted a well reasoned and rational approach to obtained new data that will be key for further NIH funding. In Specific Aim 1, Will explore gut/brain adaptations in aged rats in response to interventions performed by the UAB team, including physical exercise and renin angiotensin system-targeting probiotics. They plan to use banked PFC and HPC tissue from male rats that were treated with either a vehicle control, null probiotic or the LP-A with and without exercise (total of six groups) for 3 months. They will assess expression of proteins

involved in E/I signaling (NR1, GABA(B)R1b and GAD67. This aim is reasonable and given the experience of the team should be able to be completed successfully.

- In Aim 2, they will explore gut/brain adaptations among aged rats in response to interventions performed by the UF team in the context of a ketogenic diet. The team will used banked PFC and HPC tissue and assess E/I tone and brain inflammatory cytokines. This aim is reasonable and given the experience of the team should be able to be completed successfully.

Weaknesses

- In Aim 3, they will use 8 days of implatable vagal nerve stimulation in 36, 24 month old male FBN rats and measure brain inflammation in HPC and PFC, tryptophan metabolism and dysbiosis via 16s sequencing. This aim has some important limitations that were not addressed in the application. Primarily the investigators have summarily ignored the hemodynamic and humoral effects of vagal stimulation and how these effects on heart rate and blood pressure and circulating hormones maybe be contributing to any observed changes in inflammation and trptophan metabolism in the brain. Also, cervical stimulation will activate both vagal afferent and efferents and is not a in any way a selective activation of gut-vagal fibers. These limitation significanly distract from the enthusiasm for the project.
-
-

5. Environment

Strengths

- Excellent environment

Weaknesses

-

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes: High

Strengths

- The group proposes to assemble a team of well-funded scientists with expertise, in their specific fields, centered around gut-aging/*geroscience* and cognitive aging/*neuroscience* respectively to mentor Dr. Hernandez in her pursuit of a K99/00 applicaton and to foster inter-institutional MBI collaboration in the pursuit of a PO1 application. Drs. Christy Carter and Thomas Buford at the University of Alabama at Birmingham (UAB team) and of Drs. Sara Burke and Jennifer Bizon at the University of Florida (UF team), are all faculty of the MBRF network at their institutions. Furthermore, this application supports the career development of an early stage investigator, Dr. Abbi Hernandez, who bridges the UAB and UF teams, as a former graduate student and post-doc in the lab of Dr. Burke and who is a current post-doc in the lab of Drs. Carter and Buford.

Weaknesses

- none

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

Strengths

- This study will address the basic science animal work that must be done prior to clinical translation. Thus, this work does have some impact for the ultimate development of pro-biotic interventions to improve cognitive aging in humans.

Weaknesses

-

3. Potential for future NIH funding of the research

- High

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: Reuniting the Brain and Body to Understand Cognitive Aging: The Nexus of Geroscience and Neuroscience.

Principal Investigator(s): Abigail Hernandez

Institutions: University of Alabama at Birmingham (host institution) and 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	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 studies have demonstrated an interaction between intestinal health and brain health. Gut health appears to play an important role in cognitive function. In view of this, the goal of this study is to determine if novel therapeutic strategies targeting the gut can improve age-related cognitive decline in a rodent model of aging. From banked samples collected using resources from existing federal grants, the proposal will perform experiments to better understand the contribution of gut dysbiosis to age-related cognitive decline. The goal will be achieved in three specific aims. The first aim will explore gut/brain adaptations in aged rats in response to interventions performed by the UAB team, including physical exercise and renin angiotensin system-targeting probiotics. The second aim will explore gut/brain adaptations in aged rats in response to interventions performed by the UF team in the context of a ketogenic diet. The last aim will explore gut/brain adaptations in aged rats in response to interventions performed by the UF team in the context of vagus nerve stimulation. Strengths of this pilot proposal from a junior investigator are high clinical relevance, an experienced PI, a nice collaboration between UAB and UF, an experienced mentoring team, and the availability of banked tissues. However, some weaknesses in the experimental design were noted for this otherwise strong proposal. Also, if applicant will be able to obtain an independent funding from NIH is also a concern.

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

- Studying the mechanism by which gut dysbiosis play a role in age-related cognitive decline and how various interventions targeted to improve gut function may help alleviate age-related cognitive decline is of high clinical importance.

Weaknesses

-

2. Investigator(s)

Strengths

- The PI, Dr. Hernandez, is a post-doctoral student at the University of Alabama, Birmingham. Dr. Hernandez received her PhD in Biomedicine/Neuroscience and also did her post-doc at the University of Florida. The PI has published a total of fourteen journal articles of which she is first author on 11 articles. Based on her training, she appears well-trained to lead this project.
- Drs. Carter (present mentor), Buford (present mentor), Bizon, and Burke (PhD and prior post-doc mentor) will serve as mentors. All appear well-qualified for their role on the project.

Weaknesses

- The PI did her PhD and first post-doc under the mentorship of Dr. Sara Burke. Dr. Burke will once again mentor the PI.
- Link for PI's published work is provided from Google Scholar (minor). Only link from federal sources (.gov) are accepted by the NIH.

3. Innovation

Strengths

- Evaluating strategies to improve cognitive function by improving gut health and evaluating potential mechanisms are novel.

Weaknesses

- The concept of association between gut microbiome and cognitive function is not novel.

4. Approach

Strengths

- Aged (20 – 24 months) Fisher344 / Brown Norway rats will be used to perform the proposed experiments.
- Tissue will be generated using resources from existing grants.
- The impact of four interventions (physical exercise, renin angiotensin system-targeting probiotics, ketogenic diet, and vagus nerve stimulation) will be evaluated.
- As evidenced by the experience of the team members and support letters provided, the team has the ability to carry out the proposed experiments.

Weaknesses

- Since tissues generated from ongoing grants / projects will be used, details of those experiments are not provided. Such details (or references) would be of great help in evaluating experimental design.

- Variable sample sizes (n = 4-12 / group) will be used for experiments proposed in aims 1 – 3. Rationale for such sample size is not provided. It is mentioned that these preliminary data will be used to determine power for the future grant applications.
- It is not clear if rigorous experimental design will be used for the proposed experiments. Details on randomization, blinding, etc. are not provided.
- Only male rats will be used for the study. Considering the recent emphasis from the NIH on Sex as a Biological Variable and the importance of including female animals in experiments, conducting studies only in male animals is a weakness.
- Brain excitatory / inhibitory tone will be evaluated only by measuring levels of NR1, GABA(B)R1b, and GAD67 using immunoblotting.

5. Environment

Strengths

- Outstanding for proposed experiments.

Weaknesses

-

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes

Strengths

- There is a nice collaboration between the McKnight Brain Institutes at the University of Alabama, Birmingham and the University of Florida. Samples for the project will be generated at the University of Florida and will be analyzed at the University of Alabama – Birmingham.

Weaknesses

-

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

Strengths

- The impact of four interventions (physical exercise, renin angiotensin system-targeting probiotics, ketogenic diet, and vagus nerve stimulation) will be evaluated. If successful, these interventions can be used to improve cognitive aging and memory in the aged population.

Weaknesses

- Cognitive functions will not be studied in this project. However, those functions will be studied in projects that provide funding to generate tissues for this project.
- Only male animals will be included in the experimental design.

3. Potential for future NIH funding of the research

- Since tissues generated from already funded projects, by well-established investigators in the field, will be used for the project, I am not sure if the PI will be able to obtain independent funding for the project.

UAB MEDICINE

Knowledge that will change your world

Thursday, July 30, 2020

Dear Drs. Lazar and Levin,

Please find our McKnight Brain Research Foundation (MBRF) Cognitive Aging and Memory Intervention Core Pilot proposal "*Reuniting the Brain and Body to Understand Cognitive Aging: The Nexus of Geroscience and Neuroscience.*" The purpose of this proposal is to study gut-brain interactions in the context of cognitive aging. We would like to suggest the following MBI faculty and those external to the MBI as reviewers:

MBI

- Matt Huentelman (UA/Tgen; mhuentelman@tgen.org) – His research identifies lifestyle and genetic factors that confer cognitive resilience. He is versed in the impact of ketogenic diets and the importance to consider peripheral health as a mediator of cognitive aging.
- Meredith Hay (UA; mhay@email.arizona.edu) – Her research focuses on cardiovascular health and neuroinflammation, thus is versed in "reuniting the body" approach.

External

- Dominic D'Agostino (USF; ddagosti@health.usf.edu) - Expert on ketogenic diet and metabolic interventions.
- Christa McIntyre (UT-Dallas; christa.mcintyre@utdallas.edu) - Expert on vagus nerve stimulation.
- Jeffrey Woods (UI- woods1@illinois.edu)- Expert on gut-microbiome and exercise.

Thank you very much for considering our application and giving me the opportunity to submit.

Kindest Regards,

Abbi Hernandez Ph.D. | **Postdoctoral Trainee**
Translational Exercise, Aging, and Microbiome Laboratory
Department of Medicine; Division of Gerontology, Geriatrics, and Palliative Care;
UAB | The University of Alabama at Birmingham
Bevill Biomedical Research Building 769 | 845 19th St. South | Birmingham, AL, 35205
205-934-1047 | abigailhernandez@uabmc.edu

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

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

Project Title: Reuniting the Brain and Body to Understand Cognitive Aging: The Nexus of Geroscience and Neuroscience.

Senior/Key Personnel: Abigail Hernandez, PhD (UAB)
Christy S. Carter, PhD (UAB)
Thomas W. Buford, PhD (UAB)
Jennifer Bizon, PhD (UF)
Sara Burke, PhD (UF)

Project/Performance Sites: University of Alabama at Birmingham (host institution), University of Florida

Contact PI: Abigail Hernandez, PhD
Department of Medicine; Division of Gerontology, Geriatrics, and Palliative Care
The University of Alabama at Birmingham
Bevill Biomedical Research Building
845 19th St. South
Birmingham, AL, 35205
Phone: 205-934-1047
Email: abigailhernandez@uabmc.edu

RESEARCH PLAN

A. SUMMARY. The purpose of this proposal is to study gut-brain interactions in the context of cognitive aging. Gut health influences cognitive outcomes and alterations in brain health are often accompanied by impaired intestinal function. As gut health is likely a modifiable factor mediating cognitive resilience, several potential mechanisms of the bidirectional interactions across the gut-brain axis warrant further investigation. The ultimate goal of this study is to determine if novel therapeutic strategies targeting the gut can improve age-related cognitive decline in a validated rodent model of aging.

B. SPECIFIC AIMS. The purpose of this proposal is to study gut-brain interactions in the context of cognitive aging. Gut health influences cognitive outcomes[1,2] and alterations in brain health are often accompanied by impaired intestinal function[3] leading to global and brain-specific inflammation. As gut health is likely a modifiable factor mediating cognitive resilience, several potential mechanisms of the bidirectional interactions across the gut-brain axis warrant further investigation. First, alterations in neurotransmitter levels impact both brain and gut function. Second, dysregulated microbiome composition (i.e. dysbiosis) is common in advanced age[4,5] and is correlated with impaired cognition[6], frailty[1] and inflammation[7]. Third, metabolic processes, especially those governed by gut-mediated tryptophan metabolism, lead to systemic and brain inflammation, are impaired with age and these impairments may lead to alterations in neuronal function, which may manifest as disrupted balance between excitatory and inhibitory (E/I) neuronal signaling[8,9].

However, preclinical studies addressing the impact of age-related dysbiosis on cognitive function are lacking, perhaps due to the large range of expertise required to appropriately conduct these types of studies. In addition, the field of *neuroscience* has focused on studying cognition from the "neck up" while, fields studying the biology of aging/age-related diseases, known collectively as *geroscience,* have focused "neck down" towards the gut. This dissection is also represented nationally by funding opportunities supported separately by the National Institute on Aging divisions, by meetings attended and journals supported. Thus, these two fields rarely intersect. Indeed our group is bringing awareness to this issue by leading a series of perspectives that will be published in upcoming issues of the *Journals of Gerontology: Biological Sciences.*

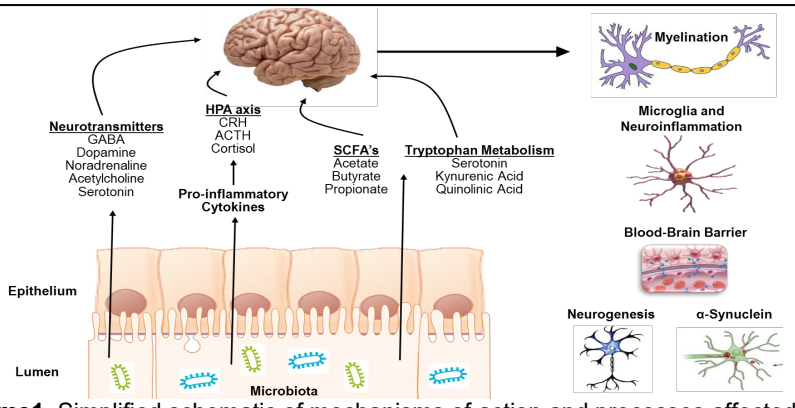
The UAB and UF MBI teams propose to utilize and generate tissues supported by our respective RO1 funded programs to bridge understanding of the contribution of gut dysbiosis (*geroscience*: neck down) to age-related cognitive decline (*neuroscience*: neck up). Critical to this mission is our need to collect similar outcome measures across these projects including those related to 1) brain inflammation; 2) brain excitatory/inhibitory tone (E/I); 3) gut dysbiosis (16s sequencing); and 4) gut tryptophan metabolomics. Importantly, our teams all use the Fisher344/Brown Norway (FBN) rat model of aging in their ongoing studies and will leverage data we have already or are currently collecting, to augment data proposed in the current proposal for future funding. Thus, we propose the following Specific Aims**:**

1. ***Explore gut/brain adaptations in aged rats in response to interventions performed by the UAB team, including physical exercise and renin angiotensin system-targeting probiotics.*** For this aim we will utilize tissues provided by the UAB Hernandez/Carter/Buford team. Measures will include quantification of proteins in the hippocampus (HPC) and prefrontal cortex (PFC) by UF's Bizon lab involved in E/I signaling that are altered in aged rats and relate to cognitive performance.
2. ***Explore gut/brain adaptations in aged rats in response to interventions performed by the UF team in the context of a ketogenic diet.*** For this aim we will utilize tissues provided by the Burke/Hernandez team. Measures include quantification of proteins involved in E/I signaling supported by the Bizon lab and inflammatory markers in PFC and HPC supported by the Hernandez/Carter/Buford UAB team.
3. ***Explore gut/brain adaptations in aged rats in response to interventions performed by the UF team in the context of vagus nerve stimulation***. For this aim we will utilize tissues provided by the Bizon lab. Measures include microbiome analysis (16s) of fecal samples, tryptophan metabolism in intestinal tissues (colon), and inflammatory markers in HPC and PFC.

Future studies will evaluate how these specific alterations can alter behavioral outcomes in aged rats. The UAB and UF teams are in the process of planning a PO1 grant, which will be further supported by the data collected through this opportunity. In addition, Dr. Hernandez is planning a K99/00 grant to study the influence of the periphery on age-related cognitive decline in the context of Alzheimer's disease (AD) and cognitive aging. This proposal will create a more nuanced understanding of how alterations in the gut result in changes in brain neurotransmitters, physiology and metabolism as well as the reverse relationship between brain health peripheral transmitters and serve to "reunite" the body in the context of studying cognitive aging and all of which are known to impact the gut and brain.

C. RESEARCH STRATEGY

C.1) SIGNIFICANCE: THE GUT MICROBIOTA IS AN UNDEREXPLORED SITE OF INTERVENTION FOR COGNITIVE AGING. Once considered the "forgotten organ",[10] the intestinal microbiota have received a tremendous amount of attention in recent years for their role in human health and disease. Notably, the majority of the body's constitutive immune function is dedicated to maintaining homeostasis with the microbiota – evidenced by the fact that 70% of the body's lymphocytes reside in the gut-associated lymphoid tissue. Once thought to contribute primarily to allergic and/or inflammatory intestinal disorders, the gut microbiota are now known to communicate with organs far from the intestine.[11,12] Indeed, the gut microbiota can communicate with the CNS in several different ways including 1) release of pro-inflammatory cytokines to activate the hypothalamic pituitary adrenal (HPA) axis or directly impact CNS immune activity, 2) production of short chain fatty-acids, 3) release of neurotransmitters, or 4) by modulating tryptophan and downstream metabolites (Scheme 1, left). Moreover, studies from "germ-free" gnotobiotic mice have demonstrated a critical impact of the microbiota on several CNS processes including myelination, neuroinflammation, regulation of blood-brain barrier integrity, as well as regulation of neurogenesis and accumulation of α-synuclein (Scheme1, right).[13–17]



Scheme1. Simplified schematic of mechanisms of action and processes affected by communication of the gut microbiota with the CNS.

Human studies report advanced age is associated with gut dysbiosis[4,5] which was subsequently associated with cognitive impairment.[6,18] To date, most approaches to preserve cognitive function in late-life directly targeted the brain/central nervous system (CNS). Studies in neurodegenerative diseases including Parkinson's[19] and Multiple Sclerosis[20] have demonstrated gut-neural communication that have contributed to calls to leverage the gut microbiota in dementia prevention.[13,21–23] In addition, advanced age is associated with changes to the composition and stability of gut microbiota[4,5] and dysregulated microbiota (i.e. dysbiosis) is associated with cognitive impairment.[6] Multiple studies have also indicated that dysbiosis in frail seniors is associated with chronic systemic inflammation[1,24–26], a hallmark of aging and biomarker of numerous age-related conditions. Yet, few studies exist that target gut microbiota as a site of intervention for age-related cognitive decline.

Within the brain, these proinflammatory factors can act on both microglia and neurons via specific receptors involved in maintenance of excitatory and inhibitory tone (E/I), which are particularly enriched in PFC and HPC.[27–30] The resulting receptor activation can modulate voltage-gated ion channel activity and GABA/glutamate signaling, resulting in long-term increases in excitability and seizure susceptibility.[27,31] Critically, dysregulated E/I tone in both the HPC[32,33] and PFC[34–36] are directly related to cognitive decline in old age. While the source of inflammation in unknown, dysbiosis may contribute. Thus, interventions that target gut dysbiosis may reduce tryptophan-mediated inflammation, enhance E/I homeostasis and mitigate age-related cognitive decline.

C.2) INNOVATION

- Harnessing of the gut microbiome as a target "organ" of intervention for addressing age-related cognitive dysfunction is innovative, as few studies have considered this approach despite evidence of microbiota involvement in other nervous system disorders with cognitive dysfunction and its role in inflammation.
- Studying the relationship between tryptophan metabolism, gut-mediated inflammation and E/I balance has not been advanced in the field and as such is an area ripe for exploration.
- Treatments utilized are innovative as they target the gut in different ways, yet all may regulate dysbiosis and modulate tryptophan metabolism and towards mitigation brain inflammation, E/I tone and cognitive decline.
- We apply a unifying approach to study age-related changes in the periphery to understand cognitive aging.

C.3) APPROACH. Our overall approach is to fill in the "missing pieces" from our respective RO1-funded grants to gather data related to gut contributions to cognitive decline (Scheme 1). For each of these experiments we will use 20-24 month old FBN male rats. Common outcome measures related to 1) brain inflammation; 2) brain excitatory/inhibitory tone (E/I); 3) gut dysbiosis (16s sequencing); and 4) gut tryptophan metabolomics are described below.

C.3.1) *Specific Aim 1. Explore gut/brain adaptations in aged rats in response to interventions performed by the UAB team, including physical exercise and renin angiotensin system-targeting probiotics.*

C.3.1.1) Rationale and Supportive Data. Authors have purported the potential benefits and therapeutic applications of genetically-modified probiotics (GMPs), particularly those from lactic acid bacteria.[37,38] Major benefits of this approach to drug delivery include 1) typical inherent benefits of the bacteria itself, 2) ease of production, 3) ability for oral administration due to the ability of the bacteria to survive gut digestive processes, and 4) ability to influence both systemic and mucosal immune responses. Thus, GMPs are a major opportunity in biotherapeutic development.[39,40] Though some recent studies have evaluated the potential utility of Ang(1-7) in cognition using genetic and/or systemic methods,[15-19] the investigation of the renin-angiotensin system – particularly the Ang(1-7) axis – in areas other than blood pressure regulation is very recent and remains limited overall. We have previously published (see attached publications), using 24 month old male FBN rats, that a Lactobacillus probiotic expressing Ang(1-7) or LP-A remediates age-associated gut dysbiosis, reduces inflammation in the prefrontal cortex, and modulates tryptophan metabolism mediated neurodegeneration inflammatory markers in circulation.[41,42] However, our "missing piece" relates to how these effects may mediate E/I tone in specific brain areas such as PFC and HPC. Furthermore, our recent RO1-supported study has also added exercise alone on in combination with probiotic administration. Thus, this application will allow us to explore each of these interventions alone or in combination regarding the impact on E/I tone.

C.3.1.2) Experimental Design. We will make use of banked PFC and HPCs from our current RO1 study (R01AG054538). Male rats were treated with either a vehicle control, null probiotic or the LP-A with and without exercise (total of six groups) for 3 months. For assessment of E/I tone (see below), we will use tissues n=4 from each group for a total of 24 samples.

C3.2) Specific Aim 2. ***Explore gut/brain adaptations among aged rats in response to interventions performed by the UF team in the context of a ketogenic diet.***

C3.2.1) Rationale and Supportive Data. Ketogenic diets have been utilized for the treatment of several disorders for a number of years. Recently, they have been implicated for use in neurodegenerative disease [36,43–46] perhaps mediated through the mitigation of neuroinflammation.[47–50] Furthermore, while KDs are commonly used or implicated in research regarding age-related disease states, how KDs influence microbiome, inflammation and cognition in the aged population remains unknown. While our group is leveraging funds from our current RO1s (R01AG054538, RO1AG060977) to collect these data regarding KD on the microbiome (16s), and cognitive function, our "missing pieces" relate to how KDs may mitigate age-related loss of E/I tone and neuroinflammation in specific brain regions such as the PFC and HPC.

C.3.2.2) Experimental Design. We will make use of banked PFC and HPCs from our current RO1 application. We will assess E/I tone and brain inflammatory cytokines (see below). We will use tissues n=8 from 20 month old male FBN rats treated for 3 months with a standard diet, time-restricted KD or a time-restricted fed control group for a total of 24 samples.

C3.3) Specific Aim 3. ***Explore gut/brain adaptations among aged rats in response to interventions performed by the UF team in the context of vagus nerve stimulation***.

C.3.3.1) VNS reduces peripheral inflammatory markers in rodents and humans[51–53] and preliminary data from our labs show similar effects. In addition, we have recently demonstrated that alterations in neuronal excitability or E/I in PFC and HPC and increases in peripheral inflammation contribute to age-associated cognitive decline.[35,54–57] Specifically, our preliminary data show that 8 days of VNS counteracts dysregulated expression of cortical GABAergic and glutamatergic proteins in aged rats and reduces inflammatory markers in young adult rats. What is noteworthy is historical data regarding VNS to influence cognition, inflammation and disease systemically. However, there are few studies that link the gut to the brain in the context of aging and E/I control of age-related cognitive decline. Our "missing pieces" include brain inflammation, tryptophan metabolism and 16s fecal sequencing to measure dysbiosis. While our other aims have banked tissue to work from, we do not have such tissues in the context of VNS. Thus, we propose to collect new data for this aim.

C.3.3.2) Experimental Design. We will obtain 36, 24 month old male FBN rats from the NIA rodent colony under the protocol of Dr. Bizon's DoD-DARPA grant. We propose an 8 day vagus nerve stimulation protocol (see below) based upon Dr. Bizon's preliminary data noting mitigation of dysregulated E/I in the same strain and age of rats: control (vagus cuff with no stimulation-n=12); control-low stimulation (vagus cuff low stimulation-n=12); and optimal stimulation (vagus cuff stimulation-n=12). We will then measure brain inflammation in HPC and PFC, tryptophan metabolism and dysbiosis via 16s sequencing (see below).

C.3.3.3) Cuff implantation and VNS stimulation. Rat will undergo surgery to implant a cuff electrode around the left cervical vagus nerve. For these surgeries, rats will be anesthetized with isofluorane gas (1-5% in O2)

and given buprenorphine (0.05 mg/kg), Meloxicam (1 mg/kg), and sterile saline (10 mL) subcutaneously. Using aseptic technique, the scalp will be incised and retracted, and 4 stainless steel sterile anchoring screws will be inserted into the skull to assist in adhering the connector to the skull. A skin incision and blunt dissection of the muscles in the neck will be used to expose the left cervical vagus nerve. After isolation from the carotid artery, the vagus nerve will be placed inside the cuff electrode, secured, and then tissue closed with sutures. The electrode leads will be tunneled subcutaneously to the scalp incision, and dental cement will be used to affix the connector to the skull and skull screws. Once the cement dries, the scalp incision will be closed around it.

After recovery, rats will undergo 8 daily 1-h sessions (at the same time each day), during which they will be tethered to a constant current stimulator. In each session, rats will receive either 100 VNS trains (30 Hz, 120 μs pulse width, 700 μA, 0.8 s train duration, charge-balanced) distributed randomly over the session or no-VNS sham control conditions (rats are tethered but no VNS is delivered). The VNS parameters are based on studies showing that similar parameters are effective for enhancing cortical plasticity and mPFC-mediated extinction learning[58,59], as well as our own experience showing that 8 days of VNS at these parameters attenuates dysregulated E/I protein expression in aged rats.

C4) Common Methods

C4.1) Brain inflammation. Brains will be dissected, and homogenates prepared from PFC and HPC tissue. We will perform processing for quantitative PCR (qPCR) analysis of markers inflammation including TNF-α, IL6, Il1a, Il1b as previously described by our group.[41]

C4.2) Brain E/I tone. Brains will be dissected, and homogenates prepared from PFC and HPC tissue. As in our published work, immunoblotting will be used to assess expression of proteins involved in E/I signaling (NR1, GABA(B)R1b and GAD67.[9,35,36,55,56]

C4.3) Fecal taxonomic analysis. Taxonomic analysis of the fecal microbiome (day 29) will beperformed via 16S-based polymerase chain reaction (PCR) procedures as previously described (Buford et al. 2018). Briefly, DNA will be extracted from samples and PCR will be used with unique bar-coded primers to amplify the V4 region of the 16S rRNA gene to create an “amplicon library” from individual samples as described by Kumar et al. (R. Kumar et al. 2014). The entire PCR reaction will be electrophoresed, the PCR product will be visualized by UV illumination, and the band will be excised and purified from the agarose.The PCR products were sequenced and paired-end reads of approximately 250 bp from the V4 region of 16S rDNA were analyzed. The samples were first quantitated using Pico Green, adjusted to a concentration of 4 nM then used for sequencing. Fastq conversion of the raw data files will be performed following de-multiplexing, and quality control of the fastq files will be performed which will be then subject to quality assessment and filtering. One sample will be removed from analysis due to failing quality control procedures. Following quality control procedures, sequences were grouped into operational taxonomic units (OTUs) and taxonomic identification and abundance information will be obtained. OTUs were then grouped together to summarize taxon abundance at different hierarchical levels of classification (e.g., phylum, class). Alpha diversity will be calculated using Shannon’s diversity matrix and beta diversity will be measured using unweighted Unifrac analysis. Principal coordinates analysis (PCoA) will be performed to visualize the dissimilarity matrix between all samples.

C4.4) Gut tryptophan metabolomics. Colon concentrations of metabolites reflective of the kynurenine, serotonin, and tryptamine/indole pathways of tryptophan metabolism will be determined. Fifty microliters of homogenized colon will be mixed with 25 ng/ml methanolic tryptophan-d5 internal standard, and 500 μl of acetonitrile 1.0% FA and added to Phree cartridges (Phenomenex, Torrance, CA) on a SPE vacuum manifold. Colon samples will be forcefully expelled into acetonitrile contained in Phree cartridge to ensure proper mixing. The mixture will be incubated at RT for 5 min. Vacuum will be applied to draw the mixture through the sorbent into a borosilicate collection tube. Samples were dried under N2 gas and then reconstituted in 100 μl 0.1% FA. The LC-MS method used was previously described by Zhu et al. with minor alterations (Zhu et al. 2011). Tryptophan-d5 will be the only internal standard employed during this analysis. A shorter Atlantis T3 3 μm 100 × 2.1 mm column (Waters, Milford, MA) will be used and a diversion valve will be employed to divert column eluent to waste for the first minute of the gradient separation. MultiQuant 3.0.3 will be employed for post-acquisition data analysis. All standard curves will be linear with 1/x2 weighting.

C5) Statistical Approach. We will use these preliminary data to determine power for the future grant applications. Generally, we will first perform analysis of variance (ANOVA) tests for the overall treatment group difference within each aim and outcome measure. We will then apply follow-up model-based contrast tests to test the effect of each of the active compounds compared to control vehicle.

D. MULTISITE MBI COLLABORATIONS. Our group proposes to assemble a team of well-funded scientists with expertise, in their specific fields, centered around gut-aging/*geroscience* and cognitive aging/*neuroscience* respectively to mentor Dr. Hernandez in her pursuit of a K99/00 applicaton and to foster inter-institutional MBI collaboration in the pursuit of a PO1 application. Drs. Christy Carter and Thomas Buford at the University of Alabama at Birmingham (UAB team) and of Drs. Sara Burke and Jennifer Bizon at the University of Florida (UF team), are all faculty of the MBRF network at their institutions. Furthermore, this application supports the career development of an early stage investigator, Dr. Abbi Hernandez, who bridges the UAB and UF teams, as a former graduate student and post-doc in the lab of Dr. Burke and who is a current post-doc in the lab of Drs. Carter and Buford. In addition, each of the teams have independently pursued research in the area of interventions which alter the gut-microbiome: vagus nerve stimulation (Dr. Bizon), ketogenic diets (Drs. Burke and Hernandez), exercise and genetically modified probiotic administration (Drs. Carter, Buford and Hernandez). However, each team has recognized gaps in their respective projects such that Drs. Bizon and Burke, while measuring sophisticated brain/behavior physiology, lack expertise in measuring gut dysbiosis; and Drs. Carter and Buford are proficient in studying gut dysbiosis yet lack expertise in studying sophisticated brain/behavior physiology.

E. TIMELINE AND FUTURE DIRECTIONS.

We anticipate a two-year timeline to complete all experiments proposed in this application. In Year 1, we will focus on processing all the samples from Aims 1 and 2. In Year 2 we will focus on experiments in Aim 3. During each year we will continue to also integrate data were are collecting in the context of our current RO1s with the data collected from the support of this proposal. We will also continue to produce our series of perspectives that will be published in upcoming issues of the *Journals of Gerontology: Biological Sciences*, and include data collected from this proposal. The ultimate impact of this study will be in determining if novel therapeutic strategies targeting the gut can improve age-related cognitive decline in a validated rodent model. The work capitalizes on our individual programs' extensive working history using our respective gut-based interventions, and our collaborative relationships as geroscientists and neuroscientists. Finally, we will use this collaboration as an opportunity to begin planning for our future grant applications. Our future PO1 application and Dr. Hernandez's K99/00 will be distinct yet overlapping. A primary aim of the K99/00 is to evaluate and implement a novel cognitive task Dr. Hernandez developed while a graduate student at UF and apply this to a rat model of AD here at UAB. We will use this task across UF and UAB labs to ensure consistency across sites to determine measurement of future behavioral outcomes for the PO1 application. Another major aim of the K99/00 is study other avenues of metabolic changes in addition to those listed here such as glucose metabolism. In the PO1 application, we will consider additional factors, beyond those proposed here, to further investigate the additional mechanisms by which interventions that target gut dysbiosis may impact age-related cognitive decline. This includes but is not limited to: sex differences, cell-specific changes and membrane permeability (gut and brain), metagemomics of fecal samples for a more nuanced understanding of gut dysbiosis. In addition, we fully expect this study to provide useful data to determine if translation to humans is warranted, and our track record in these area makes us ideally suited to carry out this work. Age-related cognitive declines are tremendous health concerns for individuals and families worldwide and this work will provide important insights into a potentially viable therapeutics with substantial runway for future work in both animals and humans.

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Department of Pharmacology and Toxicology

July 24, 2020

Abigail Hernandez, PhD
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933 19th Street S.
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Dear Abbi,

I'm writing in support of your proposed McKnight Foundation Cognitive Aging and Memory Intervention Core Inter-Institutional Pilot Program project entitled, "*Reuniting the Body Brain and Body to Understand Cognitive Aging: The Nexus of Geroscience and Neuroscience*".

As Director of the UAB Targeted Metabolomics and Proteomics Laboratory, we serve many UAB investigator groups in developing and providing analytical methods for measurement of a variety of small molecule metabolites. This is done by using targeted LC-Multiple Reaction Monitoring (MRM) mass spectrometry assays. Where possible, we employ isotope dilution methodologies for absolute quantification. Indeed, last year with Drs. Carter and Buford, we optimized protocols for measuring tryptophan metabolism with $^{13}C,^{15}N$-tryptophan as an internal standard. This is important for your project since these are the methods you propose for your current proposal. Accordingly, our lab will be happy to advise you in sample preparation, perform LC-MRM-MS analysis of tryptophan and its metabolites, and provide help regarding quantification and interpretation of the data.

If there is anything else I can do to help, please let me know.

Sincerely,

Stephen Barnes

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July 20, 2020

Abigail Hernandez, PhD Department of
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Dear Abbi,

I'm writing to document my willingness to collaborate on your proposed The MBRF Cognitive Aging and Memory Intervention Core Inter-Institutional Pilot Program project titled " Reuniting the Body Brain and Body to Understand Cognitive Aging: The Nexus of Geroscience and Neuroscience".

I've been impressed by your group's interest in and passion for exploring the role of the gut microbiome on age- related pathologies. As you know, I share your passion in developing and executing research projects designed to elucidate the impact of the gut microbiome on health.

As Director of the UAB Microbiome Core facility, I am committed to serving the UAB community in completing microbial taxonomic analyses for their projects. I thoroughly enjoyed working with you to collect, analyze, and disseminate your innovative findings and preliminary data indicating altered serum microbial profiles of healthy older adults compared to younger peers. It was a pleasure to work through these data with you to produce meaningful results. For this project, the Microbiome Core will support you in the biologic and bioinformatics analysis of rat gut taxonomic data. I am also happy to work with you on the development of manuscripts and if necessary the development of future projects from this work. If there is anything else I can do to help, please let me know.

Best

Casey D. Morrow, PhD
Professor
UAB, Department of Cell, Developmental and Integrative Biology
Director, UAB Microbiome Resource

PI — Abigail Hernandez, PhD
McKnight Brain Foundation Pilot - Start Date: 10/01/2020

UAB

A.-KEY PERSONNEL	**Base salary**	**effort (cal. Months)**	**requested salary**	**Fringe rate**	**Fringe benefits***	**Funds requested**	**YEAR 1 TOTALS**
Abigail Hernandez (Principal Investigator)	$50,376	0.00	$0	23.0	$0	$0	
							$0
B.-OTHER PERSONNEL							
Christy Carter, PhD (Mentor)	$150,858	0.00	$0	24.7	$0	$0	
Thomas Buford, PhD (Mentor)	$166,060	0.00	$0	24.7	$0	$0	
Sara Burke, PhD (Mentor--UF)	$0	0.00	$0	0	$0	$0	
Jennifer Bizon, PhD (Mentor--UF)	$0	0.00	$0	0	$0	$0	
							$0
C.- EQUIPMENT							
D.- TRAVEL						$0	$0
E.- TRAINEE SUPPORT COST						$0	$0
F.- OTHER DIRECT COSTS							
E/I brain analyses (24 LPA samples and 24 Keto samples for 3 proteins = 144 @ 50)						$7,200	
Brain Inflammation, Multiplex (24 LPA samples and 24 Keto samples @ 100)						$4,800	
Metabolomics Core Tryp Analyses (24 Keto colon samples @ 150)						$3,600	
Supplies (Consummables, gloves, pipette tips etc)						$8,000	$23,600

	DIRECT	**INDIRECT**	**TOTAL**	
TOTAL OTHER DIRECT COSTS				$23,600
A. DIRECT COSTS				
TOTAL DIRECT COSTS				**$23,600**

B. INDIRECT (F&A) COSTS	**Base**		
MTDC (48.5%)-- UAB base= $0 + $25,000 of subaward = $25,00(	$0		$0
TOTAL INDIRECT COSTS	$0		**$0**
C. TOTAL DIRECT & INDIRECT			**$23,600**

PI — Abigail Hernandez, PhD
McKnight Brain Foundation Pilot - Start Date: 10/01/2020

UAB							YEAR 2 TOTALS
A.-KEY PERSONNEL	**Base salary**	**effort (cal. Months)**	**requested salary**	**Fringe rate**	**Fringe benefits***	**Funds requested**	
Abigail Hernandez (Principal Investigator)	$50,376	0	$0	23.0	$0	$0	
	$0	0	$0	0	$0	$0	
	$0	0	$0	0	$0	$0	
	$0	0	$0	0	$0	$0	
	$0	0	$0	0	$0	$0	
							$0
B.-OTHER PERSONNEL							
Christy Carter, PhD (Mentor)	$150,858	0.00	$0	24.7	$0	$0	
Thomas Buford, PhD (Mentor)	$166,060	0.00	$0	24.7	$0	$0	
Sara Burke, PhD (Mentor--UF)	$0	0.00	$0	0	$0	$0	
Jennifer Bizon, PhD (Mentor--UF)	$0	0.00	$0	0	$0	$0	
							$0
C.- EQUIPMENT							
Stimulation cuffs (active: 24 @ 550 and sham: 12@250)						$16,200	$16,200
D.- TRAVEL							
						$0	$0
E.- TRAINEE SUPPORT COST						$0	$0
F.- OTHER DIRECT COSTS							
Brain Inflammation, Multiplex (36 VNS samples @ 100)						$3,600	
Metabolomics Core Tryp Analyses (36 colon VNS samples @ 150)						$5,400	
Microbiome Core Analyses (36 VNS fecal samples @ 100)						$3,600	
Supplies (Consummables, gloves, pipette tips etc)						$8,000	
						$0	
				DIRECT	**INDIRECT**	**TOTAL**	
TOTAL OTHER DIRECT COSTS							$20,600
A. DIRECT COSTS							
TOTAL DIRECT COSTS							**$36,800**
B. INDIRECT (F&A) COSTS	Base						
MTDC (48.5% — base= uab direct cost)		$0					$0
TOTAL INDIRECT COSTS							**$0**
C. TOTAL DIRECT & INDIRECT							**$36,800**

Budget Justification

A. Personnel
Senior/Key Personnel:

Abigail Hernandez, Principal Investigator: Dr. Hernandez received her PhD in Biomedicine/Neuroscience from the University of Florida, where she then did a one-year Postdoc Teaching Fellowship. She is currently funded through the UAB Interdisciplinary Training in Pathobiology and Rehabilitation Medicine Program T32. She is interested in the intersection between metabolic health and biological/cognitive aging. Dr. Hernandez will serve as the PI for this project and will including overseeing all aspects of regulatory activity, data collection and analysis – including biologic analyses, coordination of team members, as well as data interpretation and dissemination. No effort will be requested for Dr. Hernandez from this pilot grant since she is a postdoc on a T32 program and this grant is part of her training. As a T32 postdoc, all her stipend/salary-effort is covered by the T32 program.

Other Personnel:

Christy Carter, Mentor: Dr. Carter is an expert in biological aging/geroscience with particular expertise in behavioral interventions to combat age-related cognitive and physical decline. She has conducted much of the foundational pre-clinical work informing about the role of the renin-angiotensin system in age-related changes in these domains. Dr. Carter will provide scientific and administrative leadership through her mentorship of Dr. Hernandez. No effort will be requested for Dr. Carter from this pilot grant.

Thomas Buford, Mentor: Dr. Buford is a physiologist with expertise in aging, the renin-angiotensin system, and the microbiome. Dr. Buford has published both clinical and pre-clinical work related to the influence of the renin-angiotensin system on functional status in aging as well as several important findings related to the gut and serum microbiomes in aging. He will provide scientific input as well as data interpretation and dissemination. Dr. Buford has a long standing collaboration with Dr. Carter (>10 years). No effort will be requested for Dr. Buford from this pilot grant.

Jennifer Bizon, Mentor: Dr. Bizon is a neuroscientist whose research is broadly focused on determining the neural processes that support cognition and that contribute to cognitive impairments in aging and disease. Using rodent models, of GABAergic and glutamatergic signaling improves specific forms of prefrontal cortical (PFC)-dependent cognition in aged rats. Most recently, we have been exploring how vagus nerve stimulation (VNS) modulates both cognitive functions and age-associated alterations in GABA/glutamate signaling in PFC and hippocampus. Experience gained from these lines of work and my 20+ years of work in cognitive/brain aging and rodent models of cognition will be used to meet the objectives of the current proposal. No effort will be requested for Dr. Bizon from this pilot grant.

Sara Burke, Mentor: Dr. Burke is a neuroscientist. Her long-term goals of my NIH-funded research program are to 1) pinpoint alterations in how different brain regions communicate over the lifespan and how this contributes to loss of function in advanced age, and 2) to design therapeutic strategies for alleviating cognitive dysfunction in order to promote positive health outcomes in the elderly. To answer these questions, her lab integrates data across multiple levels of analysis that includes neurophysiology, gene expression, anatomy and behavioral assays. Using these integrative approaches, current projects in her laboratory are focused on uncovering mechanisms of age-related impairments in hippocampal-dependent sensory discrimination across modalities in normal aging, identifying age-associated changes in medial temporal lobe-prefrontal functional connectivity that contribute to memory deficits, and testing whether a ketogenic diet can globally improve neural network function in old animals. Our rationale is that by elucidating how aging influences systems-level dynamics, we will be better positioned to develop interventions that broadly improve cognition and everyday living. No effort will be requested for Dr. Burke from this pilot grant.
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B. Equipment & Supplies.

Vagus nerve cuff electrodes. The 4-channel cuff electrodes used for electrical stimulation of the vagus nerve are made by Qualia Labs and are composed of titanium nitride overlaid on a shape memory polymer substrate. The cuffs are attached to a 6- channel plug and packaged into a complete, ready-to-implant device by Microprobes, Inc. These cuffs have proven to be highly reliable across months of daily behavioral testing in our labs, and thus they are ideal for use in the proposed project, which requires 1 month of daily use. Note that the ready-to-use design of the cuffs and their high degree of reliability results in substantial savings of funds that would otherwise be spent on labor costs (to construct cuff electrodes in-house) and testing of additional animals (to compensate for the inevitably greater failure rate of in-house-made cuffs). We require 24 stimulating cuffs @ $550 and 12 sham cuffs @ $250 each for a **total of $16,200.**

C. Other Direct Costs.

Coordination of all purchases for this project will be supervised by Dr. Hernandez at UAB. We will budget $8000/year for year 1 and 2 for lab consumables, **total of $16,000**.

Year 1
Tissue analyses: **total of $15,600**

E/I brain analyses (24 LPA samples and 24 Keto samples for 3 proteins = 144 @ 50)	$7,200
Brain Inflammation, Multiplex (24 LPA samples and 24 Keto samples @ 100)	$4,800
Metabolomics Core Tryp Analyses (24 Keto colon samples @ 150)	$3,600

Year 2
Tissue analyses: **total of $12,600**

Brain Inflammation, Multiplex (36 VNS samples @ 100)	$3,600
Metabolomics Core Tryp Analyses (36 colon VNS samples @ 150)	$5,400
Microbiome Core Analyses (36 VNS fecal samples @ 100)	$3,600

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: Abigail Lynn Hernandez

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

POSITION TITLE: Post-Doctoral Student

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
Florida Atlantic University- Boca Raton, FL	BA	12/2012	Chemistry
Florida Atlantic University- Boca Raton, FL	BS	12/2012	Biological Sciences
Florida Atlantic University- Boca Raton, FL	MS	12/2013	Biomedicine/Neuroscience
University of Florida- Gainesville, FL	PhD	08/2018	Biomedicine/Neuroscience

A. Personal Statement

My current research as a T32 supported post-doctoral student in the laboratory of Drs. Christy Carter and Thomas Buford focuses on the neurobiological mechanisms of age-related cognitive decline, diet-based metabolic interventions, and microbiome contributions to improve cognitive outcomes in the elderly. One barrier to developing therapeutics that minimize functional loss in old age is that no single mechanism can account for the varying levels of neuronal dysfunction observed across the aged brain, including declining metabolic function that influences the periphery towards creating an imbalance between inhibition and excitation neurotransmission. Lifestyle interventions that have the benefit of potentially improving function involving peripheral systems may be necessary for changing the quality of life and positively influencing both cognitive and peripheral health across a range of domains. My experience with rodent behavior during my Master's, Doctoral and Post-doctoral experiences allows me to develop and implement sensitive measures of cognitive function across the lifespan. Additionally, I have gained expertise in several other techniques that allow me to probe circuit function at the molecular and pharmacological level. I continue to strive to gain a deeper understanding of the various neurobiological aspects of aging and cognition, as well as molecular approaches to quantifying inhibitory and excitatory imbalances and ultimately to obtain the expertise and experience necessary to integrate various molecular and behavioral techniques, in order to address the problem of cognitive aging using a multi-level approach, to aid me in achieving my career goals of becoming an independent researcher.

B. Positions and Honors

Positions and Employment

2010 Undergraduate Student Researcher, University of Florida, Boca Raton, FL
2013-2014 Graduate Student Researcher, Florida Atlantic University, Boca Raton, FL
2013-2014 Graduate Teaching Assistant for CHM 2045: General Chemistry Laboratory, Florida Atlantic University, Boca Raton, FL
2014-2018 Graduate Student Research Assistant, Laboratory of Dr. Sara Burke, McKnight Brain Institute, University of Florida, Gainesville, FL
2018-2019 Postdoctoral Associate, Laboratory of Dr. Sara Burke, McKnight Brain Institute, University of Florida, Gainesville, FL
2018-2019 Postdoctoral Teaching Fellow, Department of Neuroscience, University of Florida, Gainesville, FL

2020- Postdoctoral trainee supported by Interdisciplinary Training in Pathobiology and Rehabilitation Medicine NIH National Center for Medical Rehabilitation Research T32HD071866: Drs. Christy Carter and Thomas Buford, Mentors

Other Experience and Professional Memberships

2018- Faculty for Undergraduate Neuroscience
2018- International Behavioral Neuroscience Society National Member
2017- Summer Neuroscience Internship Program, University of Florida
  Admissions Chair 2019
  Co-Director 2018
  Graduate Advisor 2017
2015- Society for Neuroscience National Member
2014- North Central Florida Chapter of the Society for Neuroscience Member
  President '17-'18
  Conference Coordinator '16-'17
  Conf. Vice Chair '15'-16
2016 UF Graduate Student Organization- Neuroscience Representative
2011-2012 Omicron Delta Kappa National Honor Society
2010-2012 Recreation Activities and Leadership Committee at Florida Atlantic University
2010-2011 National Residence Hall Honorary

Honors

2019 North Central Florida Chapter; Society for Neuroscience Travel Award
2018 Evelyn F. McKnight Brain Institute Poster Reception First Place
2018 Spotlight on Aging Poster Session First Place Winner
2018 McKnight Brain Institute Training Enhancement Opportunity Award
2018 Neuroscience Departmental Award (Luttge Award) Third Place
2017 UF Graduate Student Research Day Poster Competition First Place
2017 Neuroscience Departmental Award (Luttge Award) First Place
2017 North Central Florida Chapter; Society for Neuroscience Travel Award
2017 Advancement to Candidacy Award; UF Interdepartmental College of Medicine
2017 Evelyn F. McKnight Brain Institute Poster Reception Second Place
2017 UF Graduate Student Council Travel Award
2016 Bryan Robinson Endowment Honorable Mention
2015 Graduate Student Mentorship Award University of Florida
2015 North Central Florida Chapter; Society for Neuroscience Travel Award
2014 Board of Education Fellowship
2010 Florence Bayuk Scholarship- Awarded for Academic Excellence in Science

C. Contributions to Science

1. **Assessment of age-related cognitive decline utilizing rodent models.** As the population of individuals living beyond 65 years old increases, translational animal models are necessary to investigate age-related cognitive decline. My first publication as a graduate student validated the use of a biconditional association task (BAT) to assess age-related cognitive decline (a). This task requires the integration of spatial information with object recognition, therefore utilizing several key brain regions vulnerable to cognitive aging. In fact, this work demonstrated that the BAT was more sensitive to age-related cognitive decline than the commonly utilized Morris Water Maze test of spatial memory in two different aged rodent strains. Furthermore, this task is appropriate for both male and female aged rats, and consistent across cohorts even when the task difficulty is increased (b). Improving human health outcomes requires the utilization of an animal model that not only resembles cognitive deficits of aged humans, but is directly translatable. Therefore I collaborated with an additional mentor to work on a cross species model of this task utilizing human subjects. This work, recently accepted for presentation at an international conference (c), demonstrated alterations in prefrontal cortical signaling in humans that is similar to those observed in rodents.
    a. Hernandez, Abbi R., Maurer, Andrew P., Reasor, Jordan E.*, Turner, Sean M.*, Barthle, Sarah E.*, Johnson, Sarah A., Burke, Sara N., (2015). Age-related impairments in object-place

associations are not due to hippocampal dysfunction. Behav. Neurosci.
   b. Hernandez, Abbi R., Truckenbrod, Leah M.*, Campos, Keila T. *, Williams, Sonora A., Burke, Sara N. (2019) Sex Differences in Age-related Impairments Vary across Cognitive and Physical Assessments in Rats. Behavioral Neuroscience.
   c. David Clark, Abbi Hernandez, Steven Winesett, Sara Burke. A Cross-Species Paradigm for Testing Dual-Task Costs of Walking and Cognition with Aging. Combined Sections Meeting of the American Physical Therapy Association, Denver, CO February 2020.

2. **Neuronal network disruptions in age-related cognitive decline.** The underlying neural mechanisms of age-related cognitive decline remain largely unknown, hindering the potential for the identification of strategies to improve human health outcomes. Furthermore, no single neurobiological deficit can account for the wide spectrum of behavioral impairments observed in old age, therefore understanding how different brain regions interact to support adaptive behaviors over the lifespan is critical for uncovering the neurobiological mechanisms of age-associated cognitive decline. To begin investigating this, we utilized a temporary lesion strategy to probe the neural circuitry requirements for the BAT described above. This work showed the necessity of prefrontal-perirhinal cortical network interactions for complex, integrated behaviors but not for simple discriminations. Two additional studies utilized an *in situ* hybridization technique to label immediate early gene activity within each of these regions, which demonstrated changes in both age- and region-specific neuronal activity (b & unpublished data). The use of retrograde tracers allowed us to determine that not only are there age-related changes in neuronal activity, but this activity was predominantly altered within long range projection neurons. The enhanced connectivity of these long-range projection neurons increases the influence of their declining function, likely due to declining resources available to these metabolically costly neuronal 'hubs', which (c). An additional body of work utilizing aged rodents demonstrated changes at the protein level in both excitatory and inhibitory signaling-related transporter expression within the regions required for the BAT and that are commonly impaired in aged subjects (d).
   a. Hernandez, Abbi R., Reasor, Jordan E.*, Truckenbrod, Leah M.*, Lubke, Katelyn N., Johnson, Sarah A., Bizon, Jennifer L., Maurer, Andrew P., Burke, Sara N., (2017). Medial prefrontal-perirhinal cortical communication is necessary for flexible response selection. Neurobiol. Learn. Mem.
   b. Hernandez, Abbi R., Reasor, Jordan E.*, Truckenbrod, Leah M.*, Campos, Keila T.*, Federico, Quinten P.*, Fertal, Kaeli E., Lubke, Katelyn N., Johnson, Sarah A., Clark, Benjamin J., Maurer, Andrew P., Burke, Sara N., (2018). Dissociable effects of advanced age on prefrontal cortical and medial temporal lobe ensemble activity. Neurobiol. Aging.
   c. Hernandez, Abbi R., Burke, Sara N., (2018). Age-related changes in 'hub' neurons. Aging.
   d. Hernandez, Abbi R, Hernandez, Caesar M., Campos, Keila*, Truckenbrod, Leah*, Sakarya, Yasmin, McQuail, Joseph A., Carter, Christy S., Bizon, Jennifer L., Maurer, Andrew P., Burke, Sara N., (2018). The Antiepileptic Ketogenic Diet Alters Hippocampal Transporter Levels and Reduces Adiposity in Aged Rats. J. Gerontol. Ser. A.

3. **Influence of metabolic impairment and potential interventions for the treatment of age-related cognitive decline.** As the proportion of elderly individuals increases, the incidence of metabolic syndrome, Alzheimer's disease, mild cognitive impairment, seizure disorders, cancer and diabetes increases as well. Alterations in peripheral and central nervous system metabolism greatly influence cognitive outcomes and increase risk for several neurological and neurodegenerative disorders. Ketogenic diets have been used for nearly a century to treat both epilepsy and diabetes, and more recently cancer and neurodegenerative disease. However, animal models testing the effects ketogenic diets and nutritional ketosis on age-related disease states have used young animals to do so. Therefore, we tested the safety and efficacy of nutritional ketosis through the implementation of a ketogenic diet in aged rats, who demonstrate impaired metabolic switching (a). This body of work not only determined aged rats are able to initiate and sustain nutritional ketosis, resulting in positive physical and cognitive outcomes, but is capable of enhancing cognitive outcomes (b). While there are several mechanisms by which altering dietary consumption may improve cognition, we went on to show the ketogenic diet resulted in region-specific alterations in neuronal signaling-related gene expression (c). However, recent pilot data has demonstrated life-long alterations in food consumption patterns alone may be enough to prevent age-related cognitive decline (d). This work will be continued through

the investigation of other peripheral health factors on metabolic and cognitive outcomes in aged rodent models as well as rodent models of Alzheimer's disease.

a. Hernandez, Abbi R., Truckenbrod, Leah M., Federico, Quinten P., Campos, Keila T., Moon, Brianna M., Ferekides, Nedi, Hoppe, Meagan, D'Agostino, Dominic P., Burke, Sara N., (2020). Metabolic switching is impaired by aging and facilitated by ketosis independent of glycogen. Aging.
b. Hernandez, Abbi R., Hernandez, Caesar M., Campos, Keila*, Truckenbrod, Leah*, Federico, Quinten*, Moon, Brianna*, McQuail, Joseph A., Maurer, Andrew P., Bizon, Jennifer L., Burke, Sara N., (2018). A ketogenic diet improves cognition and has dissociable biochemical effects in hippocampus and prefrontal cortex. Frontiers in Aging.
c. Hernandez, Abbi R., Hernandez, Caesar M., Truckenbrod, Leah*, Campos, Keila*, Bizon, Jennifer L., Burke, Sara N. (2019). Age and ketogenic diet have dissociable effects on synapse-related gene expression across hippocampal subregions. Frontiers in Aging Neuroscience.
d. Abbi Hernandez, Quinten Federico, Sara N. Burke. Time-Restricted Feeding From Adulthood to Old Age Improves Biconditional Associative Learning in Geriatric Rats Regardless of Macronutrient Composition. International Behavioral Neuroscience Society Annual Meeting, August 2020.

Complete list of published works:
https://scholar.google.com/citations?hl=en&user=I3I42NsAAAAJ&view_op=list_works&sortby=pubdate

D. RESEARCH SUPPORT

Ongoing Research Support

Scholar Award; NIH National REACT (Rehabilitation Research Resource to Enhance Clinical Trials)
Title: Investigating the Effects of Age and Diet on Microbiome and Inflammation
04/2020; $9,472

Interdisciplinary Training in Pathobiology and Rehabilitation Medicine
NIH National Center for Medical Rehabilitation Research; 1T32HD071866 Post-Doctoral Training Program
02/2020 - present

Completed Research Support

McKnight Brain Institute Training Enhancement Opportunity Award
Postdoctoral Teaching Fellowship, McKnight Brain Institute
08/18-05/19; $22,500

McKnight Brain Institute Training Enhancement Opportunity Award
Predoctoral Teaching Fellowship, McKnight Brain Institute
06/18-08/18; $2,500

1F31AG058455, Ruth L. Kirschstein Predoctoral Individual National Research Service Award, National Institute on Aging
Title: Metabolic Mechanisms for Treating Cognitive Aging
2017/09/15-2018/08/14; $35,688 Year 1

University of Florida Board of Education Fellowship
06/14-08/14; $3,500

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: Carter, Christy S.

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

POSITION TITLE: Associate Professor, Department of Medicine, Division of Gerontology, Geriatrics, and Palliative Care, McKnight Brain Institute, co-Leader Research Development Core Nathan Shock Center for Excellence in the Biology of Aging.

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 Colorado, Colorado Spring, CO	BA	12/1991	Psychology
University of North Carolina, Chapel Hill, NC	PhD	12/1998	Experimental and Biological Psychology; Minor Neurobiology

A. Personal Statement

I am currently an Associate Professor in the Department of Medicine at the University of Alabama at Birmingham (UAB), following fourteen years as faculty at the University of Florida. I have supported my own research through NIH and pharmaceutical grants. My research activities have resulted in 83 peer-reviewed papers and reviews in leading scientific journals and one book chapter. The total citation number of these publications is 8017 with h-index = 35 as of July 19, 2020 (Google Scholar). Of these, several publications are published in top scientific journals such as Nature, JAMDA, Lancet and Trends in Genetics.

Globally, my current research interests lie in preserving health-span during aging; and in particular, focus on the use of a preclinical rodent models of aging to test a variety of late-life interventions designed to mitigate loss and rehabilitation of mobility and cognition. Furthermore, I have demonstrated that the application of standardized physical performance measures to a variety of animal models (flies, mice and rats) of aging may help to define similarities between species in the underlying mechanisms of loss of mobility, the age-related decline in performance, cognition, disability, disease and longevity. I have extended this area of research to other special aging populations such as the frail and obese, and have developed combinatorial therapies. These interventions include diet, exercise, as well and nutritional and pharmaceutical approaches. Many of the pharmaceutical compounds my laboratory studies modulate the renin-angiotensin system (RAS). We have translated these preclinical findings to humans through collaboration with clinical researchers. More recently, we have developed a growing interest in the role of the gut microbiome in the development of age-related pathologies – with particular interest in the contributions of the gut to age-related increases in systemic inflammation and Alzheimer's Disease. My current and past roles as PI and co-PI on several NIH and foundation grants supports these areas of research.

B. Positions and Honors

Positions and Employment

1992 - 1994 Research Assistant, Center for Environmental Medicine and Lung Biology, University of North Carolina, Chapel Hill, NC
1994 - 1995 Trainee, Toxicology Training Grant, University of North Carolina, Chapel HIll, NC
1995 - 1998 NIMH Pre-doctoral Fellow, NRSA F31MH11292, University of North Carolina, Chapel HIll, NC

1999 - 2001	Research Associate, Department of Internal Medicine, Division of Geriatrics and Gerontology, Wake Forest University School of Medicine, Winston-Salem, NC
2001 - 2004	Instructor, Department of Internal Medicine, Division of Geriatrics and Gerontology, Wake Forest University School of Medicine, Winston-Salem, NC
2003 - 2005	Co-Director, Claude D. Pepper Older Americans Independence Center, Pilot and Exploratory Studies Core, Winston-Salem, NC
2003 - 2005	Assistant Professor, Department of Internal Medicine, Division of Geriatrics and Gerontology, Department of Phsyiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC
2005 - 2008	Associate Director for Research, North Florida/South Georgia GRECC, Gainesville, FL
2006 - 2008	Chair, Research and Development Committee, North Florida/South Georgia VMAC, Gainesville, FL
2007 - 2018	Leader, Pilot and Exploratory Studies Core, Claude D. Pepper Older Americans Independence Center, University of Florida College of Medicine, Gainesville, FL
2005 - 2018	Assistant Professor, Department of Aging and Geriatric Research, University of Florida College of Medicine, Gainesville, FL Program Director
2018-	Associate Professor, Tenure-accruing, Department of Medicine, University of Alabama at Birmingham
2018-	Faculty, University of Alabama at Birmingham Evelyn F. McKnight Brain Institute
2018-	Co-Leader, Research Development Core, University of Alabama at Birmingham Nathan Shock Center for Excellence in the Biology of Aging

UAB Center Memberships

UAB Center for Exercise Medicine (member); UAB McKnight Brain Institute (faculty).

Other Experience and Professional Memberships

2001 -	Member, Gerontological Society of America
2002 -	Member, American Aging Association
2009 -	National Scientific Advisory Board, AFAR
2012-	Section Editor, Pathobiology of Aging and Age-related Diseases
2013-2015	Review Editor, Frontiers in Integrative Physiology
2013 - 2015	Chair, BS Membership Committee, Gerontological Society of America
2014-	Editorial Board, Geroscience
2014-	Fellow, Gerontological Society of America
2017-2019	BS Member Representative to Education Committee, Gerontological Society of America
2020-2023	Board Member, American Association of Aging Research

Honors

1995	National Research Service Fellowship Award (NRSA) (#MH11262 F31) at University of North Carolina, Chapel Hill, The National Institute of Mental Health (NIMH)
1996	Travel Award, Neurobehavioral Teratology Society
2001	Austin Bloch Post-Doctoral Fellowship Award, Gerontological Society of America
2001	American Federation for Aging Research (AFAR)/Pfizer Research Award
2003	New Investigator Award, American Geriatrics Society
2004	Travel Award, American Aging Association
2008	Outstanding Rating, US Department of Veterans Affairs
2010	UF COM Teaching Incentive Award
2016	UF Online Education Excellence Award in the category of Graduate Course
2016	UF COM Teaching Incentive Award
2019	UAB Department of Medicine Leadership Program
2019	UAB Transforming Success Leadership Program
2019	UDB DOM Impact Funding

C. Contributions to Science

1. The Gut Microbiome in Aging. Over the past two years, Drs. Jumbo-Lucioni, Li and I have developed and documented a strong research interest in understanding how the gut microbiome contributes to aging-related pathologies, particularly as it relates to systemic inflammation and cognitive decline. This interest includes the first report of differences in circulating microbial populations between health young and older adults and the first use of a genetically modified probiotic in curbing age-related systemic/brain inflammation. I also recently chaired a symposium on this topic at the 2019 Gerontological Society of American annual meeting in Austin TX and guest edited a special Issue of The Journals of Gerontology: Biological Sciences to dove-tail with this symposium. Thus, our team is building a strong research program around the gut is a potential target for translational studies to provide rehabilitation in a variety of disabled populations.

a. Sun Y, Baptista LC, Roberts LM, Jumbo-Lucioni P, McMahon LL, Buford TW, et al. The gut microbiome as a therapeutic target for cognitive impairment. J Gerontol A, Biol Sci Med Sci. 2019 Epub ahead of print. PMID: 31811292

b. **Carter CS**, Morgan D, Verma A, Lobaton G, Aquino V, Sumners E, et al. Therapeutic Delivery of Ang(1-7) Via Genetically Modified Probiotic: A Dosing Study. J Gerontol A, Biol Sci Med Sci. 2019 Epub ahead of print. PMID: 31586210; PMCID: PMC7109904

c. AL.Y Qi, R Goel, S Kim, EM Richards, **CS Carter**, CJ Pepine, MK Raizada, TW Buford. Intestinal Permeability Biomarker Zonulin is Elevated in Healthy Aging. *J Am Med Dir Assoc.* 17: 30297-9. 2017. PMID: 28676292; PMCID: PMC5581307

d. Buford TW, **Carter CS**, VanDerPol WJ, Chen D, Lefkowitz EJ, Eipers P, Morrow CD, Bamman MM. Composition and Richness of the Serum Microbiome Differ by Age and Link to Systemic Inflammation.Geroscience. 2018 Jun; 40(3); 257-268. PMID: 29869736; PMCID: PMC6060185

2. Animal Models of Functional and Cognitive Decline. I was the first to demonstrate that physical function is predictive of longevity in a rodent model of aging. In humans, physical performance declines with increasing age, and in nondisabled older persons, scores on standardized performance measures, such as walking speed, repeated chair stands, and a balance test, predict the incidence of disability and reduced longevity. I demonstrated in aged Brown Norway x Fischer 344 male rats that conceptually similar performance measures, such as swimming speed and an inclined plane procedure, can be assessed longitudinally, and that over time, performance declines progressively with increasing age. High baseline performance scores predict long-term longevity, a relationship that is also found in humans. The application of standardized physical performance measures to a variety of animal models of aging may help to define similarities between species in the underlying mechanisms of the age-related decline in performance, cognition, disability, rehabilitation longevity and other age-related health outcomes.

a. **Carter CS**, Richardson A, Huffman DM, Austad S. Bring Back the Rat! Gerontol A Biol Sci Med Sci. 2020;75(3):405-415. PMID:31894235; PMCID: PMC7021637

b. Justice JN, **Carter CS**, Beck HJ, Gioscia-Ryan RA, McQueen M, Enoka RM, Seals DR. Battery of behavioral tests in mice that models age-associated changes in human motor function. Age (Dordr). 2014 Apr;36(2):583-92. PMID: 24122289; PMCID: PMC4039275.

c. **Carter CS**, Marzetti E, Leeuwenburgh C, Manini T, Foster TC, Groban L, Scarpace PJ, Morgan D. Usefulness of preclinical models for assessing the efficacy of late-life interventions for sarcopenia. J Gerontol A Biol Sci Med Sci. 2012 Jan;67(1):17-27.PMID: 21636833; PMCID: PMC3260483.

d. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, **Carter CS**, Pahor M, Javors MA, Fernandez E, Miller RA. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature. 2009 Jul 16;460(7253):392-5. PMID: 19587680; PMCID: PMC2786175.

e. **Carter CS**, Sonntag WE, Onder G, Pahor M. Physical performance and longevity in aged rats. J Gerontol A Biol Sci Med Sci. 2002 May;57(5):B193-7. PMID: 11983716.

3. Inflammation and Aging. I have long been interested in both systemic and skeletal muscle inflammation in aging, and their contributions to health and disease. Globally my interests involves the contributions of inflammation to physical and cognitive decline and the use of interventions with known anti-inflammatory outcomes (renin-angiotensin system, exercise, calorie restriction).

a. Scarpace PJ, Matheny M, Strehler KY, Toklu HZ, Kirichenko N, **Carter CS**, Morgan D, Tümer N.

Rapamycin Normalizes Serum Leptin by Alleviating Obesity and Reducing Leptin Synthesis in Aged Rats. J Gerontol A Biol Sci Med Sci. 2015 Jan 23. PMID: 25617379; PMCID: PMC4906318.

b. Marzetti E, Calvani R, DuPree J, Lees HA, Giovannini S, Seo DO, Buford TW, Sweet K, Morgan D, Strehler KY, Diz D, Borst SE, Moningka N, Krotova K, **Carter CS**. Late-life enalapril administration induces nitric oxide-dependent and independent metabolic adaptations in the rat skeletal muscle. Age (Dordr). 2013 Aug;35(4):1061-75. PMID: 22639176; PMCID: PMC3705103.

c. **Carter CS**, Leeuwenburgh C, Daniels M, Foster TC. Influence of calorie restriction on measures of age-related cognitive decline: role of increased physical activity. J Gerontol A Biol Sci Med Sci. 2009 Aug;64(8):850-9. PMID: 19420296; PMCID: PMC2709546.

d. **Carter CS**, Khamiss D, Matheny M, Toklu HZ, Kirichenko N, Strehler KY, Tümer N, Scarpace PJ, Morgan D. Rapamycin Versus Intermittent Feeding: Dissociable Effects on Physiological and Behavioral Outcomes When Initiated Early and Late in Life. J Gerontol A Biol Sci Med Sci. 2015 Jan 23. PMID: 25617380; PMCID: PMC4906319.

4. RAS and Age-related Systemic Metabolic Decline. Evidence in animals suggest that modulation of the RAS is associated with metabolic and biochemical changes in a variety of tissues including influence on oxidative stress, metabolic and inflammation pathways. Our group has established such preclinical models of RAS intervention for declining cardiovascular, cognitive and physical decline. Understanding the molecular mechanisms governing these effects has been critical to the design of human clinical trials, especially with regards to declining physical and cognitive function.

a. **Carter CS**, Cesari M, Ambrosius WT, Hu N, Diz D, Oden S, Sonntag WE, Pahor M. Angiotensin-converting enzyme inhibition, body composition, and physical performance in aged rats. J Gerontol A Biol Sci Med Sci. 2004 May;59(5):416-23. PMID: 15123750.

b. Kasper SO, **Carter CS**, Ferrario CM, Ganten D, Ferder LF, Sonntag WE, Gallagher PE, Diz DI. Growth, metabolism, and blood pressure disturbances during aging in transgenic rats with altered brain renin-angiotensin systems. Physiol Genomics. 2005 Nov 17;23(3):311-7. PMID: 16131528.

c. **Carter CS**, Groban L. Role of the renin-angiotensin system in age-related sarcopenia and diastolic dysfunction. Aging health. 2008 Feb 1;4(1):37-46. PMID: 20445808; PMCID: PMC2863036.

D. Additional Information: Research Support and/or Scholastic Performance

Current Research Support

R01AG054538 (Buford/Carter) 08/1/2017-5/31/2022
NIH/NIA
ACE2 as a novel therapeutic to preserve physical function in late life
This pre-clinical study is designed to evaluate the impact of systemic increases in angiotensin converting enzyme 2 (ACE2) in attenuating declines in physical function in late life. This grant is also associated with an equipment supplement and an AD supplement.
Role: PI

R01AG056769 (Buford) 09/01/2017-08/30/2022
NIH/NIA
ACES - ACE inhibitors Combined with Exercise for hypertensive Seniors
The objective of this project is to compare the efficacy of physical exercise for improving physical function among hypertensive older adults when given in concert with differing classes of antihypertensive medications.
Role: Collaborator

P30AG050886 (Austad) 7/15/2015-7/14/2020
NIH/NIA
Comparative Energetics and Aging (Nathan Shock Center of Excellence)
The Center explores the complex relationship among cellular and organismal energetics and their relationship to health and aging.
Role: Research Development Core co-Leader

T32HD071866 (Bamman) 05/1/2017-04/30/2022
NIH/NICHD
Interdisciplinary Training in Pathobiology and Rehabilitation Medicine
The overarching goal of the mixed predoctoral and postdoctoral T32HD071866 training program is to develop burgeoning scientists into future leaders in translational rehabilitation research. (Mentee: Abigail Hernandez, PhD)
Role: Mentor

Past Research Support (last 3 years)

P30AG050886-Pilot (Buford) 4/1/2018-3/31/2019
UAB Nathan Shock Center-NIH/NIA
Role of the Gut Microbiome in Inflammation of Aging
The objective of this pilot is to utilize a gnotobiotic mouse model to document inflammatory responses to fecal transplants from donors of differing chronological ages.
Role: co-Investigator

P30AG028740-01 (Pahor) 04/01/17-03/31/22
NIH/NIA
Claude D. Pepper Older Americans Independence Center
The major goals of this program are to assess the mechanisms leading to sarcopenia and functional decline, and to develop and test interventions for the treatment and prevention of physical disability in older adults.
Role: Leader of the Pilot and Exploratory Core and Investigator Research Education Core, Leadership and Administration Core.

P30AG028740-01 (Pahor) 06/01/12-03/31/17
NIH/NIA
Claude D. Pepper Older Americans Independence Center
The major goals of this program are to assess the mechanisms leading to sarcopenia and functional decline, and to develop and test interventions for the treatment and prevention of physical disability in older adults.
Role: Leader of the Pilot and Exploratory Core and Investigator Research Education Core, Leadership and Administration Core.

3SDG17080033 (Buford) 07/01/13-06/30/17
American Heart Association
Multi-modal intervention to reduce cardiovascular risk among hypertensive older adults
The objective of this project is to compare the efficacy of physical exercise for improving physical function among hypertensive older adults when given in concert with differing classes of antihypertensive medications.
Role: Collaborator

BIOGRAPHICAL SKETCH

NAME: Buford, Thomas W.

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

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Oklahoma Baptist University	BSE	05/2004	Social Science
Oklahoma State University	MS	05/2006	Exercise Physiology
Baylor University	PhD	08/2009	Preventive Health Sciences
University of Florida	Scholar	12/2011	Geriatrics/Clinical & Translational Science

A. Personal Statement

I am currently an Associate Professor in the Department of Medicine (Division of Gerontology, Geriatrics, and Palliative Care) at the University of Alabama at Birmingham (UAB). Along with Dr. Carter, our group has been a leader in publishing on the influence of the renin-angiotensin system (RAS) on age-related physiology and health. We have published studies using both clinical and pre-clinical models and evaluated the influence of pharmacologic RAS modulation both in isolation and in combination with exercise on physical function – ultimately leading to ongoing clinical trial in this area. More recently, we have developed a growing interest in the role of the gut microbiome in the development of age-related changes in cognitive function. The current pre-clinical project is designed to evaluate the potential therapeutic efficacy of a variety of interventions targeting the gut. Should results show efficacy, our long-term aim is to translate this approach to humans as we have for our work on existing FDA-approved. Given widespread calls for new investigators and new strategies for the treatment of cognitive fragility, this approach represents a timely and novel direction for the field.

Positions and Honors

Positions and Employment

2009-11 Research Associate and Lecturer, Dept. of Aging and Geriatric Research, Univ. of Florida
2012-17 Assistant Professor, Dept. of Aging and Geriatric Research, Univ. of Florida
2017- Associate Professor with Tenure, Dept of Medicine, University of Alabama at Birmingham
2017- Associate Director, UAB Center for Exercise Medicine
2018- Associate Director, UAB Nathan Shock Center

Other Experience

2016 Ad Hoc Member: NIH Special Emphasis Panel, ZRG1 BDCN-N 55, Fogarty Global Brain Disorders
2017-18 Ad Hoc Member: NIA GEMSTAR Review Panel
2018- Ad Hoc Member: Aging Systems and Geriatrics Review Panel (ASG)

2014- Editorial Board: Frontiers in Medicine – Geriatric Medicine
2015- Editorial Board: Experimental Gerontology
2020- Editorial Board: J Gerontology Series A – Biological Sciences

2016- Elected Fellow, American Heart Association (2016), American College of Sports Medicine (2016), and the Gerontological Society of America (2018)

2019- Co-Editor, Special Issue on “The Gut Microbiome”, *J. Gerontol A – Biol Sci.*

B. Contribution to Science

To date I have established a successful record of scholarly activity, including 121 peer-reviewed publications (55 as first or senior author) and an h-index ≥ 29 (ISI Web of Science: 29; Google Scholar: 37). These publications have been in journals from several inter-related fields relevant to the current application including general medicine (*JAMA, BMJ*), multidisciplinary (*Cell*, *PNAS, PLOS One*) and cardiovascular (JAHA, JAMA Cardiol, Am Heart J) sciences, aging biology (*AGE, Aging Cell, J Gerontol Biol Sci*), geriatrics (e.g. *Exp Gerontol*, *J Gerontol Med Sci, J Am Geriatr Soc),* rehabilitation and sports medicine (*PM&R, Sports Med*), as well as applied physiology and exercise science (e.g. *J Appl Physiology*, *Physiol Genomics, Med Sci Sports Exerc*). I also have a strong record of extramural funding having served as PI or Co-I on numerous externally-funded, investigator-initiated projects.

1. The Gut Microbiome in Aging. Over the past several years, I have developed and documented a strong research interest in understanding how the gut microbiome contributes to aging-related pathologies, particularly as it relates to systemic inflammation. I also chaired a symposium on this topic at the 2018 Gerontological Society of American annual meeting in Boston, MA, presented an oral presentation on links between the gut microbiome and late-life cognition at the 2018 McKnight Brain Institute Inter-Institutional Meeting, and recently served as Co-Editor for a Special Issue on the gut microbiome to be released shortly in in *J Gerontol A - Biol Sci*.

a. Y Qi, R Goel, S Kim, EM Richards, CS Carter, CJ Pepine, MK Raizada, TW Buford. Intestinal Permeability Biomarker Zonulin is Elevated in Healthy Aging. *J Am Med Dir Assoc.* 17: 30297-9. 2017. PMID: 28676292. PMCID: 5581307.

b. TW Buford. (Dis)Trust Your Gut: The Gut Microbiome in Age-Related Inflammation, Health, and Disease. Microbiome. 5(1): 80. 2017. PMID: 28709450. PMCID: 512975.

c. TW Buford, CS Carter, WJ VanDerPol, D Chen, EJ Lefkowitz, P Eipers, CD Morrow, MM Bamman. Composition and Richness of the Serum Microbiome Differ by Age and Link to Systemic Inflammation. In press, GeroScience. 40(3): 257-268. 2018. PMID: 29869736. PMCID: PMC6060185.

d. J Adriansjach, ST Baum, EJ Lefkowitz, WJ Van Der Pol, TW Buford, RJ Colman. Age-related differences in the gut microbiome of Rhesus macaques. J Gerontol A- Biol Sci. Online ahead of print. PMID: 32052009. PMCID: pending

2. The renin-angiotensin system, exercise and late-life health: pre-clinical/review. For the past ten years, I worked alongside Dr. Carter investigating the impact of the renin-angiotensin system on aging and health. We have published both clinical and pre-clinical findings highlighting the potential benefits and limitations of antihypertensive drugs for maintaining both physical and cognitive functions. Our experiences to date suggest that the Ang(1-7) axis may provide greatest benefit, possibly when paired with physical exercise. We also recently published evidence regarding the efficacy of our genetically-modified probiotic in increasing systemic Ang(1-7).

a. CS Carter, S Giovaninni, D Seo, J DuPree, D Morgan, HY Chung H Lees, M Daniels, G Hubbard, S Lee, Y Ikeno, T Foster, TW Buford, E Marzetti. Differential effects of enalapril and losartan on body composition and indices of muscle quality in aged male Fischer 344 x Brown Norway rats. *AGE.* Jun;33(2):185. 2011. PMID: 21153712. PMCID: PMC3127467.

b. E Marzetti, R Calvani, J DuPree, HA Lees, S Giovannini, D Seo, TW Buford, K Sweet, D Morgan, KYE Strehler, D Diz, SE Borst, M Moningka, K Krotova, CS Carter. Late-life enalapril administration induces nitric oxide-dependent and independent metabolic adaptations in the rat skeletal muscle. *AGE*. 35(4): 1061-75. 2013. PMID: 22639176. PMCID: PMC3705103.

c. CS Simon, B Lee-McMullen, D Phelan, J Gilkes, CS Carter, TW Buford. The Renin-Angiotensin System and Prevention of Age-related Functional Decline: Where Are We Now? AGE. 37(1): 9753. 2015.

d. CS Carter, D Morgan, A Verma, G Lobaton, V Aquino, E Sumners, M Raizada, Q Li, TW Buford. Therapeutic delivery of Ang(1-7) via genetically modified probiotic: a dosing study. J Gerontol Series A: Biol Sci. Online ahead of print. PMID: 31586210. PMCID: pending.

3. The renin-angiotensin system, exercise and late-life health: clinical. For the past ten years, I worked alongside Dr. Carter investigating the impact of the renin-angiotensin system on aging and health. We have published both clinical and pre-clinical findings highlighting the potential benefits and limitations of antihypertensive drugs for maintaining both physical and cognitive functions. Our experiences to date suggest that the Ang(1-7) axis may provide greatest benefit, possibly when in conjunction with exercise.

a. TW Buford, TM Manini, FC Hsu, M Cesari, SD Anton, S Nayfield, RS Stafford, TS Church, M Pahor, CS Carter, for the LIFE Research Group. Angiotensin-converting enzyme inhibitor use by older adults is associated with greater functional responses to exercise. J Am Geriatr Soc. 60(7): 1244-1252. 2012. PMCID: PMC3625953

b. TW Buford, FC Hsu, TE Brinkley, CS Carter, TS Church, JA Dodson, BH Goodpaster, MM McDermott, BJ Nicklas, V Yank, JA Johnson, M Pahor, LIFE Research Group. Genetic influence on Exercise-Induced Changes in Physical Function among Mobility-Limited Older Adults. Physiological Genomics. 46(5): 149-58. 2014. PMCID: PMC3949106. ******* This study evaluated the influence of a polymorphism in the Angiotensin Converting Enzyme gene on functional responses to chronic exercise. *******

c. TW Buford, ME Miller, TS Church, TM Gill, R Henderson, FC Hsu, MM McDermott, N Nadkarni, M Pahor, RS Stafford, CS Carter, LIFE Study Research Group. Antihypertensive use and the effect of a physical activity intervention in the prevention of major mobility disability among older adults: the LIFE Study. J Gerontol. Med. Sci. 71(7): 974-981. 2016. PMID: 268665496. PMCID: PMC4906322.

d. LC Baptista, BC Jaeger, SD Anton, AA Bavry, EM Handberg, AK Gardner, SA Harper, LM Roberts, B Sandesara, CS Carter, TW Buford. Multimodal intervention to improve functional status in hypertensive older adults: a pilot randomized controlled trial. J Clin Med. 8(2): pii: E196. 2019. PMID: 30736317. PMCID: PMC6406861.

4. Late-life brain health and interactions with the gut microbiome. Recently our group has begun to document our growing interest in late-life cognitive function, with particular interest in interactions with the gut microbiome. We continue to develop work in this area, with growing collaborations and we are recruiting trainees into our group from neuroscience backgrounds. Our investigative team also includes additional neuroscience expertise which will to help us to continue to expand our work in this area.

e. TW Buford, Y Sun, LM Roberts, A Banerjee, S Peramsetty, A Knighton, A Verma, D Morgan, G Torres, Q Li, CS Carter. Angiotensin (1-7) delivered orally via probiotic, but not subcutaneously, benefits the gut-brain axis in older rats. Geroscience (in press)

f. Y Sun, LC Baptista, LM Roberts, P Jumbo-Lucioni, LL McMahon, TW Buford, CS Carter. The Gut Microbiome as a Therapeutic Target for Cognitive Frailty. J Gerontol Series A: Biol Sci. Online ahead of print. PMID: 31811292. PMCID: pending.

g. LC Baptista, Y Sun, CS Carter, TW Buford. Crosstalk between gut microbiome and bioactive lipids: therapeutic targets in cognitive frailty. Frontiers in Nutrition. Online ahead of print. PMID: 32219095. PMCID: pending.

h. AA Wanigatunga, TM Manini, DR Cook, JA Katula, RA Fielding, AF Kramer, J Verghese, SR Rapp, KM Sink, AC King, TW Buford, SD Anton, N Nadkarni, JJ Jennings, KF Reid, MA Espeland, TM Gill, M Pahor, JR Nocera. Community-based activity and sedentary patterns associated with cognitive performance in mobility-limited older adults. Frontiers Aging Neurosci. 10: 341. 2018.

5. Inflammation and Aging. I have long been interested in both systemic and skeletal muscle inflammation in aging, and their contributions to health and disease. Until recently, my primary interest was in contributions of inflammation to physical decline. The gut microbiome represents a promising area for intervening upon inflammation, and given the documented gut-brain axis, I have also now gained an important appreciation for and interest in cognitive function and inflammation which we aim to explore in the proposed project.

a. R Calvani, F Marini, M Cesari, TW Buford, TM Manini, M Pahor, C Leeuwenburgh, R Bernabei, F Landi, E Marzetti. Systemic inflammation, body composition, and physical performance in old community-dwellers. J Sarcop Cachex Muscle. 8(1): 69-77. 2017.

b. MA Wallet, TW Buford, AM Joseph, M Sankauratri, C Leeuwenburgh, M Pahor, TM Manini, JW Sleasman, MM Goodenow. Increased inflammation but similar physical composition and function in older-aged, HIV-1 infected subjects. BMC Immunol. 16:43. 2015.

c. E Marzetti, F Landi, F Marini, M Cesari, TW Buford, TM Manini, G Onder, M Pahor, R Bernabei, C Leeuwenburgh, R Calvani. Patterns of circulating inflammatory biomarkers in older persons with varying levels of physical performance: a Partial Least Squares-Discriminant Analysis. Frontiers in Medicine: Geriatric Medicine. 1:27. 2014.

d. TW Buford, MB Cooke, TM Manini, C Leeuwenburgh, DS Willoughby. Effects of Age and Sedentary Lifestyle on Skeletal Muscle NFkB Signaling in Males. J Gerontol A Biol Sci Med Sci. 65(5): 532-537. 2010.

Complete List of Published Work
https://www.ncbi.nlm.nih.gov/myncbi/thomas.buford.1/bibliography/public/

C. Research Support

Active

1R01NR018391 Co-I (PIs: A. Webel/A. Willig) 9/26/18-6/30/2023
NIH/NINR
Impact of Physical Activity Routines and Dietary Intake on the Longitudinal Symptom Experience of People Living with HIV (PROSPER-HIV)
The study will explore the relationships of diet and physical activity to symptom management in HIV+ individuals.

P30AG050886 Associate Director & Core Leader (PI: Austad) 7/15/2015-7/14/2020
NIH/NIA
Comparative Energetics and Aging (Nathan Shock Center of Excellence)
The Center explores the complex relationship among cellular and organismal energetics and their relationship to health and aging.

R01AG054538 PI 08/1/2017-5/31/2022
NIH/NIA
ACE2 as a novel therapeutic to preserve physical function in late life
This pre-clinical study is designed to evaluate the impact of systemic increases in angiotensin converting enzyme 2 (ACE2) in attenuating declines in physical function in late life.

R01AG056769 PI 09/01/2017-08/30/2022
NIH/NIA
ACES - ACE inhibitors Combined with Exercise for hypertensive Seniors
The objective of this project is to compare the efficacy of physical exercise for improving physical function among hypertensive older adults when given in concert with differing classes of antihypertensive medications.

U01AR071133 Co-I (PI: Bamman) 12/6/2016-11/30/2022
NIH/NIAMS
The Exercise and Physical Activity Collaborative Team: A Proposed MoTrPAC Clinical Center
The goals are to help lead the NIH Common Fund initiative – Molecular Transducers of Physical Activity Consortium (MoTrPAC) – by serving as one of six adult clinical centers.

P2CHD086851 Co-I (PI: Bamman) 9/17/2017-06/30/2020(in NCE)
NIH/NICHD
Rehabilitation Research Resource to Enhance Clinical Trials (REACT)
The overarching purpose of this Medical Rehabilitation Research Resource is to catalyze high-impact clinical trials that will define optimal rehabilitation strategies.

Completed (last three years)

1R21AG049974 PI 04/1/2016-03/31/2018
Resveratrol and exercise to treat functional limitations in late life
This study will evaluate the potential of two doses of resveratrol for improving the efficacy of physical exercise in treating age-related functional limitations

P30AG050886-Pilot PI 4/1/2018-3/31/2019
NIH/NIA (via UAB Nathan Shock Center)
Role of the Gut Microbiome in Inflammation of Aging
The purpose of this pilot project is to capture critical preliminary data related to the role of the gut microbiome in age-related inflammation.

P2CHD086851-Pilot PI 9/1/2017-6/30/2018
NIH/NICHD (via UAB REACT Center)
The Serum Microbiome, Aging, and Inflammation
The objective of this project was to evaluate age-related differences in the composition of the serum microbiome in humans.

16IRG27250237 PI 01/01/2016-12/31/2017
American Heart Association
Wearable technology to reduce sedentary behavior and CVD risk in older adults
This study will evaluate the impact of combining an exercise intervention with an intervention designed to increase daily non-exercise physical activity among older adults at risk for cardiovascular events.

R01AG042525 Co-I (PI: Manini) 07/15/2013–08/31/2018
NIH/NIA
Metabolic cost of daily activities in older adults
This study will determine the age-related differences in metabolic cost of common daily activities. It will also evaluate the impact that functional impairment has on the metabolic cost of performing daily activities. (Withdrawn from grant upon leaving University of Florida)

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: Bizon, Jennifer Lynn

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

POSITION TITLE: Professor and Interim Chair, Department of Neuroscience

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 North Carolina at Chapel Hill, Chapel Hill, North Carolina	BS	05/1993	Psychology
University of California, Irvine, Irvine, California	PhD	08/1998	Neurobiology and Behavior
John Hopkins University, Baltimore, MD	Postdoctoral Fellow	09/2002	Neuroscience and Psychological Sciences

A. Personal Statement

My NIH-funded research program is broadly focused on determining the neural processes that support cognition and that contribute to cognitive impairments in aging and disease. Using rodent models, my laboratory employs an integrative approach that combines sensitive cognitive assessments with cellular, molecular, optogenetic and pharmacological methodologies. We have uncovered disruptions in both glutamatergic and GABAergic signaling in the aged brain (ref a-c) that contribute to impairments in cognitive flexibility, memory and decision making (ref a-d). Moreover, we have demonstrated that pharmacological targeting of GABAergic and glutamatergic signaling improves specific forms of prefrontal cortical (PFC)-dependent cognition in aged rats (ref a-c). Most recently, we have been exploring how vagus nerve stimulation (VNS) modulates both cognitive functions and age-associated alterations in GABA/glutamate signaling in PFC and hippocampus. In addition, we are now extending our investigation of cognitive decline into Alzheimer's disease models, using virally-mediated delivery of wild type and mutant tau to middle-aged and aged rat perirhinal cortex and locus coeruleus. Using this model, we have identified age-unique aspects of tau hyperphosphorylation and misfolding. Experience gained from these lines of work and my 20+ years of work in cognitive/brain aging and rodent models of cognition will be used to meet the objectives of the current proposal.

a. Bañuelos C, Beas BS, McQuail JA, Gilbert RJ, Frazier CJ, Setlow B, **Bizon JL**. (2014) Prefrontal cortical GABAergic dysfunction contributes to age-related working memory impairment. *The Journal of Neuroscience.* 34(10):3457-66. PMCID: 3942567.

b. McQuail JA, Frazier CJ, **Bizon JL.** (2015) Molecular aspects of age-related cognitive decline: Role of GABA signaling. *Trends in Molecular Medicine* 2015 Jul;21(7):450-60.

c. McQuail JA, Beas BS, Simpson K, Kelly K, Frazier CJ, Setlow B, **Bizon JL** (2016) NR2A-containing NMDA receptors in the prefrontal cortex are required for working memory and predict age-related cognitive decline. *The Journal of Neuroscience.* 36(50):12537-12548. PMCID: 5157101.

d. Hernandez CM, Orsini CA, Labiste CC, Wheeler A-R, Ten Eyck TW, Bruner MM, Frazier CJ, Setlow B, **Bizon JL** (2019). Optogenetic dissection of basolateral amygdala contributions to intertemporal choice in young and aged rats. *eLife.* Apr 24;8. pii: e46174. PMCID 6530979

B. Positions and Honors

Positions and Employment

1993-1998 Graduate Student Assistant, University of California, Irvine

1998-2003	Postdoctoral Fellow, Johns Hopkins University
2002-2004	Assistant Research Scientist, Dept. of Psychology, Johns Hopkins University
2004-2010	Assistant Professor of Psychology, Texas A&M University
2004-2010	Faculty of Neuroscience, Texas A&M University
2010-2016	Associate Professor of Neuroscience and Psychiatry, University of Florida College of Medicine
2016-present	Professor, Department of Neuroscience, University of Florida College of Medicine
2020-present	Chair, Department of Neuroscience, University of Florida College of Medicine

Other Experience and Professional Memberships

2009	Member, NIA Special Emphasis Panel (ZAG1 ZIJ-5), Mechanisms of Cognitive Aging
2010 -	Advisory Board, Alzheimer's Drug Discovery Foundation
2010-11, 2015	*Ad hoc* member, NIH Clinical Neuroscience and Neurodegeneration Study Section
2011-2015	Director, Neuroscience Graduate Program, University of Florida College of Medicine
2012	*Ad hoc* member, NIH Chronic Dysfunction and Integrative Neurodegeneration
2013 -	Member, NIH Neurodevelopment, Synaptic Plasticity, Neurodegeneration Fellowship Study Section
2014	Member, NIEHS Special Emphasis Panel (ZES1 LWJ-K), Environmental Contributors to Neurodegeneration
2015-2016	*Ad hoc* member, NIH National Institute on Aging Neuroscience Study Section (NIA-N)
2016 -	Section Editor, Cognition, Behavior and Physiology Section, Neurobiology of Aging
2016 - 2018	Chair, NIH Neurodevelopment, Synaptic Plasticity, Neurodegeneration Fellowship Study Section
2017 - 2020	Associate Chair, Department of Neuroscience, University of Florida

Honors

1994	UC Regents Graduate Fellowship, UC Regents
1995	Individual NRSA, F31 pre-doctoral award, National Institute of Mental Health
2001	Individual NRSA, F32 post-doctoral award, National Institute on Aging
2008	Montague Center for Teaching Excellence Award, Texas A&M University
2009	Leadership and Service Award, Faculty of Neuroscience, Texas A&M University
2011-2016	Exemplary Teaching Award, College of Medicine, University of Florida
2017-present	Term Professor, University of Florida
2018-present	Research Foundation Professor, University of Florida

C. Contributions to Science

URL for full list of published work: https://www.ncbi.nlm.nih.gov/pubmed/?term=bizon+jl

1. A primary focus of my laboratory is to understand how alterations in excitatory/inhibitory (E/I) signaling dynamics in the prefrontal cortex contribute to age-related cognitive decline. To date, much of our work has focused on GABA(B) receptors (refs a,b), which contribute to GABA signaling via both pre- and postsynaptic mechanisms. In PFC, we have documented a number of biochemical (refs a,c) and electrophysiological (ref b) changes in GABA(B)R signaling, which together suggest that pyramidal neurons in this brain region are subject to age-related increases in tonic inhibition (refs a, c). Potentially in response to this increased inhibition, GABA(B)R subunit expression is significantly reduced in the aged PFC (refs b, c). We have found that lower PFC GABA(B)R subunit expression strongly predicts better working memory abilities among aged rats (ref a). We have further identified specific excitatory signaling alterations that contribute to working memory impairments in aging, including reductions in presumptive synaptic NR2A-NMDARs (ref d). Based on these findings, my laboratory has provided preclinical validation of GABA(B)R antagonists and positive allosteric modulators of synaptic NMDARs for improving age-related cognitive decline.

   a. Bañuelos C, Beas BS, McQuail JA, Gilbert RJ, Frazier CJ, Setlow B, **Bizon JL**. (2014) Prefrontal cortical GABAergic dysfunction contributes to age-related working memory impairment. *The Journal of Neuroscience.* 34(10):3457-66. PMCID: 3942567.

   b. Carpenter HE, Kelly KB, **Bizon JL**, Frazier CJ. (2016) Age related changes in tonic activation of pre- and post-synaptic GABA(B) receptors in medial prefrontal cortex. *Neurobiology of Aging*. 45:88-97. PMCID: 523522.

c. Beas BS, McQuail JA, Bañuelos C, Setlow B, **Bizon JL**. (2017) Prefrontal cortical GABAergic signaling and impaired behavioral flexibility. *Neuroscience.* 345:274-286. PMCID: 5333995.

d. McQuail JA, Beas BS, Simpson K, Kyle K, Frazier CJ, Setlow B, **Bizon JL.** (2016) NR2A-containing NMDA receptors in the prefrontal cortex are required for working memory and predict age-related cognitive decline. *The Journal of Neuroscience.* 36(50):12537-12548. PMCID: 5157101.

2. My laboratory has developed sensitive behavioral methods to model hippocampal/medial temporal lobe-mediated deficits in aged rodents (refs a, b, c) and has used these behavioral models to investigate underlying neural mechanisms of cognitive decline in aging. Specifically, in the past several years, we have established sensitive behavioral tools for investigating how the perception and encoding of sensory stimuli is altered in aging and how such alterations contribute to mnemonic decline (refs a, c, d*).* We are now employing these same rigorous psychophysical methods (ref d) to better understand cognitive decline associated with Alzheimer's disease, using viral mediated delivery of wildtype and mutant tau to middle-aged and aged rat perirhinal cortex. Using this model, we are exploring whether perceptual discrimination learning assessments have utility as a behavioral biomarker for disease pathology.

   a. LaSarge CL, Montgomery KS, Tucker C, Slaton GS, Griffith WH, Setlow B, **Bizon JL**. (2007) Deficits across multiple cognitive domains in a subset of aged Fischer 344 rats. *Neurobiology of Aging*. Jun;28(6):928-36.

   b. **Bizon JL**, LaSarge CL, Montgomery KS, McDermott AN, Setlow B, Griffith WH. (2009) Spatial reference and working memory across the lifespan of male Fischer 344 rats. *Neurobiology of Aging*. 30(4):646-55. PMCID: 2703480.

   c. Montgomery, KS, Edwards, G, Kumar, A, Levites, Y, Meyers CA, Gluck M, Setlow, B and **Bizon, JL.** (2016) Deficits in hippocampal-dependent transfer generalization learning and synaptic function in mouse models of amyloidosis. *Hippocampus*. 26(4):455-71.PMCID: 4803574.

   d. Yoder WM, Gaynor, L, Burke SN, Setlow B, Smith DW, **Bizon JL.** (2017) Interaction between age and perceptual similarity in olfactory discrimination learning: relationship with spatial learning impairment. *Neurobiology of Aging.* 53:122-137. PMCID: 5393344.

3. Deciding among options that include both benefits and risks of adverse outcomes is fundamental to our ability to effectively navigate everyday life. As part of a long-standing collaboration with Dr. Barry Setlow, my laboratory has a strong interest in using animal models to understand the neural processes that support decision making. One element of this work involves elucidation of the neural circuits and signaling mechanisms that mediate how individuals weigh rewards against putative costs such as punishment or delay to reward delivery (refs c, d). A second element of this work is to determine how cost-benefit decision making changes across the lifespan (refs a, b). Our work was the first to show that aged rats have a strong preference for delayed over immediate rewards relative to young adult rats. These data are consistent with observations showing that aged humans are better at delaying gratification, and suggest that age-related neurobiological alterations are not universally detrimental but can support some beneficial cognitive outcomes (ref a).

   a. Simon NW, LaSarge CL, Montgomery KS, Williams MT, Mendez IA, Setlow, B, **Bizon, JL.** (2010) Good things come to those who wait: attenuated discounting of delayed rewards in aged Fischer 344 rats. *Neurobiology of Aging*. 31(5):853-62. PMCID: 2866647.

   b. Hernandez CM, Vetere LM, Orsini CA, McQuail JA, Maurer AP, Burke SA, Setlow B, **Bizon JL** (2017) Decline of prefrontal cortical-mediated executive functions but attenuated delay discounting in aged Fischer 344X brown Norway hybrid rats. *Neurobiology of Aging*. 60: 141-152. PMCID: 5669385.

   c. Orsini CA, Trotta RT, **Bizon JL**, Setlow B. (2015) Dissociable Roles for the Basolateral Amygdala and Orbitofrontal Cortex in Decision-Making under Risk of Punishment. *The Journal of Neuroscience*. 35(4):1368-79. PMCID: 4308589.

   d. Orsini CA, Hernandez CM, Kelly KB, Sarthak S, Frazier CJ, **Bizon JL**, Setlow B. (2017) Optogenetic inhibition reveals distinct roles for basolateral amygdala activation during discrete timepoints in risky decision making. *The Journal of Neuroscience.* 37, 11537-11548. PMCID: 5707761

4. My early research showed that memory loss is associated with impaired HPA axis function and protracted glucocorticoid release following a stressor, and that such changes occur in the absence of frank hippocampal neural loss. Instead, we found that these changes are likely attributable to attenuated GR/MR expression within both aged hippocampus and prefrontal cortex (ref a). Other findings in neuroscience at the time highlighted the remarkable neurogenic capacity of the adult hippocampus (Kempermann and Gage, 1998;

Gould and McEwen, 1993), and led to questions about whether age-related changes in this phenomenon could contribute to decline of mnemonic abilities associated with aging. My postdoctoral studies examined hippocampal neurogenesis in relation to age-related memory loss and showed that while there is a marked attenuation of new neurons born in the aged hippocampus (>-90%), new neuron production and differentiation did not predict the memory abilities of aged rats (refs b-d). Indeed, many aged rats were able to maintain spatial learning performance on par with young adults despite dramatic reductions in hippocampal neurogenesis. While these studies did not specifically address the role of hippocampal neurogenesis in normal learning and memory, they do indicate that reduced neurogenesis in normal aging is not sufficient to account for spatial memory dysfunction.

a. **Bizon JL**, Helm KA, Han JS, Chun HJ, Pucilowska J, Lund, PK, Gallagher, M (2001) Hypothalamic-pituitary-adrenal axis function and corticosterone receptor expression in behaviourally characterized young and aged Long-Evans rats. *European Journal of Neurosci*ence 14(10):1739-51.

b. **Bizon JL**, Gallagher M. (2003) Production of new cells in the rat dentate gyrus over the lifespan: relation to cognitive decline. *European Journal of Neuroscience*. 18(1):215-9.

c. **Bizon JL**, Lee HJ, Gallagher M. (2004) Neurogenesis in a rat model of age-related cognitive decline. *Aging Cell*. 3(4):227-34.

d. **Bizon JL**, Gallagher M. (2005) More is less: neurogenesis and age-related cognitive decline in Long-Evans rats. *Science Aging Knowledge Environment*. 2005(7):re2.

5. I have had a long-standing interest in the role of basal forebrain and cholinergic signaling in the modulation of cortical circuits and memory function. Highlights of this work include several studies from my pre-doctoral training in the laboratory of Dr. Christine Gall, in which we identified sources of local trophic support for basal forebrain and striatal cholinergic neurons (ref a, Bizon et al., 1996, Lauterborn et al., 1995). Subsequently, I used the selective neurotoxin 192-IgG saporin to show that removal of cholinergic neurons alters spatial learning strategies (ref b) and HPA function (Han et al., 2002) in young rats. More recently, we investigated both the number (ref d) and electrophysiological properties (ref c, Dubois et al., 2014) of cholinergic neurons in relation to age-related hippocampal-dependent spatial memory impairment. Our findings show that while there is modest cholinergic neuron loss with advanced aging, such changes cannot fully account for spatial learning deficits. Notably, our studies highlight a role for co-distributed basal forebrain GABAergic neurons in both cholinergic dysfunction (Dubois et al. 2014) and impaired memory (ref d).

a. **Bizon JL**, Lauterborn JC, Gall CM. (1999) Subpopulations of striatal interneurons can be distinguished on the basis of neurotrophic factor expression. *Journal of Comparative Neurology*. 408(2):283-298.

b. **Bizon JL**, Han JS, Hudon C, Gallagher M. (2003) Effects of hippocampal cholinergic deafferentation on learning strategy selection in a visible platform version of the water maze. *Hippocampus*. 13(6):676-84.

c. Murchison D, McDermott AN, LaSarge CL, Peebles KA, **Bizon JL**, Griffith, WH (2009) Enhanced calcium buffering in F344 rat cholinergic basal forebrain neurons is associated with age-related cognitive impairment. *Journal of Neurophysiology*. 102(4):2194-207 PMCID: 2775378.

d. Bañuelos C, LaSarge CL, McQuail JA, Hartman JJ, Gilbert RJ, Ormerod, B, **Bizon, JL**. Age-related changes in rostral basal forebrain cholinergic and GABAergic projection neurons: relationship with spatial impairment. *Neurobiology of Aging*. 2013 Mar;34(3):845-62. PMCID: 3632262.

D. CURRENT RESEARCH SUPPORT

RF1AG060778 (NIH-NIA) 2018/09/01-2023/08/31
Decision making and basolateral amygdala dysfunction in aging
Principal Investigator: Jennifer L Bizon (Setlow, Frazier MPIs)
The goal of this project is to determine the contributions of basolateral amygdala and related circuitry to age- and tau pathology-associated alterations in cost-benefit decision making

RF1AG064942 (NIH-NIA) 2019/08/15-2024/03/31
Immunotherapy targeting the HPA axis in Alzheimer's disease
Principal Investigator: Jennifer L. Bizon (Golde MPI)

The goal of this project is to determine the efficacy of an antibody against CRF at blocking neuropathology and cognitive deficits associated with Alzheimer's disease pathology

R21AG058240 (NIH-NIA) NCE
Interactions of perirhinal tau pathology and aging in cognitive dysfunction
Principal Investigator: Jennifer L Bizon, (Burke MPI, Chakrabarty co-I)
The goal of this project is to determine the contributions of perirhinal cortical tau pathology to perceptual and cognitive dysfunction in an aged rat model

R01 DA036534 (NIH-NIDA) NCE
Risk taking and cocaine use: interactions, mechanisms, and therapeutic targets
Co-Investigator: Jennifer L Bizon (Setlow PI)
The goal of this project is to determine neural mechanisms underlying relationships between risk taking behavior and cocaine self-administration.

R01 R01AG049722 (NIH-NIA) 2016/01/05-2021/01/15
The contribution of declines in functional connectivity to cognitive aging
Co-Investigator: Jennifer L Bizon (Burke PI)
The goal of this project is to investigate how disrupted communication between the prefrontal cortex and hippocampus contributes to age-associated cognitive decline.

R01MH109548 (NIH-NIMH) 2016/01/01-2021/10/01
Testing and forecasting hippocampal theta wave propagation in learning and memory
Co-Investigator: Jennifer L Bizon (Maurer PI)
The goal of this project is to investigate how basal forebrain and entorhinal input to hippocampus regulate brain rhythms in behaving animals.

Targeted Neuroplasticity Training Award (DoD-DARPA) 2017/01/01-2021/01/01
Cognitive augmentation through neuroplasticity
Project Leader: Jennifer L Bizon (Otto PI)
The goal of this project is to explore peripheral nerve stimulation as a means to enhance cognition.

T32AG061892 (NIH-NIA) 2018/09/01-2023/08/31
Clinical and Translational Pre-doctoral Training in Alzheimer's and Related Dementias
Principal Investigator: Jennifer L Bizon (Lewis, MPI)
The goal of this project is to support graduate training in Alzheimer's disease and related dementias

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: BURKE, SARA

eRA COMMONS USER NAME (agency login): sburke

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.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Oregon, Eugene, OR	BS	08/1999	Psychology, Chemistry
University of Oregon, Eugene, OR	MS	12/2000	Psychology
University of Arizona, Tucson, AZ	PHD	05/2009	Neuroscience, pharmacology
University of Arizona, Tucson, AZ	Postdoctoral Fellow	09/2013	Non-human primate and rodent models of cognitive aging

A. PERSONAL STATEMENT

My NIH-funded research program is focused on determining the mechanisms that are responsible for cognitive decline that occurs during normal aging, and potential interventions for alleviating age-related memory loss (e.g. ref a, b). To do this, my laboratory uses multiple levels of analysis that span from gene expression to large-scale neurophysiological recordings during behaviors that encompass olfactory and object discrimination, associative memory, behavioral flexibility and episodic memory. Currently, we are quantifying large-scale circuit interactions across levels of analysis as well as labeling the expression of activity dependent immediate-early genes in anatomically defined circuits to identify the populations of neurons across the CNS that are activated during behavior (ref c). Recently, we have also formulated a ketogenic diet that improves behavioral performance, reveres age-related impairments in transporter expression (ref a), and improves overall metabolic health in aged rats (ref d). We are implementing this diet in ongoing studies in the lab and comparing it to exogenous ketone ester. With my collaborators at the University of Alabama, Birmingham in the Evelyn F. McKnight Brain Institute, we are excited by the possibility of examining how the ketogenic diet may modulate the gut-brain axis to improve cognitive health in older adults.

a. Hernandez AR, Campos KT, Truckenbrod LM, Hernandez CM, Sakarya Y, McQuail JA, Carter CS, Bizon JL, Maurer AP, **Burke SN** (2018). The anti-epileptic ketogenic diet reduces adiposity and alters hippocampal transporter levels in aged rats. *Journal of Gerontology, Series A.*
b. Hernandez AR, Truckenbrod LM, Campos KT, Williams SA, **Burke SN** (2019). Sex Differences in age-related impairments vary across cognitive and physical assessments in rats. *Behavioral Neuroscience, in press.* DOI: 10.1037/bne0000352.
c. Hernandez AR, Reasor JE, Truckenbrod LM, Campos KT, Federico QP, Fertal KE, Lubke KN, Johnson SA, Clark BJ, Maurer AP, **Burke SN** (2018). Dissociable effects of advanced age on prefrontal cortical and medial temporal lobe ensemble activity. *Neurobiology of Aging,* 70:217-232.
d. Hernandez AR, Truckenbrod LM, Federico QP, Campos KT, Moon BM, Ferekides N, D'Agostino D, **Burke SN** (2020). Metabolic switching is impaired by aging and facilitated by ketosis independent of glycogen. *In press Aging*. Preprint available: https://www.biorxiv.org/content/10.1101/2019.12.12.874297v1

B. POSITIONS AND HONORS

Positions and Employment

1997 - 1999	Undergraduate Research Assistant, Dr. Richard Marrocco's Visual-Attention laboratory, University of Oregon, Eugene, OR
1999 - 2000	Graduate Research Associate, Dr. Richard Marrocco's Visual-Attention laboratory, University of Oregon, Eugene, OR
2000 - 2002	Research Associate, Dr. Alvin Eisner's Visual Adaptation laboratory, Oregon Health & Science University, Portland, OR
2003 - 2004	Graduate Teaching Assistant for MSB407: Cellular, Molecular Neuroscience, University of Arizona, Tucson, AZ
2006 – 2011	Teaching Assistant for NRSC4/524: Gerontology, University of Arizona, Tucson, AZ
2013 – 2019	Assistant Professor, Department of Neuroscience, University of Florida, Gainesville, FL
2019 – *present*	Associate Professor, Department of Neuroscience, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

2008 - 2009	Mentor and small group leader, Undergraduate Biology Research Program, Univ. of Arizona
2010 - 2011	Membership Survey Advisory Group, Society for Neuroscience
2010 - 2011	Mentor, University of Arizona Assurance Program
2015 - 2016	Member of Council for Undergraduate Research
2016 - 2019	Director of the UF Summer Neuroscience Internship Program
2017 - 2019	President of Florida Consortium on the Neurobiology of Cognition (http://fcneurocog.org/)
2002- *present*	Member, Society for Neuroscience
2014 - *present*	Member, North Central Florida Chapter of the Society for Neuroscience
2014 - *present*	Mentor, University of Florida Scholar Award
2015 - *present*	Member Faculty for Undergraduate Neuroscience

Honors

1999	Departmental Honor's in Psychology, University of Oregon
1999	Magna Cum Laude, University of Oregon
1999	Inducted, Phi Beta Kappa
2002	National Institute of Health Training Grant Recipient, University of Arizona
2006	Recipient of the Ruth L. Kirschstein National Research Service Award, National Institute of Health
2008	D.G. Marquis Behavioral Neuroscience Award, American Psychology Association
2009	Mentor of the Year Award, Undergraduate Biology Research Program, University of Arizona
2010	D.G. Marquis Behavioral Neuroscience Award, American Psychology Association
2012	Honorable Mention, Mentor of the Year, Undergraduate Biology Research Program, University of Arizona
2014	Best Talk, Department Data Blitz, Department of Neuroscience, University of Florida
2014-2015	Exemplary Teaching Award, University of Florida College of Medicine
2015	Claude D. Pepper Older Americans Independence Junior Scholar
2015-2016	Exemplary Teaching Award, University of Florida College of Medicine
2016	Excellence Awards for Assistant Professors
2017	American Psychological Association Early Career Award for Distinguished Contribution in Cognitive and Behavioral Neuroscience
2016-2017	Exemplary Teaching Award, University of Florida College of Medicine
2017-2018	Exemplary Teaching Award, University of Florida College of Medicine
2018-2019	Exemplary Teaching Award, University of Florida College of Medicine
2018	McKnight Brain Institute Leadership Award
2019-2020	Exemplary Teaching Award, University of Florida College of Medicine
2020	University Term Professorship Award

C. Contribution to Science

1. **Metabolic interventions for improving cognitive function in old age.** In aged animals and humans there is a reduced ability of the brain to use glucose as a primary source for ATP. This is associated with a multitude of neurobiological alterations that disrupt the balance between inhibition and excitation, leading to cognitive impairment. We have developed a ketogenic diet for rats that shifts energy metabolism from glycolysis to ketosis, bypassing these age-related impairments in glucose/insulin signaling. We have shown that our ketogenic diet normalizes the expression of transporters related to synaptic transmission (a,b), improves cognition (b), reduces transcription of genes involved in hippocampal synaptic transmission (c) and restores peripherical metabolic health (d).
   a. Hernandez AR, Hernandez CM, Campos KT, Truckenbrod LM, Sakarya Y, McQuail JA, Carter CS, Bizon JL, Maurer AP, **Burke SN** (2018). The antiepileptic ketogenic diet alters hippocampal transporter levels and reduces adiposity in aged rats. *Journal of Gerontology*, *Series A Biological Sciences and Medical Sciences*, 73(4):450-458.
   b. Hernandez AR, Hernandez CM, Campos K, Truckenbrod L, Federico Q, Moon B, McQuail JA, Maurer AP, Bizon JL, **Burke SN** (2018). A ketogenic diet improves cognition and has biochemical effects in prefrontal cortex that are dissociable from hippocampus. *Frontiers in Aging Neuroscience*, 10:391.
   c. Hernandez AR, Hernandez CM, Truckenbrod LM, Campos KT, McQuail JA, Bizon JL and **Burke SN** (2019). Age and ketogenic diet have dissociable effects on synapse-related gene expression between hippocampal subregions. *Frontiers in Aging Neuroscience*, 13(11):239.
   d. Hernandez AR, Truckenbrod LM, Federico QP, Campos KT, Moon BM, Ferekides N, D'Agostino D, **Burke SN** (2020). Metabolic switching is impaired by aging and facilitated by ketosis independent of glycogen. *In press Aging*. Preprint available: https://www.biorxiv.org/content/10.1101/2019.12.12.874297v1

2. **Network mechanisms of cognitive aging.** Published data regarding mechanisms of cognitive aging in animal models has primarily examined a single brain region, with many focusing on the hippocampus or prefrontal cortex in isolation. While this work has been foundational, it cannot uncover mechanisms of distributed network dysfunction. Thus, one aspect of my current research program is to examine the alterations in network-level interactions across multiple brain structures that underlie cognitive dysfunction in aging and the early stages of Alzheimer's disease. In support of this objective, we have published a series of experiments that examine the role of prefrontal cortical-medial temporal communication in higher cognition. Specifically, we have shown that performance on the working memory/bi-conditional task (WM/BAT), which assesses multitasking abilities is highly sensitive to detecting deficits in old age compared to more traditional cognitive tests used to quantify age-related impairments, such as the Morris watermaze (Hernandez et al., 2015). This task (formerly called the object-place paired association task) detects behavior deficits in both aged male and female rats, and performance is not affected by sex or estrus phase (a). Moreover, we have linked age-associated impairments on the WM/BAT to disrupted communication between the medial prefrontal cortex and the perirhinal cortex (b,c). Finally, we have recently shown that cognitive training on WM/BAT altered the functional connectome of aged rats, and elevated resting state connectivity between the prefrontal cortex and dorsal striatum is correlated with suboptimal response-based strategies during training on this task (d).
   a. Hernandez AR, Truckenbrod LM, Campos KT, Williams SA, **Burke SN** (2019). Sex Differences in age-related impairments vary across cognitive and physical assessments in rats. *Behavioral Neuroscience, in press.* DOI: 10.1037/bne0000352.
   b. Hernandez AR, Reasor JE, Truckenbrod LM, Lubke, K, Johnson SA, Bizon JL, Maurer AP, **Burke SN** (2016). Medial Prefrontal-Perirhinal Cortical Communication is Necessary for Flexible Response Selection. *Neurobiology of Learning and Memory,* 137:36-47.
   c. Hernandez AR, Reasor JE, Truckenbrod LM, Campos KT, Federico QP, Fertal KE, Lubke KN, Johnson SA, Clark BJ, Maurer AP, **Burke SN** (2018). Dissociable effects of advanced age on prefrontal cortical and medial temporal lobe ensemble activity. *Neurobiology of Aging,* 70:217-232.
   d. Colon-Perez LM, Turner SM, Lubke KN, Febo M*, **Buke SN*** (2019). Multi-scale Imaging Reveals Aberrant Functional Connectome Organization and Elevated Dorsal Striatal Arc Expression in Advanced Age. *eNeuro*, Dec 26;6(6).

3. **Rodent mnemonic similarity deficits.** A long-standing presumption in the field of cognitive aging had been that aged animals have difficulty recognizing stimuli because they "forget" items that have been previously experienced. This idea, however, was difficult to reconcile with other data showing that aged subjects have

an increase in false memories. I designed a series of experiments to elucidate the origins of age-associated recognition memory impairments that led to the novel observation that old animals have recognition memory deficits because they have a reduced ability to discriminate novel stimuli from those that are familiar, which manifests as a false memory (a). This work led to foundational insights regarding age-associated declines in recognition memory, which presumably arise from perirhinal cortical dysfunction, and was later replicated in monkeys (b) and humans (Ryan et al., 2012). We have recently extended this work to show that recognition impairments are due to a reduced ability of aged rats to discriminate between similar stimuli with a LEGO©-object discrimination task (c), and this is related to hyperactivity in CA3 of the hippocampus and the lateral entorhinal cortical neurons that project to CA3 (d).

a. **Burke SN**, Wallace JL, Nematollahi S, Uprety AR, Barnes CA (2010). Pattern separation deficits may contribute to age-associated recognition impairments. *Behav Neurosci*. 2010 Oct;124(5):559-73.
b. **Burke SN**, Wallace JL, Hartzell AL, Nematollahi S, Plange K, Barnes CA (2011). Age-associated deficits in pattern separation functions of the perirhinal cortex: a cross-species consensus. *Behav Neurosci*. 125(6):836-47.
c. Johnson SA, Turner SM, Santacroce LA, Carty KN, Shafiq L, Bizon JL, Maurer AP, **Burke SN** (2017). Rodent age-related impairments in discriminating perceptually similar objects parallel those observed in humans. *Hippocampus*. 27(7):759-776.
d. Maurer AP, Johnson SA, Hernandez AR, Reasor J, Cossio DM, Fertal KE, Mizell JM, Lubke KN, Clark BJ, **Burke SN** (2017). Age-related changes in lateral entorhinal and CA3 neuron allocation predict poor performance on object discrimination. *Frontiers in Systems Neuroscience*, 30;11:49.

4. **Understanding and treating age-related hippocampal dysfunction.** In young animals, dynamic hippocampal activity patterns support learning and memory. I have been involved in a series of papers that show how behavior-dependent modulation of hippocampal activity is compromised in aged animals to produce memory deficits (a,b). Moreover, we have shown that altering NMDA receptor currents with the Alzheimer's disease therapeutic memantine can restore experience-dependent plasticity in aged memory-impaired rats (a). This paper, on which I was first author, received the D.G. Marquis Behavioral Neuroscience Award from the American Psychological Association for the best paper published in *Behavioral Neuroscience* in 2008. More recently, we have shown that disrupted activity deficits in the hippocampus may be linked to impaired neurometabolism. Specifically, we have observed that expression of several ATP-dependent transporters is reduced in old compared to young rats. Importantly, reduced transporter expression in old animals can be normalized by a ketogenic diet (c), which also improves WM/BAT performance (see Contribution 1, d). These papers demonstrate my expertise regarding the physiological signatures of neural dysfunction and a commitment to explore new therapeutics for treating cognitive aging.
   a. **Burke SN**, Maurer AP, Yang Z, Navratilova Z, Barnes CA (2008). Glutamate receptor-mediated restoration of experience-dependent place field expansion plasticity in aged rats. *Behav Neurosci*. 122(3):535-48.
   b. Gerrard JL, **Burke SN**, McNaughton BL, Barnes CA (2008). Sequence reactivation in the hippocampus is impaired in aged rats. *J Neurosci*. 28(31):7883-90.
   c. Hernandez AR, Campos KT, Truckenbrod LM, Hernandez CM, Sakarya Y, McQuail JA, Carter CS, Bizon JL, Maurer AP, **Burke SN** (2018). The anti-epileptic ketogenic diet reduces adiposity and alters hippocampal transporter levels in aged rats. *Journal of Gerontology, Series A.*
   d. Hernandez AR, Hernandez CM, Campos K, Truckenbrod L, Federico Q, Moon B, McQuail JA, Maurer AP, Bizon JL, **Burke SN** (2018). A ketogenic diet improves cognition and has biochemical effects in prefrontal cortex that are dissociable from hippocampus. *Frontiers in Aging Neuroscience,* 10:391.

5. **Age-related perirhinal cortical dysfunction.** My prior publications were the first to demonstrate that age-related deficits in object recognition memory are mediated by perirhinal cortical dysfunction. The perirhinal cortex is an area of the brain that receives sensory information from all modalities and is interconnected with the hippocampus to support memory. Using neurophysiological approaches (a) and activity-induced gene expression (b), my work showed that both excitatory and inhibitory perirhinal activity is blunted in aged rats (c) during an object exploration task and that this decline in perirhinal activity is tightly related to behavioral performance.
   a. **Burke SN**, Hartzell AL, Lister JP, Hoang LT, Barnes CA (2012). Layer V perirhinal cortical ensemble activity during object exploration: a comparison between young and aged rats. *Hippocampus* 22(10):2080-93.

b. **Burke SN**, Maurer AP, Nematollahi S, Uprety A, Wallace JL, Barnes CA (2014). Advanced age dissociates dual functions of the perirhinal cortex. *J Neurosci.* 34(2):467-80.
c. Maurer AP*, **Burke SN***, Diba K, Barnes CA (2017). Advanced Age is Associated with Attenuated Principal Cell and Interneuron Activity in the Perirhinal Cortex. *J Neurosci,* 37(37):8965-8974. *These authors contributed equally.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/sara.burke.1/bibliography/47433007/public/?sort=date&direction=ascending

D. RESEARCH SUPPORT

Ongoing Research Support

NIH/NIA RF1AG060977, Role: PI 02/01/2019-01/31/2024
Title: Metabolic Interventions for Enhancing Cognitive Resilience in Aging and Alzheimer's Disease
The goal of this award is to determine the mechanisms by which dietary ketosis improves cognition in aged animals.

NIH/NIA 1R01AG049722, Role: PI 2016/01/01-2020/11/30
Title: The Contribution of Declines in Functional Connectivity to Cognitive Aging
The major goal of this proposal is to determine how alterations in systems-level neural coordination in old animals produce cognitive impairments.

DARPA Targeted Neuroplasticity Training**,** Role: Project leader for Task 1.1 (PI: Otto) 2017/01/01-2020/12/31
Title: Cognitive Augmentation through Neuroplasticity
The major goal of this award is to define the mechanisms by which peripheral stimulation of the vagus nerve improves behavioral performance.

NIH/NIMH R01MH109548, Role: co-I (PI: Maurer) 2017/04/01-2022/01/31
Title: Testing and forecasting hippocampal theta wave propagation in learning and memory
The goal of this award is to understand the relationship between hippocampal oscillatory dynamics and memory.

NIH/NIA R01AG055544, Role: co-I (PI: Maurer) 2017/09/15-2019/08/30
Title: Age-associated changes in hippocampal circuits and cognitive function
The goal of this award is to determine if age-related changes in hippocampal circuit dynamics is due to synaptic senescence for adaptive compensation.

NIH/NIA 1R01AG060778-01, Role: co-I (PI: Bizon) 07/01/2018-06/30/2023
Title: Decision making and basolateral amygdala dysfunction in aging
The goal of this project is to understand how basolateral amygdala dysfunction contributes to altered decision making in aging.

McKnight Brain Research Foundation, Role: PI 10/01/2013-09/30/2021
Title: Neural system dysfunction and cognitive aging
This goal of this award is to provide institutional support and seed funds for supplementing the maintenance of a rigorous research program aimed and determining the neurobiological basis of cognitive impairments in the elderly and to identify potential therapeutic strategies.

Mentored Support

NIH/NIA K99AG058786 PI: Johnson, Role: Mentor 04/01/2018-04/31/2020
Title: Hippocampal and dopaminergic mechanisms of novelty detection underlying cognitive resilience in aging
The goal of this mentored award is to provide Dr. Johnson with training in neurophysiological recording, analysis and optogenetics and she prepares to transition to research independence.

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: Sleep Intervention to Enhance Specific markers of cognition in The older Adult population: the SIESTA study

Principal Investigator(s): Kaur, Visscher, Taylor

Institutions: UM, UAB, UA

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

Overall Impact: 4

The investigative team proposes a pilot project focused on examining the impact of an internet-delivered CBT-I intervention on a number of cognitive and neural markers in older adults. The significance of this line of research is a clear strength. The impact of insomnia and CBT-I on cognition and brain functioning in older adults is highly significant to our understanding and prevention of age-related cognitive decline and dementia. In regard to innovation, the Investigators proposal to use an internet-based CBT-I intervention in older adults, and the proposed neural outcome measures, standout as novel in the context of insomnia and CBT-I. These strengths, however, were counterbalanced by a few notable weaknesses that could limit the immediate and sustained impact of the planned work. One conceptual concern is that the inclusion/exclusion criteria are unclear regarding cognitive status, i.e., cognitively normal versus mild cognitive impairment/dementia. This raises the possibility that the investigative team will not learn whether the effects (or lack of) of CBT-I on the outcomes of interest are applicable to cognitively unimpaired older adults, clinically impaired older adults (mild cognitive impairment or dementia) or both. Another weakness of the application is the proposed sample size. While acknowledging that this is a pilot project, it seems very underpowered to reveal reliable effect size estimates (a key objective), especially given that there appears to be little evidence speaking to the effectiveness of CBT-I delivered in a self-guided, online format to older adults who have subjective cognitive concerns. Overall, these weaknesses reduced enthusiasm for the potential impact of what is a promising line of work.

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

- If improving sleep quality mitigated, or reversed, cognitive decline and brain alterations associated with aging and dementia, the proposed line of work could have broad and sustained effects on how we promote successful cognitive aging and combat dementia.
- In the era of COVID-19 and the ongoing pandemic, there is an immediate need for internet-based clinical interventions designed for older adult, including for sleep disorders.

Weaknesses

- If the aims are successful, we still will not know whether the effects apply to cognitively unimpaired older adults, clinically impaired older adults (mild cognitive impairment or dementia) or both, given that clinical status of cognition is not clearly accounted for in inclusion/exclusion.
- It is not clear if the proposed line of work will provide much insight into the mechanisms through which improved sleep affects cognition or brain functioning and resting state functional connectivity, as likely pathways for such outcomes are not directly addressed in the proposal.

2. Investigator(s)

Score: 1

Strengths

- The co-PI team combines expertise in neuropsychology, neuroimaging, and CBT-I

Weaknesses

- No significant weaknesses noted

3. Innovation

Score: 3

Strengths

- The application of an internet-based CBT-I intervention in older adults is novel
- Examining network segregation can provide novel insight into the effect of insomnia and CBT-I on large-scale brain network integrity
- Investigating the effects of CBT-I on NAA, ratios of mI, levels of GABA is innovative

Weaknesses

- No novel neuropsych tests are proposed and therefore this project will not have the potential to improve how we assess cognitive aging or sleep effects on cognition among older adults.
- The CBT-I intervention is not designed/tailored for older adults

4. Approach

Score: 5

Strengths

- The CBT-I intervention has been validated for internet delivery (although feasibility and effectiveness in older adults is unclear, see Weaknesses in this section)
- Pre-post design provides a strong evaluation of the aims.
- The analytic plan thoroughly accounts for multiple comparisons.

Weaknesses

- The neuropsychological battery appears not to include a screen for mild cognitive impairment or dementia. The cover letter states that the investigators are focusing on "healthy" older adults, but it is not clear how this is determined, especially since enrollment requires that participants have subjective cognitive concerns. As such, it seems unclear if we will know which older adults meet criteria for clinical cognitive impairment, and how this might impact study outcomes.
- With expected group sizes of 10, the present project seems very underpowered to reveal reliable effect size estimates (a key objective), especially given that among older adults, ~30% of CBT-I participants may not show a clinically significance response to treatment (Siversten et al., 2006).
- Further affecting the sample sizes, the investigators do not address the possibility that many older adults (more so than young and middle-aged adults) may struggle with an internet-based intervention that unfolds over multiple weeks. The Investigators cite several studies reportedly demonstrating efficacy of CBT-I in older adults, but all of these studies had an upper age limit of 65 or lower (refs 21-24). The cited research therefore does not directly address whether older adults should be expected to struggle with the online format, and in particular if they are vulnerable to higher dropout rates or lower treatment effectiveness. The fact that the inclusion criteria includes subjective cognitive concerns amplifies worry about treatment adherence.
- The investigators do not propose to include a younger adult control group. We therefore will not know whether null effects for the outcomes of interest are specific to older age (or whether treatment effectiveness moves outcomes towards those of younger adults).

5. Environment

Score: 1

Strengths

- Miami provides a wealth of resources for studying cognitive and brain aging in demographically diverse cohorts
- UAB and UA augment the primary data collection site with required expertise

Weaknesses

- None noted.

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes

Score: 3

Strengths

- The proposal brings together investigators from three McKnight Brain Institutes

Weaknesses

- The possibility of collecting internet-based CBT-I effectiveness data, and at least behavioral/neuropsychological data, across McKnight sites seems like a missed opportunity and something that could make for a more compelling future grant application.

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

Score: 1

Strengths

- An internet-based CBT-I intervention for cognitively unimpaired older adults is very innovative and could be an important strategy for mitigating cognitive and brain decline in some older adults.

Weaknesses

- No significant weaknesses noted.

3. Potential for future NIH funding of the research

Score: 2

- The project is addressing a topic of high importance for NIH/NIA.

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: Sleep Intervention to Enhance Specific markers of cognition in The older Adult population: the SIESTA study

Principal Investigator(s): Sonya Kaur

Institutions: Miami, Birmingham

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 *Write a brief paragraph summarizing the factors that informed your Overall Impact score.*
The proposal addresses a relevant topic (examination of the effectiveness of an 9-week internet-based treatment program in improving cognition and brain health in healthy older adults with insomnia and memory complaints). Overall the project is well motivated based on the existing literature; and clear, testable research hypotheses are formulated. The project has potential to contribute to the development of a useful, wider-ranging health intervention. The project links two currently separate literatures (combined brain and behavior effects intervention to enhance sleep quality) and has the potential to generate relevant and novel results that could also be used for extramural funding applications (determine effect sizes and demonstrate feasibility of the research and successful team collaboration). However, reducing enthusiasm is that the novelty of the proposed work is limited; the proposed small very small; and the details on the study population (it appears that an unimpaired group is selected which may result in very small intervention effect sizes) and recruitment procedures are not clear. Further reducing overall impact is the lack of information in the approach section such as pertaining to the specific content of the treatment intervention as well as the nature of the control group. The team is strong and comprises relevant, non-overlapping expertise to suceesfully complete the proposed work. The PI is a young investigator with promise, who currently holds the position of an instructor and research focus is not entirely clear; which may have impact on the competitiveness of an extramural training grant. The budgeted effort for the PI in light of the various responsibilities the PI is taking over in the project, it is not entirely clear if sufficient research time is secured to complete the proposed work. Information regarding the environment is limited and thus cannot be fully evaluated. Interdepartmental collaboration is mostly justified via expertise of the team but benefits of a cross-site collaboration are not spelled out clearly and may not outweigh the challenges of the cross-site coordianation.

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

- Significance is high given that sleep dysfunction is common in older age and has been associated with increased risk for brain health and cognitive impairment.
- The proposal is significant in its focus on demonstrating feasibility of an internet-based intervention to improve sleep quality with the goal to prevent cognitive decline.
- The proposal also has the potential to shed light on the efficacy of sleep interventions in ameliorating brain vulnerability for cognitive decline
- The proposal is conceptually strong by linking cognitive behavioral and brain imaging evidence on interventions to enhance sleep quality.

Weaknesses

- Normative age-related cognitive decline seems to be equated with pathological aging (dementia) regarding the expected effects of the intervention on cognitive function and brain health.
- The literature review on effects of sleep quality intervention on cognition and brain chemistry and function is largely age-unspecific.
- The proposed mechanistic model is underspecified; it remains unclear if a mediation via brain vulnerability is predicted or another form of mechanistic relationship between the central constructs.

2. Investigator(s)

Strengths

- The PI is a young investigator with promise.
- A strong team of experts with relevant, non-overlapping expertise (cognition, sleep intervention, brain markers, MRI data collection and analysis) is in place.

Weaknesses

- The PI's position is indicated as 'instructor' and previous research expertise is somewhat limited;
- PI responsibilities in the project are extensive (but only very minimal effort is budgeted; and only limited personnel is in place to do the actual data collection for the behavioral and brain data)
- Data analysis will be conducted by a research assistant (under co-PI supervision) but it is unclear if this person has prior experience in these complex analyses.
- Biosketches from some team members are missing.

3. Innovation

Strengths

- Adaptation of an existing validated CBT-I treatment to improve sleep quality for use online to allow wider reach and less involvement of expert trained staff for treatment assessment.
- Novel approach in linking cognition- and brain health-enhancing sleep intervention effects.
- Integration of both function and brain chemistry markers for brain health with standard cognitive measures is novel and a strength.

Weaknesses

- Overall the discussion of the novelty of the proposal is underdeveloped and it remains largely unclear how the proposal goes beyond previous research (it appears that the oline intervention already exists; and it is not clear what the proposed project adds to its content).
- A larger than 3T magnetic field is mentiond as innovative and a methodological strength, but then data collection on a 3 T scanner is proposed in the approach.

4. Approach

Strengths

- An existing intervention (SHUTi) will be used via internet-based protocol to address an unmet need on wider-reaching sleep quality enhancing interventions; this intervention has the potential to reach individuals in more rural areas and to overcome shortage of trained personnel to run such training interventions.
- Modification of CBT-I as a previously validated treatment to improve sleep quality for use online; use of SHUTi well-researched internet based CBT-I protocol with established efficacy in multiple populations.
- The proposed project combines behavioral (cognitive function) and brain (central metabolite levels, brain functional connectivity) outcome measures for a more comprehensive approach to sleep intervention outcomes.
- A bain network approach is adopted that will also allow to determine network segregation/modularity.
- The proposal builds on previous evidence in the literature on effects of sleep intervention on enhancing cognitive function and reducing brain vulnerability.
- Self-paced, internet-administered intervention to assure user friendliness and wider reach.
- Telemedicine modalities will be used to administer cognitive battery before and after the intervention
- Planned analyses are well described and specifically address the study aims.

- **Weaknesses**
  - Very limited information is presented about the content of the actual intervention, which significantly limits the potential to evaluate the quality of this crucial methodological aspect of the proposal.
  - It is not well specified what the targeted population will be (e.g., individuals with sleep disorders/or just a generally healthy population); exclusion/inclusion criteria are insufficiently described.
  - Information regarding specific recruitment strategies is missing.
  - Given the small sample size, use of a generally healthy population with no reported sleep quality concerns may result in insufficient power to detect expected intervention effects.
  - The proposal is inconsistent in its application to middle-aged adults (in some places those are listed, while in other places the focus appears to be on older adults).
  - It is unclear how actigraph data will be used.

5. Environment

Strengths

- The application brings together expert investigators from three institutes (Miami, Arizona, Alabama)

Weaknesses

- Information pertaining to facilities available at the three sites is very limited.
- It is not fully described why experts from all three sites and facilities across three sites are needed; also given that this poses logistic challenges.
- Plans for communication logistics between the three institutes lack detail.

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes
Strengths • Invetigators from three different sites are involved. • A meeting schedule across the three sites is in place. **Weaknesses** • The specific need for the interinstitutional collaboration for this project remains somewhat unclear. • Specific expertise available at the AZ is not fully described. • A detailed communication plan and study responsibility overview is not provided.

2. Potential for clinical translational impact of the intervention on cognitive aging and memory
Strengths • Successful enhancement of sleep quality could beneficially impact cognition (including memory) in aging. **Weaknesses** • Since the content of the intervention is not described it is difficult to evaluate the potential clinical impact of the proposed work. • It remains unclear what type of treatment the control group will undergo.

3. Potential for future NIH funding of the research
• It is well stated that the proposal aims at collection pilot data necessary to determine effect sizes and demonstrate fundability for an extramural funding application. • The pilot objectives directly align with NIH interest in the concept of sleep in cognitive aging ("*PAR-18-497: Sleep disorders and circadian clock disruption in Alzheimer's disease and other dementias of aging"*). • Overall, presentation of planned future applications remains vague • It appears that primarly a career development award is planned, and it is somewhat unclear who will be the individual serving as PI on this application and the strength of this candidate. Also, in this context, it is not reflected on how the proposal will be used to demonstrate mentoring team success.

Title: Sleep Intervention to Enhance Specific markers of cognition in The older Adult population: the SIESTA study

Investigators: Sonya Kaur, Kristina Visscher, Daniel Taylor, Noam Alperin, Alberto Ramos

Dear Dr. Levin and Dr. Lazar,
Thank you for considering our study entitled **"Sleep Intervention to Enhance Specific markers of cognition in The older Adult population: the SIESTA study" for** the McKnight Brain Research Foundation Interventional Core Pilot Program. We believe this study will be of interest to the McKnight Brain Research Foundation given the group interest in facilitating healthy aging.

The purpose of this study is to directly examine the effectiveness of a 9 week internet-based treatment program in improving cognition and neuroimaging correlates of aging in healthy older adults with insomnia and memory complaints. Sleep dysfunction is common in older age, in fact, more than half of adults over the age of 65 years report sleep complaints. Sleep has been associated with increased risk for cardiometabolic changes that are known to impinge on central nervous system functioning such as higher blood pressure and insulin resistance. In addition, poor sleep is independently associated with risk for incident dementia and the literature on older adults with chronic insomnia further suggests a high incidence of cognitive impairment. Exciting new research on the neurobiological underpinnings of poor sleep have highlighted changes in concentrations of crucial cerebral metabolites, changes in connectivity between linked brain regions and accumulation of amyloid protein. While sleep interventions such as cognitive behavioral therapy for insomnia have been proven to be efficacious in improving sleep quality in older adults, there is limited data with regards to the efficacy of these interventions in ameliorating cognitive decline. Furthermore, despite impressive efficacy data, widespread implementation of traditional cognitive behavioral therapy for insomnia is challenging due to limited numbers of trained practitioners, particularly in rural areas. SHUTi, our internet based protocol was developed to address this unmet need. We hope to obtain crucial effect sizes to inform a larger grant examining the efficacy of SHUTi as a prophylactic treatment to slow or delay cognitive decline in older adults with insomnia.

We suggest Sarah Getz PhD (sarah.getz@med.miami.edu) and Maria Agustina Rossetti, PhD (maria.a.rossetti@uth.tmc.edu) as potential reviewers for the grant.

Thank you very much for your consideration of our study.

Sonya Kaur, Ph.D

Form Approved Through 02/28/2023

Department of Health and Human Services
Public Health Services

LEAVE BLANK—FOR PHS USE ONLY. OMB No. 0925-0001

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

Grant Application

Do not exceed character length restrictions indicated.

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

Sleep Intervention to Enhance Specific markers of cognition in The older Adult population: the SIESTA study

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENTOR SOLICITATION NO YES
(If "Yes," state number and title)

Number: Title:

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)
Kaur, Sonya Sarjit

3b. DEGREE(S)
PhD

3h. eRA Commons User Name

3c. POSITION TITLE
Instructor

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

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

3f. MAJOR SUBDIVISION
Neuropsychology

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 No Yes

4a. Research Exempt No Yes

If "Yes," Exemption No.

4b. Federal-Wide Assurance No. -

4c. Clinical Trial No Yes

4d. NIH-defined Phase III Clinical Trial 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 ($)	8b. Total Costs ($)
10/01/2020	10/01/2022	60000	60000	119969	119969

9. APPLICANT ORGANIZATION

Name University of Miami Miller School of Medicine

Address
1120 NW 14th Street
Suite #1369
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 Robyn O Reilly

Title Senior Manager, Research Support

Address
1420 NW 9th Avenue
1420 NW 9th Avenue, Suite 112
Miami, FL 33136

Tel: (305) 323- 7086 FAX:

E-Mail: roreilly@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

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)	3b. DEGREE(S)	3h. NIH Commons User Name
Visscher, Kristina	PhD	VisscherPI

3c. POSITION TITLE
Associate Professor

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

3f. MAJOR SUBDIVISION
Neurobiology

3d. MAILING ADDRESS *(Street, city, state, zip code)*
CIRC 252D
1719 6th Avenue South
Birmingham, AL 35294

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 205-934-026 7 FAX:

E-MAIL ADDRESS:
kmv@uab.edu

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name
Taylor, Daniel J	PhD	djtaylor

3c. POSITION TITLE
Professor

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

3f. MAJOR SUBDIVISION
Psychology

3d. MAILING ADDRESS *(Street, city, state, zip code)*
1503 E University Blvd.
Building 68
Tucson, AZ 85721

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

E-MAIL ADDRESS:
danieljtaylor@email.arizona.edu

3. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. NIH Commons User Name

3c. POSITION TITLE

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT

3f. MAJOR SUBDIVISION

3d. MAILING ADDRESS *(Street, city, state, zip code)*

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

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT

3f. MAJOR SUBDIVISION

3d. MAILING ADDRESS *(Street, city, state, zip code)*

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

E-MAIL ADDRESS:

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 Miller School of Medicine		
DUNS:		
Street 1: 1150 NW 14th Street	Street 2:	
City: Miami	County: Dade	State: Florida
Province:	Country: United States of America	Zip/Postal Code: 33136
Project/Performance Site Congressional Districts:		
Additional Project/Performance Site Location		
Organizational Name: University of Alabama at Birmingham		
DUNS:		
Street 1: 1719 6th Avenue South	Street 2:	
City: Birmingham	County:	State: Alabama
Province:	Country: United States of America	Zip/Postal Code: 35294
Project/Performance Site Congressional Districts:		

SENIOR/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 senior/key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Sonya Sarjit Kaur	-	UM	PI
Kristina Visscher	VisscherPI	UAB	PI
Daniel J. Taylor	djtaylor	UA	PI
Noam Alperin	-	UM	Co-I
Alberto Ramos	aramos1	UM	Co-I

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project
Lee Sang Hoon	UM	Collaborator

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

DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY	FROM 10/01/2020	THROUGH 10/01/2021

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 (UM)	PD/PI	1	1	0	-	9059	-	9059
Lee Sang Hoon (UM)	MRI data collection	2.4	2.4	0	-	19060		19060
TBD (UAB)	MRI data analysis	1.8	1.8	0		15000		15000
								0
								0
								0
SUBTOTALS →						43119	0	43119

CONSULTANT COSTS Overseeing of implementation of intervention (UA)	2400
EQUIPMENT *(Itemize)* None	0
SUPPLIES *(Itemize by category)* None	0
TRAVEL Travel for meetings	2031
INPATIENT CARE COSTS None	0
OUTPATIENT CARE COSTS Intervention or waitlist control condition for 10 participants	6950
ALTERATIONS AND RENOVATIONS *(Itemize by category)* None	0
OTHER EXPENSES *(Itemize by category)* MRI scanning for 10 participants pre and post intervention or waitlist Participant transportation costs ($25 per visit)	5500

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$** 60000
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$** 60000

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.*	43119	43859			
CONSULTANT COSTS	2400	1200			
EQUIPMENT	-	-			
SUPPLIES	-	-			
TRAVEL	2031	-			
INPATIENT CARE COSTS	-	-			
OUTPATIENT CARE COSTS	6950	3910			
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES	5500	11000			
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	60000	59969	0	0	0
F&A CONSORTIUM/ CONTRACTUAL COSTS					
TOTAL DIRECT COSTS	60000	59969	0	0	0

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD	**$** 119969

BUDGET JUSTIFICATION

A. PERSONNEL

Sonya Kaur, Ph.D., Principal Investigator (effort = 1 calendar month in the Year 01, 0.5 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.

Lee Sang Hoon (effort =2.4 calendar months per year). Mr. Lee is an experienced MRI research associate. He will be responsible for coordinating all MRI visits at the University of Miami, implementing the MRI protocol under the supervision of Noam Alperin, PhD, perform scanning, pre-process images, organize and de-identify MRI data and transfer the data to the University of Alabama at Birmingham for analysis.

B. OTHER PERSONNEL

TBA Research Assistant, University of Alabama at Birmingam (effort = 1.8 calendar months in Year 01 , 2.4 calendar months in Year 02). This individual will manage MRI data at the University of Alabama at Birmingham. They will also conduct MRI data analysis under the supervision of the Imaging Principal Investigator, Dr. Kristina Visscher, PhD.

C. EQUIPMENT

None

D. TRAVEL **- $2301 in Year 01 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

$6950 in Year 01 and $3910 in Year 02 are requested for 15 participant and 15 waitlist control licenses to the SHUTi intervention program. Waitlist control participants will obtain access to the intervention after completion of the study. The detailed costs for the program are as follows: $5250 for project setup, $170 per active treatment or control participant for individual licenses.

$5000 in Year 01 and $10,000 in Year 02 are requested for MRI scanning pre and post intervention or after 9 weeks for waitlist control participants.

$500 in Year 01 and $1000 in Year 02 are requested for participant transportation costs to and from MRI visits.

F. OTHER DIRECT COSTS

F.1 Materials and Supplies

None

F. 3. Consultants

Dr. Daniel Taylor, PhD will manage intervention and waitlist control data at the University of Alabama at Birmingham and participate in weekly consultation meetings. A total of $2400 in Year 01 and $1200 in Year 02 are requested for this purpose.

F.5. Subawards/Consortium/Contractual Costs

None

PROJECT SUMMARY

The goal for this project is to examine if internet cognitive behavior therapy for insomnia (I-CBT-I) is a feasible intervention to improve sleep quality and prevent cognitive decline in older adults with subjective memory complaints and insomnia. 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]. Sleep disruption in older adults is associated with increased risk for falls, pain and reduced health related quality of life [2, 3]. In addition, sleep disruption 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]. The literature on older adults with chronic insomnia further suggests a high incidence of cognitive impairment [6, 7]. Longitudinal research also indicates that sleep disruption can predict declines on measures of memory and global cognitive functioning at 1 year [8]. Recent research has made clear that the neurobiological underpinnings of sleep disruption can be observed at both the level of metabolites and of connections among brain networks. Cognitive vulnerability to sleep disruption occurs when there are atypical concentrations in crucial cerebral metabolites such as myo-inositol (mI), an organic osmolyte believed to be a marker of glial functioning elevated in several neurological conditions including mild cognitive impairment [9-11], n-acetyl aspartate (NAA), a metabolite directly linked to changes in cognitive function [12-14], and γ aminobutyric acid (GABA), a critical neurotransmitter associated with synaptic function [15, 16]. More recently, resting state functional magnetic resonance imaging (fMRI) studies have shown that insomnia is associated with alterations in the structure and pattern of brain network connections [9,10]. Patterns of connections between these networks are essential for cognitive function [17] and are particularly influenced in aging [18]. **While there is preliminary evidence showing that changes in select neuroimaging/cognitive correlates of poor sleep may be reversible [19], there is limited evidence of efficacy of sleep interventions in ameliorating brain vulnerability for cognitive decline**. Given that cognitive function is the most important predictor of functional ability and quality of life in older adults [20], it is critical to develop and study the impact of targeted interventions. We will utilize SHUTi, a *convenient, non-invasive* internet based CBT-I protocol with proven efficacy at improving sleep quality [21-23], to examine if improving insomnia may prevent subsequent cognitive decline. Successful completion of this project will provide crucial pilot data and effect sizes to determine sample size and design characteristics for a larger career development award, such as an NIH K23 mentored research grant or American Academy of Neurology Career Development Award. Of note, these pilot objectives directly align with NIH interest in the concept of sleep in cognitive aging, as evidenced by the recent extension of the grant call "*PAR-18-497: Sleep disorders and circadian clock disruption in Alzheimer's disease and other dementias of aging"*.

SPECIFIC AIMS

Aim 1: To determine if SHUTi enhances cognition in middle aged to older adults with insomnia and self-reported memory complaints. Because of the well-established relationship between sleep quality and cognition [4, 5, 8], and well documented efficacy of SHUTi on improving sleep quality in multiple populations including middle aged and older adults [21-23], we will compare scores on executive function, processing speed, learning and delayed recall pre-and-post SHUTi using a repeated-measures within-subjects design. We hypothesize participants will exhibit improvements on neurocognitive test scores post SHUTi relative to age and education matched controls.

Aim 2: To determine if SHUTi induces changes in markers of brain vulnerability in middle aged to older adults with insomnia and self-reported memory complaints. Given previously described relationships between sleep and markers of brain vulnerability such as concentrations of mI, NAA [11, 14] and GABA [15] localized in the posterior cingulate cortex and hippocampus as well as patterns of connectivity of resting state neural networks [24] we hypothesize that participants will exhibit favorable changes on these markers relative to age and education matched controls, making these markers more similar to those in younger adults.

SIGNIFICANCE

Cognitive function is the most important predictor of nursing home admissions, functional independence and quality of life in older adults[20]. Poor sleep quality has consistently been associated with incident dementia and declines in memory and executive function [4, 5, 8, 25-27]. Given that 28.3% of adults in the United States report insufficient sleep, [28], it is critical to identify and evaluate the efficacy of interventions aimed at ameliorating the cognitive sequelae associated with poor sleep. CBT-I is a validated treatment with proven effects on sleep quality among patients with insomnia across the lifespan[29, 30], including older adults [31]. Of note, meta-analysis of CBT-I treatment trials have demonstrated equal or superior improvements in sleep when compared to pharmacological interventions [32]. However, despite these impressive findings, widespread implementation of traditional CBT-I has been challenging due to limited numbers of trained practitioners [33]. In order to address this need, internet based CBT-I programs have been developed and validated [23]. We aim to expand on this exciting research by directly examining the potential for SHUTi, a well-researched internet based CBT-I protocol [34] as a prophylactic treatment to reduce brain vulnerability in older adults with insomnia and subjective memory complaints.

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 [35]. By 2047, it is projected that one in every 45 Americans will have neurodegenerative dementia [36]. Interventions that delay the disease onset by as little as two years could reduce the number of projected new cases by 1.94 million [36]. In addition, approximately 30% of adults aged 65 and older will experience cognitive decline or dementia after a stroke [37] The elderly population (aged 65 and older) is projected to reach 70 million by 2030 [36]. 13.93% of the elderly population in the United States had a diagnosis of any dementia, including vascular dementia in 2002 [36]. As dementia leads to significant public health costs in the form of nursing home admissions, adult day care and respite services for caregivers [38], 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, 8, 39]. Poor sleep quality has consistently been linked with increased risk for incident dementia [25-27, 40]. In addition, measures of sleep quality such as sleep duration and efficiency predicted better scores on measures of global cognitive function [41]. 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 [42]. Chronic sleep restriction is also associated with poorer performances on measures of alertness, vigilance, working memory and arithmetic [43]. Given that the relationship between sleep and cognition thus appears robust across the lifespan, efficacious sleep interventions such as internet CBT-I are a plausible early intervention to prevent or reverse cognitive decline in older adults with insomnia and memory complaints who may be at risk for neurodegeneration.

Sleep quality is a predictor of brain vulnerability

There is a growing body of evidence detailing how changes in sleep may be indicative of underlying pathology, particularly in neurodegenerative conditions. In particular, sleep has been associated with two brain measures that are well known to be related to general cognitive functioning: metabolite levels and large scale network connectivity. Poor self-reported sleep quality is associated with increased levels of hippocampal mI [11], a metabolite hypothesized as a marker of glial functioning and is elevated in a host of conditions including mild cognitive impairment [9, 10] and metabolic syndrome [44]. Adults with disordered sleep also exhibit lower ratios of frontal NAA [14, 45], a metabolite found exclusively in the adult central nervous system that is thought to be a marker of neuronal viability[12] and is decreased in a variety of neurological conditions including dementia [13, 46], epilepsy [47] and multiple sclerosis [48]. In addition, other studies have highlighted perturbations in hippocampal levels of γ aminobutyric acid (GABA), a critical neurotransmitter associated with synaptic function among individuals with insomnia [15, 16] and neurodegenerative conditions [49].

Brain functional connectivity has also been related to sleep disturbances. Among healthy adults without disordered sleep, connectivity between regions of the default mode network changes throughout the sleep cycle [50]. Furthermore, changes in functional connectivity between parietal and frontal lobes [51], hippocampus and frontal regions [52] as well as the default mode network [53] have been reported in younger to middle aged adults with primary insomnia. In the elderly, daytime sleepiness has been associated with reduced functional connectivity in the default mode network [54]. Despite these promising results, there is preliminary evidence indicating possible increases in functional connectivity of discrete regions within the default mode among individuals with primary insomnia [53]. Attempts to reconcile these apparent disparate findings have led to the hypothesis that individuals with insomnia/disordered sleep exhibit differences in synchronization of larger brain networks [55]. In addition, the brain-wide distribution of observed effects suggests that sleep quality may relate to a larger-scale network-level property of brain connectivity such as network segregation. Network segregation is high when different networks, such as the default mode network and the salience network, have stronger connections between nodes within a network, and weaker connections between nodes between networks [56] This concept is also measured using network modularity, where stronger segregation relates to a more modular network. Sleep deprivation has been shown to be related to decreased network segregation and modularity [57, 58]. Chronic sleep deprivation and earlier age of onset of insomnia is associated with decreased segregation of the default mode network and supplementary motor area [59]. As segregation of brain networks is exacerbated by aging [18] and is associated with poorer cognitive function [17], it is likely that these changes in segregation of brain networks seen in adults with insomnia could be reflective of suboptimal organization of whole brain networks as a result of chronic poor sleep. Given the strong evidence of structural and functional neurological changes in individuals with poor sleep, it is reasonable to hypothesize that sleep intervention would slow down or reverse brain vulnerability in older adults with insomnia.

Sleep interventions may have promising effects on cognitive function and brain vulnerability

Animal models of Huntington's disease have demonstrated that medication to manage sleep/wake cycles slow the decline of cognitive function and apathy [60]. In humans, behavioral interventions such as Tai Chi have been effective in improving sleep quality and global cognition in older adults [61]. 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 [62]. 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 [63, 64]. 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 [65]. In addition, one month of CPAP therapy is associated with hypertrophic changes in the thalamus with concomitant improvements in verbal memory [66]. Early pilot data on traditional CBT-I has demonstrated possible improvements in functional connectivity between subcortical brain regions after five weeks of intervention [67]. While traditional CBT-I is considered the gold standard treatment for insomnia/poor sleep quality and is documented as more effective than pharmacological treatment of sleep quality[30, 31], there is a paucity of published research studies examining the potential neuobiological and cognitive effects resulting from internet delivered behavioral treatments of sleep, particularly among older adults who may be at risk for neurodegeneration. Since the coronavirus disease 19 (COVID 19) pandemic in 2020, there has been renewed interest in safe, effective internet delivered treatments.

INNOVATION

We propose to provide the first evidence of the efficacy of SHUTi, an internet-based protocol of a well-known sleep intervention on neuroimaging correlates of brain vulnerability (changes in ratios of NAA, mI and GABA, and segregation of brain networks measured during resting state fMRI) as well as cognitive function in human participants. The project will not only provide a potential treatment for sleep dysfunction related cognitive impairment, but it will also establish an important link between studies documenting the neuroimaging and cognitive correlates of poor sleep. Thus, we will make a significant contribution to the fields of aging, cognitive

neuroscience as well as sleep medicine. The examination of the neural mechanisms underlying sleep related facilitation of cognitive function is enabled by advances in neuroimaging technology (magnetic field strengths > 3T), which have allowed separation between the resonances of GABA, NAA and mI. Furthermore, the use of a self-paced internet CBT-I protocol will allow us to access typically underserved populations that may not have access to traditional CBT-I. Our internet-based intervention, remote cognitive assessment battery and relatively brief MRI protocol also has the advantage of allowing for minimal physical interactions between patients and research staff, which would allow for safe data collection despite the COVID-19 pandemic. Our focus on older adults with insomnia and memory complaints would also fit well with the NIH's current focus on sleep and circadian research in cognitive aging. It is hoped that this pilot data will provide the foundation for a larger career development award which would allow closer examination of changes in neural networks in conjunction with other biomarkers associated with cognitive decline.

APPROACH

The specific aims of this project will be accomplished by examining cognitive test performance and neuroimaging correlates (cerebral and hippocampal ratios of NAA, mI, GABA and segregation of resting state functional magnetic resonance imaging networks) in older adults with insomnia and subjective memory complaints pre and post a 9 week internet based CBT-I protocol and age matched controls. The SHUTi program would consist of weekly online sessions focused on implementation of sleep hygiene techniques, sleep restriction (i.e. restricting time in bed to ensure maximum sleep efficiency) and tailored stimulus control instructions addressing individual habits that may be interfering with sleep. A battery of neuropsychological tests will be administered via telemedicine modalities with special emphasis on memory, attention, processing speed and executive function, all of which are vulnerable in adults with poor sleep [63].

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 assessments, cognitive testing and brain imaging before and after internet CBT-I or after 9 weeks for controls.

Study Population

Participants will be recruited from the University of Miami sleep medicine clinic. We are confident that our sample will reflect the gender, ethnic and racial composition of our state (23.2% Hispanic or Latino of any race, 75.9% Caucasians, 16.1% African American) as we have previously demonstrated capacity to recruit ethnically diverse samples [68]. Based on research on attrition rates for traditional CBT-I, we estimate a 30% drop out, leaving a minimum of 10 participants in the CBT-I group [69].

Inclusion criteria: Participants will be included in the study if they are aged 50 years and older, have diagnoses of insomnia and report subjective memory complaints. Participants will be randomly assigned to treatment or control groups and groups will be matched by age, sex and education.

Exclusion criteria: Participants will be excluded if they have a history of neurological disease (e.g. stroke, seizure disorder, moderate to severe traumatic brain injury), major psychiatric illness (e.g. schizophrenia, bipolar disorder), current substance abuse or MRI contraindications. In addition, participants will be excluded if they are taking prescribed medication for sleep.

Month	Study Events
1	Research assistant training; MRI protocol set up; commence recruitment & pre-intervention visits
2-20	Complete recruitment & pre-intervention visits; initiate monitoring & follow-up visits
21-24	Complete data analysis; present results at conference; prepare NIH R01 for submission

Procedures

Participants will be screened for eligibility prior to their first visit. Virtual cognitive testing for all participants will take place via telehealth modalities prior to MRI scanning. MRI scanning will take place at the University of Miami. Intervention will involve a self-paced internet program. Baseline characteristics of participants in each group will be carefully examined and any differences will be included as covariates in all statistical analyses. The procedural timeline for the study is presented in table 1.

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 [70]. All questionnaires will be administered via REDCap a HIPAA compliant data repository that allows for secure sharing of survey forms [71].

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 [72]. 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 before each MRI study visit. On the day of each MRI visit, participants will also be asked to quantify their perceived sleepiness (on a scale of 0 to 10, with 10 being the highest possible sleepiness), the number of hours of sleep they had obtained on the previous night and the subjective quality of sleep they had obtained the previous night (on a scale of 0 to 10, with 10 being the worst possible sleep quality). These will be entered into subsequent analyses as covariates.

Neuropsychological Evaluation: Participants will undergo a comprehensive virtual neuropsychological evaluation pre and post intervention or after 8 weeks for controls with emphasis on measures of attention, executive function and processing speed. These domains were selected based on documented relationships with measures of sleep quality [4, 39]. Attention will be measured with the Test My Brain gradual onset continuous performance test, as well as select subtests from the Neuropsychological Assessment Battery Attention module (NAB digits forward & backwards). Executive function will be measured with select tasks from the Test My Brain digital Neuropsychology Toolkit (TMB Flanker Test, TMB Delayed Discounting,) 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 Test My Brain Digital Neuropsychology Toolkit (TMB simple reaction time, TMB choice reaction time, TMB symbol digit

matching). Memory will be assessed using the Hopkins Verbal Learning Test, Revised (HVLT-R). In addition to the above, participants will be screened for depression using the Beck Depression Inventory, 2nd edition (BDI-II). Of note, most selected measures have been validated for use with telehealth platforms [73].

Neuroimaging acquisition: MRI data will be acquired on a 3T Siemens Vida MRI scanner. Imaging will include anatomical scans of the entire brain in the sagittal plane using a high-resolution ultrafast Gradient Echo 3D (MPRAGE) sequence (256 × 256 matrix, flip angle=7°, field of view=16 × 16 cm^2, 1 mm slice thickness, 0 gap, 1mm x 1 mm x 1mm resolution) and one Magnetic Resonance Spectroscopy (^{1}H MRS) scan using stimulated echo sequence (TE/TR=30/3000 ms, 80 excitations, 2000 Hz spectral width, volume ~6 cm^3) from occipitoparietal grey matter [10, 74]. An example of this voxel placement is presented in Figures 1 and 2. To quantify hippocampal GABA, a separate ^{1}H MRS scan using a MEGA-PRESS sequence (TE/TR=68/2000 ms, 256 excitations, 2000 hz spectral width, volume ~16 cm^3) will be acquired. For resting state data, task-free T2 weighted echoplanar Blood Oxygen Level Dependent (BOLD) fMRI scans will be acquired, axial orientation with interleaved ordering, field of view=230 x 230 x 129mm, matrix size = 92 x 92, effective voxel resolution = 2 x 2 x 2 mm, TR=2000 ms, TE=27ms. Three runs, each 6.5 minutes long will be acquired. During the BOLD fMRI runs, participants will be asked to rest quietly with their eyes on a fixation cross. In order to confirm participants' compliance, we will record their eyes during scans, and may do follow up analyses using pupil size or other eye measures of attentiveness as covariates.

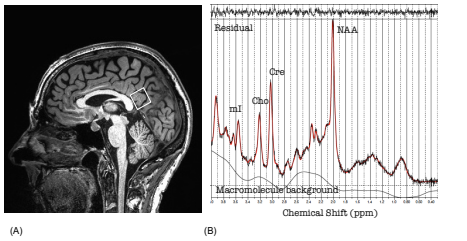

Fig. 1 & 2 Voxel placement (A) and example fitted spectrum (B)
NAA=N-acetyl-aspartate; Cr=Creatine and phosphocreatine; Cho=choline and phosphocholine; mI=*myo*-Inositol

^{1}H MRS processing: NAA and mI concentrations will be calculated using LCModel, a commercially available software with good reliability in quantifying NAA and mI concentrations [75]. GABA concentrations will be calculated using GANNET software available at: https://www.nitrc.org/projects/gannet due to superiority in quantifying GABA resonances [76].

fMRI processing: Network segregation will be calculated using previously published methods [18, 77] following strict pre-processing of fMRI data, correcting for motion and other potential confounds [78]. Dr. Visscher has previously completed similar analyses in a cohort of health older adults aged ≥ 85 years from the McKnight Brain Aging Registry [77]. Regions of interest from prior work in older adults [79] will be defined and classified based on prior work into networks including Default Mode Network, Dorsal Attention Network, Ventral Attention Network, etc. The segregation metric gives one number per participant per timepoint that is largest when there is strong within-network connectivity and weak between-network connectivity. Other metrics, for example, connectivity among default mode network may also be examined using these data. To assess the within-subject reliability of these data, these metrics will be calculated using a leave one (run) out cross validation procedure.

Intervention

Older adults who are eligible and consent to the study will complete the SHUTi program or act as matched controls. They will undergo health, neuropsychological and sleep quality assessments as well as MRI scanning pre and post intervention. Control participants will undergo the abovementioned assessments, complete sleep diary recording using the SHUTi and scanning at baseline and after 9 weeks. They will receive active treatment after the study is completed. All cognitive and health assessments will be carried out via telemedicine modalities, limiting the amount of time participants will be required to attend in person visits.

Data analysis

Data analysis will be carried out with the support of Dr. Chuanhui Dong, PhD (Statistician). In addition, Dr. Noam Alperin, PhD will provide support for MRI data acquisition at the University of Miami. Dr. Kristina Visscher, PhD will lead MRI data processing and analysis at the University of Alabama at Birmingham.

Hypothesis testing

Aim 1: To determine if SHUTi enhances cognition in middle aged to older adults with insomnia and subjective memory complaints.

Hypothesis 1: Older adults receiving SHUTi will have improvements in cognitive function relative to age matched controls. To test this hypothesis, an individual 2 x 2 repeated measures analysis of covariance will model the main effects of SHUTi (SHUTi or control), time (pre or post) and intervention x time interaction, controlling for sleepiness at the time of the evaluation and any baseline differences between groups. A false discovery rate (FDR) adjustment will be applied across all models to mitigate Type 1 error. *Prediction:* We predict that we will find an intervention x time interaction. Relative to their own baseline, participants in the SHUTi group will exhibit better cognitive scores post intervention. No change in cognitive function is expected among control participants.

Aim 2: To determine if SHUTi induces changes in markers of brain vulnerability in middle aged to older adults with subjective memory complaints.

Hypothesis 1.1, & 1.2: Participants receiving SHUTi will have improvements in markers of brain vulnerability (increased ratios of NAA, reduced ratios of mI, increase levels of GABA, improved segregation) relative to age matched controls. Hypothesis 1.1 (i.e. that participants receiving SHUTi will exhibit higher ratios of NAA, lower ratios of mI, higher ratios of GABA) will be tested using three separate 2x2 repeated measures ANCOVA procedure described above with NAA, mI and GABA as dependent variables. A false discovery rate (FDR) adjustment will be applied across all models to mitigate Type 1 error. Hypothesis 1.2 (i.e. that participants receiving SHUTi will exhibit improved segregation relative to age matched controls) will be tested by comparing network segregation measures across subjects in a 2x2 repeated measures ANCOVA [80-82], with participants' self-reported sleepiness, hours of sleep on the night prior to scanning and subjective sleep quality on the night prior to scanning as well as other baseline differences between the groups entered as covariates.

Exploratory Follow-up analyses: Effect sizes measuring our primary hypotheses will be calculated for a larger grant proposal [83]. Secondary analyses directly examining the default mode network will also be performed with the hypothesis that within-network connectivity will increase with individual differences of efficacy of SHUTi training. In addition, the contribution of 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 models specified above.

Experimental design considerations

General: Our goal is to examine the effects of SHUTi on brain function. Therefore, it will be necessary to control for other factors known to also affect brain function (e.g. age, medical conditions and treatments). We have taken three general approaches to account for these factors: 1) control through exclusion, 2) control by experimental design (e.g. within subject design, groups matching scheme) and 3) statistical control though assessment and co-variance (e.g. controlling for cardiovascular risk factors).

Interpretation of alternative findings: We have hypothesized that SHUTi enhances cognitive performance and improves brain vulnerability in older adults with insomnia and subjective memory complaints. 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 ratios of NAA and mI as well as sleep quality 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 SHUTi exerts its modulation of brain function.

MCKNIGHT CROSS-SITE COLLABORATION

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 (Visscher, Kaur), and sleep medicine (Taylor, Ramos). Dr. Taylor is an expert in CBT-I and has published extensively in the areas of insomnia and behavioral sleep medicine. In addition, our investigators have published multimodal neuroimaging data (Visscher, Alperin, Kaur). Dr. Visscher has extensive experience in modeling neural networks using fMRI. We will collect necessary preliminary data and determine effect sizes for uncovering the efficacy of SHUTi 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 [71]. Neuroimaging data will collected at the University of Miami Coral and transferred to the University of Alabama Birmingham for analysis, with all study investigators being provided with access.

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 SHUTi modulates cognitive function in older adults. In particular, we would like to conduct follow-up studies examining the effects of SHUTi on brain networks. Additional follow-up studies include the long term effects of SHUTi on amyloid and tau.

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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):

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 broad research interest in the area of cognitive aging. As an instructor at the University of Miami Miller School of Medicine, I am heavily involved with the McKnight Brain Research Institute, where I have participated in multi-site collaborations characterizing cognition in the oldest old, frailty and cognition in middle aged to older adults with subjective memory complaints. Prior to my appointment, I conducted multi-modal neuroimaging research examining the neural consequences of metabolic syndrome in middle aged adults who do not exhibit cognitive decline. My long term goal is to examine the efficacy of interventions aimed at maintaining brain health.

1. Banerjee N, Slugh M, Kaur S, Sun-Suslow N, McInerney KF, Sun X, Levin BE. Neuropsychological correlates of subjective fatigue in non-demented older adults and the moderating effect of physical activity. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2020 Mar;27(2):254-269. PubMed PMID: 31025596.
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. Oleson S, Eagan D, Kaur S, Hertzing WJ, Alkatan M, Davis JN, Tanaka H, Haley AP. Apolipoprotein E genotype moderates the association between dietary polyunsaturated fat and brain function: an exploration of cerebral glutamate and cognitive performance. Nutr Neurosci. 2018 Nov 22;PubMed PMID: 30465491; PubMed Central PMCID: PMC6531361.
4. 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.

B. Positions and Honors

Positions and Employment

2008 - 2009	Research Psychologist, National University Health System, Singapore
2010 - 2016	Teaching Assistant, University of Texas at Austin
2016 - 2017	Neuropsychology Intern, Henry Ford Health System
2017 - 2019	Post Doctoral Fellow, University of Miami Miller School of Medicine
2018 - 2019	Ad-hoc reviewer, Journal of the International Neuropsychological Society
2018 - 2019	Ad-hoc reviewer, Neurobiology of Aging
2019 -	Instructor, University of Miami

Other Experience and Professional Memberships

2010 -	Member, American Academy of Clinical Neuropsychology

2018 - Member, Sleep Research Society
2019 - Member, American Academy for Sleep Medicine

Honors

2010 Ira and Lousie Ischoe Fellowship, University of Texas at Austin
2016 Lee Willerman Award for Research Excellence, University of Texas at Austin
2016 Graduate student travel award, University of Texas at Austin
2019 Young Investigators Research Forum, American Academy of Sleep Medicine Foundation

C. Contribution to Science

1. Examining the association between cardio-metabolic risk and brain vulnerability and elucidating the mechanisms that drive these relationships has been an important focus of my research. In particular, I have demonstrated that obesity in midlife is strongly associated with multi-modal imaging markers of brain vulnerability even prior to onset of cognitive decline.

    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 PMID: 28390146; 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 PMID: 28144886; 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 PMID: 24418893; PubMed Central PMCID: PMC4097967.

2. Given my clinical background, I have pursued research with regards to 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 May 27;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 PMID: 25376331; PubMed Central PMCID: PMC4424190.

3. An important aspect of my research program has involved examining the mediating and moderating effects of lifestyle (i.e. poor sleep quality, dietary polyunsaturated fat, exercise) on cognitive and neuroimaging biomarkers. Given the fact that neurodegeneration is irreversible, it is crucial to examine potential markers that could prevent or delay disease onset.

    a. 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.
    b. Oleson S, Eagan D, Kaur S, Hertzing WJ, Alkatan M, Davis JN, Tanaka H, Haley AP. Apolipoprotein E genotype moderates the association between dietary polyunsaturated fat and brain function: an exploration of cerebral glutamate and cognitive performance. Nutr Neurosci. 2018 Nov 22;PubMed PMID: 30465491; PubMed Central PMCID: PMC6531361.

c. 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.

d. Gonzales MM, Tarumi T, Kaur S, Nualnim N, Fallow BA, Pyron M, Tanaka H, Haley AP. Aerobic fitness and the brain: increased N-acetyl-aspartate and choline concentrations in endurance-trained middle-aged adults. Brain Topogr. 2013 Jan;26(1):126-34. PubMed PMID: 22926147; PubMed Central PMCID: PMC3537918.

4. 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. Banerjee N, Slugh M, Kaur S, Sun-Suslow N, McInerney KF, Sun X, Levin BE. Neuropsychological correlates of subjective fatigue in non-demented older adults and the moderating effect of physical activity. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2020 Mar;27(2):254-269. PubMed PMID: 31025596.

b. 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 PMID: 25720950; PubMed Central PMCID: PMC4390456.

D. Additional Information: Research Support and/or Scholastic Performance

N/A

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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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 experiences of vision loss, 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 understanding how the brain changes following increased use of peripheral vision in patients who have had central vision loss due to Age-related Macular Degeneration. The current work in my lab sets the stage for the proposal. I have extensive experience using fMRI to examine ongoing neural activity, especially functional connectivity during tasks. I also have a background using psychophysics tools to examine behavior. My lab, which currently comprises 5 graduate students, 4 undergraduate students, and two postdoctoral scholars, integrates the psychophysics and neuroimaging components of my background, examining how experience, such as central vision loss, changes the function and structure of visual cortex, and provides a new perspective on the question of neural plasticity. I am excited to be able to use similar tools to understand how sleep and improving sleep quality influences these circuits

B. Positions 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

C. Contributions to Science

1) The brain flexibly shifts activity and connectivity depending on task state.

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. 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).

Most important for the current work, 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. This work sets the stage for understanding how this flexibility of functional connectivity is modified following experience with vision loss, which is a goal of the current project.

(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

2) Training influences efficiency of information processing

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. 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). 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 examining how experience with changing vision alters the visual and cognitive control systems.

(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) Bays, BB, **Visscher**, K.M., LeDantec, C, Seitz, A (2015) Alpha-Band EEG Activity in Perceptual Learning. Journal of Vision 15, 1–12. PMID: 26370167.
(d) 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

3) Cortical Representations of central and peripheral vision show distinct connectivity and activity
The current proposal will examine how neural activity in the cortical representations of peripheral vision are altered with experience. As an important prerequisite of this work, my lab has carefully described the activity, connectivity and structure of central vs. peripheral vision in healthy adults. As shown in item 1, above, different timecourses of neural activity reflects different functions of that activity, e.g. activity that is time-locked to a cue has a different function from activity time-locked to a stimulus, which has different function from activity that is sustained throughout performance of a task. My lab has shown that all three of these signals are present in early visual areas (1c, above). 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 (d). These patterns, while reliable, are altered by a participant's task. From the perspective of anatomy, we find that older adults show atrophy in many parts of cortex, including in representations for peripheral vision, but do not show signs of atrophy of central vision representations (c).

(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. C., Burge, W. K., & **Visscher**, K. (2016). Age-dependent cortical thinning of peripheral visual field representations in primary visual cortex. Frontiers in Aging Neuroscience, 8 (October), 1–7. PMID 27826238
(d) 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

3) Neural underpinnings of vision in older and vision impaired populations
As noted above, 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. We have shown that, in the younger adult brain, levels of occipital alpha power are modulated with attention, and higher alpha suppresses visual information processing (a). In the aging brain, we do not see this phenomenon, suggesting a relationship to age-related impairment. Also in older adults, we showed that two networks of brain regions associated with cognitive control show distinct relationships to different components of executive control (b). This work indicates that, in an older adult population, cortical thinning in specific brain regions can selectively predict task performance in executive function tasks. We also found (c) that age-related cortical thinning within early visual areas is specific to peripheral visual field representations, suggesting a relationship between early visual cortex and behavioral performance in those peripheral regions. 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 (d). Together, this work shows

that age and vision loss each manipulate the brain's visual and cognitive control systems. This lays the groundwork for new and exciting studies examining the specifics of how visual experience and aging influence the brain's attention and cognitive control systems.

(a) Vaden, RJ, Hutcheson, NL, McCollum, LA, Kentros, JG, **Visscher**, KM (2012). Older adults, unlike younger adults, do not modulate alpha power to suppress irrelevant information. Neuroimage. 63: 1127-1133. PMID: 22885248
(b) Schmidt EL, Burge WK, **Visscher** KM, Ross LA (2015) Cortical Thickness in Frontoparietal and Cinglo-opercular Networks Predicts Executive Function Performance in Older Adults. Neuropsychology Oct 12. PMID: 26460586
(c) Griffis, J. C., Burge, W. K., & **Visscher**, K. (2016). Age-dependent cortical thinning of peripheral visual field representations in primary visual cortex. Frontiers in Aging Neuroscience, 8(October), 1–7. PMID: 27826238
(d) 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

5) Representations of stimuli are influenced by the context of their presentation
My work has examined how current context and memory for previous information representation of stimulus information. 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). Another example of context are the ongoing brain oscillations present during stimulus presentation. Together this work characterizes how memory representations are modified by context, including other items in memory and task state.

(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

D. Additional Information: Research Support and/or Scholastic Performance

ACTIVE:

1 U01 EY025858-01A1 Visscher (PI) 05/01/2016-04/30/2020 6.0 Calendar
NIH/NEI $ 628,071 direct
Changes in Visual Cortical Connectivity Following Central Visual Field Loss
When people lose central vision, they must use peripheral vision to do daily tasks like reading and recognizing faces. This proposal will examine how changes in the connectivity and structure of early visual cortex relate to this huge shift in experience. This is relevant to public health because it develops fundamental knowledge about how the visual system adapts after vision loss and this knowledge may be used to advance future therapies.

Visscher (PI), with Wright, Alexander, Cohen, PIs at other sites 04/01/2015-3/31/2020
Evelyn F. McKnight Foundation Brain Aging Registry. $200,000 (total UAB)

This project examines and characterizes the successfully aging brain. Our goals are to (1) establish and

standardize a Brain Aging Registry across the four geographically distributed sites (Birmingham Alabama, Gainesville Florida, Tucson Arizona, Miami Florida); and (2) to develop and standardize new neurocognitive measures designed specifically for the assessment of cognitive functions in older adults. We will recruit 200 participants age 85+ who are cognitively healthy. Extensive neuropsychological testing, functional and structural neuroimaging data will be collected on these individuals. These data will be used to relate neuropsychological and brain measures in an older adult population, and will represent a 'baseline' for subsequent studies of older patients.

1R01HD089998-01 Stavrinos (PI) 08/04/2017-05/31/2022 0.6 calendar
NIH/NICHD
$471,698 (total)

Longitudinal Examination of Driving Attention Among Adolescents
Motor vehicle collisions (MVCs) are the leading cause of death among teenagers, with inattention as the primary contributor. This longitudinal study will test the influence of age and driving experience on driving attention development under various conditions, and will identify underlying cognitive mechanisms of attention development and ultimately the occurrences of MVCs. My role is to help assessment of attention using eye tracking measures, and contribute to data interpretation.

5U01AG062370 Ross (PI) 09/30/2018-05/31/2020 0.6 calendar
NIH/NICHD
$850,322 (total)

Elucidating the necessary components and mechanisms of cognitive training
Cognitive training can target maintained health, everyaday function and maintained independence in older adults. The proposed planning project will collect preliminary data exploring the moderators and mechanisms of cognitive training for a future research project. My role within the grant is to oversee and design the MRI measures being obtained to

PENDING

None.

OVERLAP
There is no scientific overlap.

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: Daniel Taylor, Ph.D.

eRA COMMONS USER NAME: djtaylor

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
Louisiana State University, *Baton Rouge, LA*	B.A.	06/1994	Psychology
University of Louisiana-Lafayette, *Lafayette, LA*	M.S.	12/1998	Experimental Psychology
University of Memphis, *Memphis, TN*	Ph.D.	8/2003	Clinical Psychology
Warren Alpert Medical School of Brown University, *Providence, RI*	Internship	08/2003	Clinical Psychology
University of Texas Southwestern Medical School, *Dallas, TX*	Fellowship	08/2004	Behavioral Sleep Medicine

A. Personal Statement

Dr. Taylor is a Full Professor of Psychology at University of Arizona, a licensed psychologist and board certified in both Sleep Medicine and Behavioral Sleep Medicine. Dr. Taylor has extensive expertise in the area of randomized clinical trials (RCTs), having been PI of two DoD/VA funded RCTs in active duty Military personnel (W81XWH-10-1-0828; W81XWH-13-2-0065 and 1I01CU000144-01) with PTSD, and a Co-I on six other DoD funded PTSD RCTs, and is one of the PIs of the STRONG STAR PTSD Consortium and the Consortium to Alleviate PTSD. Dr. Taylor also completed the NIH Summer Institute: Design and Conduct of Randomized Clinical Trials Involving Behavioral Interventions. Relevant to the current project, Dr. Taylor has extensive expertise in the area of PTSD participant recruitment in the University of North Texas, from his 15 years working at that institution before moving to Arizona. In addition, he has developed of structured diagnostic interviews, treatment manuals, treatment fidelity ratings (see www.insomnia.arizona.edu for pdf versions).

Dr. Taylor will serve as a consultant throughout the study, working closely with Dr. Ateka Contractor (via in-person, video, and telephone conferences scheduled on a weekly/monthly basis), consulting on grants management at UNT, participant recruitment, RCT methodology, statistics, and ultimately dissemination or results. Dr. Taylor will also provide expert input into the over-arching scientific goals of the current project.

B. Positions and Honors

Employment Positions

2019 – Present	Professor, University of Arizona, Tucson, AZ
2015 - 2019	Professor, University of North Texas, Denton, TX
2013 - 2019	Director of Clinical Training, University of North Texas Denton, TX
2010 - 2015	Associate Professor, University of North Texas, Denton, TX
2004 - 2010	Assistant Professor University of North Texas, Denton, TX

National Service Positions

2014 - 2015	President-Elect, American Board of Sleep Psychology
2013 - 2015	Program Chair, Society of Behavioral Sleep Medicine Annual Conference

2013 - 2015 Member, Society of Behavioral Sleep Medicine Actigraphy Technical and Scoring Manual Task Force
2013 Member, Society of Behavioral Sleep Medicine Presidential Task Force for "Sleep Psychology"
2013 Specialty Recognition by American Psychological Association Commission for the Recognition of Specialties and Proficiencies in Professional Psychology
2011 - 2013 Society of Behavioral Sleep Medicine Annual Conference Program Committee, Member
2011 – 2012 American Board of Sleep Medicine, Executive Committee
2009 - 2012 Society of Behavioral Sleep Medicine, Executive Committee, Secretary/Treasurer
2008 Behavioral Sleep Medicine Consensus Conference, Executive Committee
2008 - 2010 American Board of Sleep Medicine, Behavioral Sleep Medicine Examination Committee
2004 - 2010 American Academy of Sleep Medicine, Education Task Force
2007 - 2008 American Academy of Sleep Medicine, Behavioral Sleep Medicine Committee
2004 – 2008 Association of Behavioral and Cognitive Therapies, Program Committee
2005 - 2006 Sleep Research Society, Head of Sleep and Behavior Section
2003 - 2004 Sleep Research Society Board, Trainee Member-at-Large
2002 - 2003 Brown Medical School Psychology Internship, Training Committee

Certifications

2020 Diplomate, Board of Behavioral Sleep Medicine
2019 Licensed Clinical Psychologist, Arizona, #PSY-005137
2007 Certified Behavioral Sleep Medicine Specialist (CBSM)
2007 Licensed Clinical Psychologist, Texas, #33054
2007 Cognitive Therapy and Supervision, Beck Institute of Cognitive Therapy and Research
2006 Diplomate, American Board of Sleep Medicine (D,ABSM)
1998 Board Registered Polysomnographic Technologist (BRPT)

Honors

2014 Distinguished Visiting Professor, Air Force
2014 Research Merit Award, Society of Behavioral Sleep Medicine
2011 Competitive Funding Award (Faculty with most extramural funding in given year), UNT
2011 Distinguished Visiting Professor, Air Force
2008 Distinguished Visiting Professor, Air Force
2008 Keynote Speaker, University of North Texas
2008 Scholars Day
2007 Pittsburgh Mind-Body Center Summer Institute
2006 NIH Summer Institute: Design and Conduct of Randomized Clinical Trials
2005 Young Investigator Award, William C. Dement Research Apprenticeship
2003 Young Investigator Award, World Federation of Sleep Research Societies
1999 Research Merit Award, Associated Professional Sleep Societies

C. Contributions to Science

1. A major arm of my research program has been to test the efficacy and effectiveness of Cognitive Behavioral Therapy for Insomnia (CBTi) in the context of comorbid conditions or unique populatoins. For instance, my dissertation was the first clinical trial assessing the efficacy and effectiveness of Cognitive Behavioral Therapy for Insomnia (CBTi) in patients with comorbid insomnia and depression (Taylor et al., 2007), which showed that treating insomnia alone could result in subsequent improvements in depression, suggesting a potential causal relationship. I subsequently completed a randomized control trial (RCT; Taylor et al., 2010) showing similar effects of CBTi on both insomnia and hypnotic withdrawal in patients with hypnotic dependent insomnia. During this time, I was a Co-I on an RCT investigating sleep treatments in fibromyalgia patients (1R03AR053266-01A2), for which I developed a brief 2-session intervention for insomnia in fibromyalgia patients receiving active or sham CPAP for sleep disordered breathing. I also completed an RCT of CBTi, modified for a college population here in the UNT psychology department (Taylor et al., 2014). I also recently completed, with my students, an RCT comparing computer-guided problem-solving treatment for depression, PTSD, and insomnia symptoms in a group of college student veterans (Bedford, Dietch, Taylor, Boals, & Zayfert, 2018). Recently, I completed and published (Taylor et al., 2017; Taylor et al., 2018) a DoD funded RCT contrasting the efficacy of traditional in-person CBTi to an Internet version, which I developed in collaboration with the DoD (PI; W81XWH-10-1-0828).

Similarly, I have been working on several grant projects to investigate how treating sleep disorders my facilitate greater change in Prolonged Exposure Therapy of PTSD (Taylor et al., 2020). I am currently the PI of a DoD funded RCT examining a version of CBT modified to treat insomnia *and* nightmares compared to or combined with cognitive processing therapy (Co-PI: Resick) of PTSD (W81XWH-13-2-0065) in active duty military. I am also a Co-I, overseeing the CBT-I RCT portion, of two grants investigating the effectiveness of Tele-CBT-I on recently discharged hospital patients (169-SR-17) and another in independent living community older adults (2R44AG056250-03A1). Most relevant to the current study, I am also collaborating with the developer of SHUTi on a PCORI grant comparing SHUTi with and without Ambien in rural primary care patients (CER-2018C2-13262).

(a) **Taylor, D.J.**, Schmidt-Nowara, W., Jessop, C., & Ahearn, J.J. * (2010). Sleep restriction therapy and hypnotic withdrawal versus sleep hygiene education in hypnotic using patients with insomnia. *Journal of Clinical Sleep Medicine, 6,* 169-175.

(b) **Taylor, D.J.,** Peterson, A.L., Pruiksma, K.E., Young-McCaughan, S., Nicholson, K., Mintz, J., & the STRONG STAR Consortium (2017). Internet and in-person cognitive behavioral therapy for insomnia in military personnel: A randomized clinical trial. *Sleep, 40(6),* 1-12. https://doi.org/10.1093/sleep/zsx075

(c) **Taylor, D. J.**, Peterson, A. L., Pruiksma, K. E., Hale, W. J., Young-McCaughan, S., Wilkerson, A., Nicholson, K., Litz, B. T., Dondanville, K. A., Roache, J. D., Borah, E. V., Brundige, A., & Mintz, J.; on behalf of the STRONG STAR Consortium. (2018). Impact of cognitive behavioral therapy for insomnia disorder on sleep and comorbid symptoms in military personnel: A randomized clinical trial. Sleep, 41(6), 1-12. https://doi.org/10.1093/sleep/zsy069

(d) **Taylor, D. J.**, Peterson, A. L., Pruiksma, K. E., Hale, W. J., Young-McCaughan, S., Wilkerson, A., Nicholson, K., Litz, B. T., Dondanville, K. A., Roache, J. D., Borah, E. V., Brundige, A., & Mintz, J.; on behalf of the STRONG STAR Consortium. (2018). Impact of cognitive behavioral therapy for insomnia disorder on sleep and comorbid symptoms in military personnel: A randomized clinical trial. *Sleep, 41(6),* 1-12. https://doi.org/10.1093/sleep/zsy069

2. A second major arm of my research has been to highlight the substantial relationship between insomnia and other mental (e.g., anxiety, depression, PTSD) health problems. For example, in an early review of the literature I found that insomnia was consistently predictive of depression, anxiety, alcohol abuse, and other drug disorders (Taylor, Lichstein, Durrence, 2003). At the time there was little research on insomnia as a risk factor for PTSD. Later, I published one of the preeminent examinations of the comorbidity of insomnia, anxiety and depression, controlling for other possible confounds (Taylor, Lichstein, Durrence, Bush, Riedel, 2005), and recently replicated and extended this work within an active duty military cohort (Taylor, Pruiksma, Hale, Kelly, Maurer, Peterson, et al., 2016). My recent R15 (Taylor, Kelly, Kohut, & Song, 2016) found that insomnia was a significant risk factor for reduced antibody response to the influenza vaccine after controlling for other confounds (R15 AI085558). Finally, my expertise in the assessment of sleep disorders have led to my involvement in a recent publication of the Common Data Elements being used in the Consortium to Alleviate PTSD. Relevant to the current proposal, this work examined sleep disturbance as a potential risk factor for other physical and mental health problems.

(a) **Taylor, D.J.**, Lichstein, K.L., & Durrence, H.H. (2003). Insomnia as a health risk. *Behavioral Sleep Medicine, 1,* 227-247.

(b) **Taylor, D.J.**, Mallory, L., Lichstein, K.L., Durrence, H.H., Bush, A.J., & Riedel, B.W. (2007). Comorbidity of insomnia with medical disorders. *Sleep, 30,* 213-218.

(c) **Taylor, D.J.,** Kelly, K.M., Kohut, M.L., & Song, K. (2016). Is Insomnia as a risk factor for decreased Influenza vaccine response? *Behavioral Sleep Medicine, 15, 270-287.*

(d) **Taylor, D.J.**, Pruiksma, K.E.,* Hale, W.J., Kelly, K, Maurer, D., Peterson, A.L., Mintz, J., Litz, B.L., Williamson, D.E., & the STRONG STAR Consortium (2016). Prevalence, correlates, and predictors of insomnia in the U.S. Army prior to deployment. *Sleep, 39*(10), 1795-1806.

3. A final major arm of my research program is to use advanced, validated subjective and objective methodologies to understand sleep activity in different populations. For the past years, I have been using actigraphy, an objective assessment tool of sleep activity, in research to obtain objective data on an individual's sleep-wake patterns. With actigraphy, I was able to capture individuals' sleep onset time, sleep offset time, and sleep duration throughout 24 hours or even longer. I recently published the clinical and research applications of actigraphy (Ancoli-Israel et al., 2015). I also have expertise in investigating and establishing the validity and

reliability of subjective sleep assessment tools, recently publishing a psychometric evaluation of a well-known measure of sleep quality (Dietch, Taylor et al., 2016), a Structured Clinical Interview for DSM-5 Sleep Disorders (Taylor et al., 2018), and a retrospective self-report of sleep validated against diaries (Dietch…, Taylor et al., 2019).

(a) Ancoli-Israel, S., Martin, J.L., Blackwell, T., Buenaver, L., Liu, L., Meltzer, L.J., ... & **Taylor, D.J.** (2015). The SBSM guide to actigraphy monitoring: Clinical and research applications. *Behavioral Sleep Medicine*, *13*(sup1), S4-S38.
(b) Dietch, J.R.,* **Taylor, D.J.**, Sethi, K.S., Bramoweth, A.D., & Roane, B.M. (2016). Psychometric evaluation of the PSQI in US college students. *Journal of Clinical Sleep Medicine, 12*(8), 1121-9.
(c) **Taylor, D.J.,** Wilkerson, A.K.,* Pruiksma, K.E., Williams, J.M., Ruggero, C.J., Hale, W., Mintz, J., Organeck, K.,* Nicholson, K.L., Litz, B.T., Young-McCaughan, S., Dondanville, K.A., Borah, E.V., Brundige, A., & Peterson, A.L.; on behalf of the STRONG STAR Consortium (2018). Reliability of the Structured Clinical Interview for DSM-5 Sleep Disorders Module. *Journal of Clinical Sleep Medicine, 14,* 459-464.
(d) Dietch, J.R., Sethi, K., Slavish, D.C., & Taylor, D.J. (2019). Validity of two retrospective questionnaire versions of the Consensus Sleep Diary: the whole week and split week Self-Assessment of Sleep Surveys. Sleep Medicine, 63, 127-136. https://doi.org/10.1016/j.sleep.2019.05.015

D. Additional Information: Research Support

Ongoing Research Support

Taylor (PI) 6/1/20-5/31/23
Pacific Athletic Conference – 12 (PAC-12)
The PAC-12 Student-Athlete Health and Well-Being Mental Health Coordinating Unit (MHCU)
Develop a scalable set of mental health screens, consistent with NCAA best practice recommendations, to be implemented at each PAC-12 school, facilitating policies and procedures to address positive mental health screens, and reporting on epidemiologic outcomes at the end of the study period.
Role: Primary Investigator (PI)

W81XWH-16-PRMRP-TTDA Taylor (PI) 7/17-7/20
DoD-PRMRP
Web-based provider training for cognitive behavioral therapy of insomnia (CBTi)
The overarching goal of this study is to develop a sophisticated, user-friendly Web-based provider training course for CBTi (CBTi*Web*) which is fully sustainable, accessible with minimal cost (financial and time) to the clinician, and results in knowledge gains similar to those of an in-person training.
Role: PI

R01AI128359-01 Taylor (PI) 12/16-11/20
NIH/NIAID
Sleep and Vaccine Response in Nurses (SAV-RN)
The overarching goal of the current study is to develop a comprehensive model detailing the effects of sleep and its specific facets, as well as other risk factors, on the short-term (1-month) influenza antibody response, as well as its long-term (12-month) degradation.
Role: PI

CER-2018C2-13262 Stone & Buysse (PIs) 5/1/19-4/30/23
Patient-Centered Outcomes Research Institute (PCORI)
Cognitive Behavioral Therapy and Zolpidem for Insomnia (COZI)
Compare the effectiveness of zolpidem, CBT-I, and combination treatment for insomnia symptoms over 12 months on insomnia symptoms, side effects, and other symptoms and problems, including health-related quality of life, mood, and health outcomes.
Roles: Site Co-PI; Patient Engagement Committee Member

Brown (PI) 1/19-12/21
Military Suicide Research Consortium
Suicide Risk and Sleep in Treatment: An Intensive Daily Sampling Study
he primary research goal of this study is to examine whether key sleep variables are significant near-term predictors of increased suicidal ideation and the critical periods of heightened suicidal ideation. The secondary

aim is to examine mediators and moderators of the associations among sleep disturbances and suicidal ideation. A final aim is to determine optimal strategies for assessing sleep and suicide risk in military personnel in treatment.
Role: Co-Investigatory (Co-I)

R15AA026079 Blumenthal (PI) 12/17-7/21
NIH/NIAAA
A Controlled Test of Interpersonal Rejection, Social Anxiety, and Alcohol Use among Female Adolescents
The primary research goal is to test whether acute social stress (i.e. rejection), as compared to non-social stress, elicits greater alcohol-relevant cognitions among socially anxious girls. A secondary goal is to evaluate the indirect effects of key cognitive (i.e. disengagement coping) and psychobiological (i.e. salivary alpha amylase/cortisol ratio) variables in this relation.
Role: Co-Investigator

2R44AG056250-03A1 Gartenberg (PI) 06/01/20 - 05/31/22
NIH/NIA SBIR
A non-pharmacological multi-modal therapy to improve sleep and cognition and reduce mild cognitive impairment risk
The overall objective of this research is to develop a non-pharmacological means to address sleep deficiencies and wellbeing in older adults.
Role: Co-I

169-SR-17 Parthasarathy (PI) 5/1/19-10/14/20
American Sleep Medicine Foundation
Non-inferiority study of telemedicine versus conventional CBT-I in recently Hospitalized Patients with Insomnia
To perform comparative effectiveness research of CBT-I administered by telemedicine versus conventional office-based CBT-I on insomnia severity in recently hospitalized patients.
Role: Co-I

1C06OD028307-01 Dake (PI) 9/20/19-5/31/24
NIH/OD
University of Arizona Health Sciences (UAHS) Sleep Research Center Construction Grant
Build a world class, state-of-the-art 8-bed sleep and circadian research center in close proximity to imaging facilities, clinical research areas, and other research laboratories within UA campus. The center will also allow manipulation of the respired gases and administration of intravenous medications and blood sampling from an adjacent anteroom.
Role: Co-I; Executive Committee Member

Relevant Completed Research Support (Past 3 years)

1I01CU000144-01 Taylor (PI) 10/15-9/19
DoD-VA
CAP-Treatment of Comorbid Sleep Disorders and PTSD
The primary aim of the proposed study is to determine if providing cognitive-behavioral therapy of insomnia and nightmares (CBTin) and Cognitive Processing Therapy of PTSD-Cognitive only version (CPT) results in greater PTSD and sleep symptom reduction than CPT only. The secondary aim is to determine if sequencing CBTin before or after CPT results in differential effects on PTSD and sleep symptom reduction.
Role: Primary Investigator

Pruiksma (PI) 9/15-8/16
American Sleep Medicine Foundation
A Pilot Randomized Controlled Trial for Treatment of Trauma-Related Nightmares in Active Duty Military Personnel
Role: Co-I/Mentor

School of Medicine

Department of Neurology

July 31, 2020

The MBRF Cognitive Aging and Memory Intervention Core
Inter-Institutional Pilot 2020-2022 Program

Dear Committee Members:

Please find attached our Inter-Institutional Pilot proposal, entitled, “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.” The collaborating MBI institutions are the University of Alabama at Birmingham and the University of Miami. Our application is targeted toward gaining a greater understanding of the underlying mechanisms that may contribute to the cognitive benefit of exercise as we age.

Potential reviewers from within the EMBI community who are not from the two collaborating institutions:

1. Jennifer Bizon, PhD, Univ of FL
2. Dawn Bowers, PhD, Univ of FL
3. Lee Ryan, PhD, Univ of AZ

Thank you for your consideration of our proposal.

Sincerely,

Ronald M. Lazar, PhD, FAHA, FAAN
Evelyn F. McKnight Endowed Chair in Learning and Memory in Aging
Professor of Neurology and Neurobiology
Director, UAB Evelyn F. McKnight Brain Institute
Director, Neuropsychology Division (Neurology)

Ronald M. Lazar, PhD, FAHA, FAAN
Evelyn F. McKnight Endowed Chair
Director, McKnight Brain Institute
Director, Neuropsychology Division
650 Sparks Center
1720 7th Avenue South
tel: 205.943.2334
fax: 205.975.3094
rlazar@uabmc.edu

The University of
Alabama at Birmingham (UAB)
Mailing Address:
SC 650 – Department of Neurology
1720 2nd AVE S
Birmingham, AL 35294-0017

The MBRF Cognitive Aging and Memory Intervention Core
Inter-Institutional Pilot Program Proposal
August 1, 2020

Proposal Title: 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

Senior/Key Personnel: Ronald M. Lazar, PhD (UAB)
Christopher Girkin, MD, MSPH (UAB)
Marcas Bamman, PhD (UAB)
Tatjana Rundek, MD, PhD (UM)
Jianhua Wang, MD, PhD (UM)

Performance Sites: University of Alabama at Birmingham (Prime Site), University of Miami

Contact PI: Ronald M. Lazar, PhD
UAB Department of Neurology
1720 7th Ave S – SC650K
Birmingham, AL. 35213
Phone: 205-934-2334
Email: rlazar@uabmc.edu

RESEARCH PLAN

A. SUMMARY

Longitudinal and cross-sectional studies confirm an association between increasing age and cognitive decline. Several common health-related factors such as cardiovascular diseases and hypertension (HTN) contribute to age-related changes in cognition. Elevations in blood pressure are highly correlated with increased risk of heart disease, ischemic and hemorrhagic strokes, vascular dementia, Alzheimer's disease and age-related cognitive decline, with studies showing an association between chronicity of HTN and late-life cognitive deficits. The late-life decrease in cognitive performance is more pronounced when blood pressure is left untreated in middle-age. White-matter hyperintensities (WMH), a known outcome of chronic HTN, has been found to affect cognitive function, but to date there are no therapeutic options to mitigate these lesions. But, there is growing evidence that other mechanisms independently or in concert with WMH affect cognition, and, importantly, may be treatable. Findings from different lines of inquiry suggest that vascular changes such as loss of microvascular density, or microvascular rarefaction (MVR), may be precursors to hypertension, and others have linked MVR with insulin-like growth factor-1 (IGF-1) deficiencies. Based on both experimental and clinical studies, we propose that among hypertensives these lines of evidence intersect and suggest that age-related decline in IGF-1 concentrations are related to greater microvascular rarefaction and vascular resistance, and therefore late-life cognitive decline. Exercise studies provide an opportunity to begin exploring this premise given the previously demonstrated effects of exercise in attenuating vascular dysfunction, HTN, IGF-1 deficiency, and age-related cognitive decline. **To test our hypothesis,** we propose baseline measurements of the retinal microcirculation using optical coherence tomographic angiography (OCT-A), serum growth factors, cardiovascular fitness, and cognition with a test battery assessing memory, attention, language, processing speed, executive function and fine-motor skills. If our hypothesis is confirmed, the potential for exercise to prevent or reverse MVR and hypertension via activation of the endocrine and paracrine growth factor (GF) pathways would have implications in our understanding and in mitigation of age-related cognitive decline. Given that untreated hypertension in middle age is associated with late-life cognitive decline, prevention of hypertensive states would have wide-reaching impact that may not only reveal the underlying mechanisms of age-related cognitive decline but may also provide an effective intervention to maintain cognitive function into old age. In the conduct of this study, our project will foster collaboration across two Evelyn F. McKnight Brain Institutes: University of Alabama at Birmingham and University of Miami.

B. SPECIFIC AIMS

Longitudinal and cross-sectional studies have consistently revealed correlations between increasing age and cognitive decline [1-3], which may be attributable to cardiovascular conditions such as HTN [4-7]. The harmful impact of HTN on cognition is especially meaningful when considering the high prevalence of HTN in the US. [8] Blood pressure elevations are highly correlated with increased risk of heart disease, ischemic and hemorrhagic strokes [9], vascular dementia [10], Alzheimer's disease, [11] WMH [12 13] and vascular cognitive impairment [14], with more pronounced cognitive effects seen in individuals with uncontrolled HTN. [15] Prospective studies have shown an association between chronicity of HTN and cognitive deficits in later life. [7 16 17] The observed late-life decrease in cognitive performance is more evident when blood pressure is left untreated in middle-age. [14 17 18] Given the high prevalence of HTN and its deleterious effects on the brain [14 19], identifying underlying causal mechanisms and targeted interventions to attenuate HTN-induced pathology and its negative impact on cognition is of critical importance. MVR has been reported in patients with established HTN [20 21], and in those with borderline or early essential HTN. [20 22] In addition, untreated HTN in middle age has resulted in reduced retinal microvascular density (MVD). [23] Decreased availability of growth hormone (GH), and insulin-like growth factor-1 (IGF-1) can lead to MVR. [24] Findings from animal [25 26] and human [24 27-29] studies show a significant age-related decrease in the GH/IGF-1 cascade. The temporal course of this decrease suggests that age-related reductions in IGF-1 may be linked to vascular pathologies in aging[30], and a reduction in these growth factors in humans is accompanied by an increased risk for HTN [31 32], loss of microvascular density [33 34], and cognitive impairment.[35-38]

Studies show an inverse relationship between blood pressure and exercise. [39 40 41 42 40 43] In addition, exercise enhances CBF [44-46] and a 40% increase in IGF-1 leading to an increase in cerebral microvascular density [47], and cerebral perfusion changes. [48-50] In addition, studies have elucidated the role of exercise-induced GF release and their role in enhanced cognition in animals [51-54], and humans. [49 55 56 57] Although low IGF-1 concentrations and onset of MVR are correlated with HTN, little is known about the mechanisms of exercise-induced reductions in blood pressure. To address this gap, the proposed project will be focused on identifying the role of GF deficiencies in MVR, HTN, and cognitive function. **We propose here to obtain pilot data showing how exercise may serve a crucial role in attenuating age-related cognitive decline via its impact on growth factor release, improving angiogenesis, vascular resistance and blood pressure.** To address our questions, we will recruit 30 older hypertensive adults who will undergo OCT-A retinal density scans, blood draws to

measure GF, and cognitive assessments at baseline, after a washout period, and again after a 10-week period of high intensity interval training (HIIT).

Specific Aim 1: To examine the relationship of retinal microvascular density, IGF-1 and cognitive function in older individuals with essential hypertension.

- **Hypothesis 1.1:** At baseline, hypertensive individuals will demonstrate an association between lower composite cognitive Z-scores and lower microvascular density on optical coherence tomography angiography.
- **Hypothesis 1.2:** At baseline, hypertensive individuals will demonstrate an association between lower composite cognitive Z-scores and lower levels of systemic serum IGF-1.

Specific Aim 2: To determine whether an exercise intervention will improve age-related growth factor deficiencies and retinal microvascular density, and, in turn, be associated with an improvement in cognition.

- **Hypothesis 2.1:** Following 10 weeks of intensive exercise training, improvements in cardiorespiratory fitness (VO_2max) will be positively correlated with increased serum IGF-1 levels and retinal microvascular density, lower mean arterial pressure, and higher composite cognitive Z-scores.

C. RESEARCH STRATEGY

C.1. SIGNIFICANCE

Chronic HTN increases the risk of vascular dementia [10], Alzheimer's disease [11] and vascular cognitive impairment [14], with more cognitive deficits seen in individuals with uncontrolled HTN. [15] Prospective studies have shown an association between chronicity of HTN and cognitive deficits in later life, [7 16 17] which appears more pronounced when blood pressure remains untreated in middle-age. [14 17 18] Additionally, HTN alters the permeability of the BBB [58], and is associated with WMH, which are known causes of cognitive dysfunction.[13] Current research, however, has not yielded therapeutic options to reduce WMH. Thus, given the high prevalence of HTN and its deleterious effects on the brain [14 19], identifying underlying mechanisms and targeted interventions to attenuate HTN-induced pathology and cognitive decline is vital. Studies show that endothelial dysfunction and MVR may predate clinical manifestations of essential HTN. [34] MVR has also been reported in patients with established HTN [20 21], and in those with borderline or early essential HTN[20 22], and middle-aged patients with untreated mild-moderate HTN have reduced retinal microvascular density. [23] MVR can result from decreased availability of growth hormone (GH), including IGF-1. [24] Evidence from animal [25 26] and human [24 27-29] studies show age-related decreases in the GH/IGF-1 cascade, and the temporal pattern of this decrease suggests that age-related reductions in IGF-1 may be causally linked to vascular pathologies in aging. [30] A decline in IGF-1 in humans is accompanied by an increased risk for HTN [31 32], loss of microvascular density [33 34], and cognitive impairment [35-38], and dementia. [59 60] It is generally acknowledged that exercise reduces the risk for cardiovascular disease and dementia [61 61-64], with evidence confirming an inverse relationship between exercise and blood pressure. [39 40 41 42 40 43] Exercise is known to enhance CBF [44-46] in older individuals, and to elicit a 40% increase in IGF-1 leading to an increase in cerebral MVD[47], and cerebral perfusion changes. [48-50] In addition, studies have elucidated the role of exercise-induced growth factor release and their role in enhanced cognition in animals [51-54], and humans. [49 55 56 57] Although low IGF-1 concentrations and onset of MVR correlate with HTN, little is known about the associated mechanisms underlying exercise-induced reductions in HTN. Therefore, the proposed pilot project aims to begin identifying the role of GF deficiencies in MVR and HTN, and the relation to cognition. In addition, while several professional groups [65] recommend exercise as a non-pharmacological modality for the treatment of hypertension, questions regarding specific exercise recommendations for improving cognitive functions in hypertensive individuals remain unanswered.

Our **Scientific Premise** is that essential HTN is partly mediated by IGF-1 deficiencies resulting in MVR and increased vascular resistance, resulting in HTN and cognitive impairment, and that exercise will increase IGF-1 and microvascular density, resulting in improved cognition function.[66] Our review of exercise studies supports this notion by demonstrating an increase in endocrine and paracrine release of IGF-1, thereby stimulating systemic and central angiogenesis, reversing vascular resistance, and improving CBF and cognitive dysfunction [66]. Our approach will allow us to test the notion that GF and MVD are lower in hypertensives and how exercise might mediate this relationship, and improve cognition.

C.2. INNOVATION

1) Retinal Scans: To test our hypothesis that increased cardiovascular fitness will correlate with improved microvascular density, we propose the innovative use of retinal density via OCT-A, a non-invasive imaging modality for visualizing retinal and choroidal capillary microcirculation. [67] OCT-A produces ultra-high resolution 3-D images displayed as individual layers of retinal vasculature, allowing visualization of the microvasculature. Using an established scan protocol[68], OCT-A

measures retinal blood flow, retinal tissue perfusion and volumetric vessel density, [68] which is our variable of interest (Figure 1). Moreover, the retina consists of the retinal ganglion cells and their axons, converging to form the optic nerve, so that the

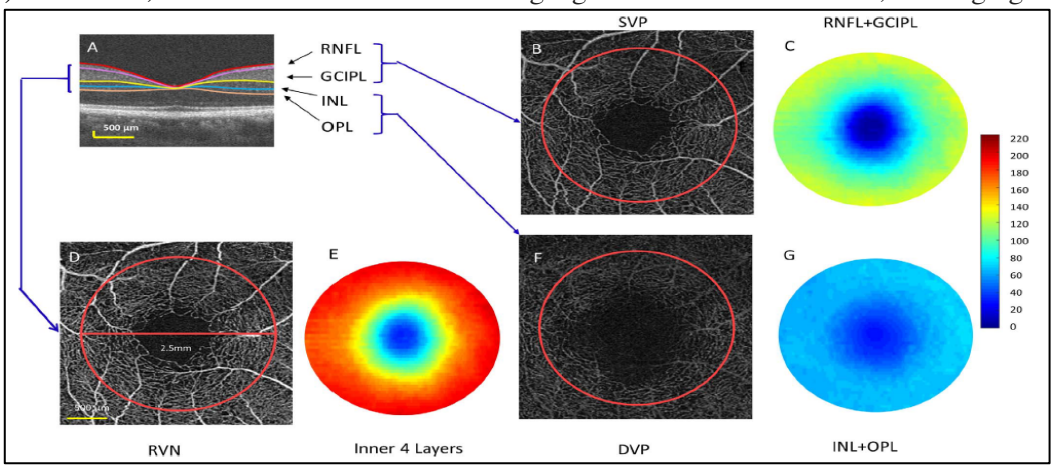


Figure 1. Tissue volumes and vessel densities. **(A)** Intraretinal layers.**(B)** Superficial Vascular plexus. **(C)** Thickness of inner retina including retinal nerve fiber layer (RNFL), ganglion cell inner plexiform layer (GCIPL). **(D)** Retinal vascular network (RVN) . **(E)** Thickness map of inner retina including RNFL, GCIPL, inner nuclear layer (INL), and outer plexiform layer (OPL). **(F)** Deep vascular plexus (DVP). **(G)** Thickness map of INL, and OPL.

retina serves is an extension of the CNS.[69] Using OCT-A, we have already demonstrated already age-related alterations in vessel density[70], and retinal tissue hypoperfusion in patients with severe cognitive decline[71]. In addition, we have also shown that diabetic retinopathy is associated with lower gray matter volume among Type II diabetics.[72]

2) Hypertension/Growth Factor/Cognition Associations: Research has focused on the etiology of HTN and the role of cardiovascular fitness on blood pressure and cognitive function, yet mechanisms that underlie the observed exercise-induced structural and physiological improvements are not well understood. We propose to address this gap with respect to GF concentrations, MVR and HTN, and then to explore exercise as an interventional method to attenuate the effects of HTN on age-related cognitive decline. To that end, we aim to assess experimentally the extent to which a brief (10 weeks) high intensity interval training (HIIT) exercise intervention improves GF concentrations, reduces MVR and HTN, and by extension, improves neurocognition**.**

C.3. APPROACH

C.3.1. Participants. Thirty (30) hypertensive participants will be recruited from the UAB cardiovascular clinics.

Inclusion Criteria: 1) Adults between 60-75 years of age; 2) essential hypertension; 3) physically able to exercise; 4) access to an upright cycle ergometer at home or via gym access; 5) access to smart device (iOS or Android phone or tablet with ability to install and use Polar Beat™ application).

Exclusion Criteria: 1) diagnosis of dementia; 2) resting systolic blood pressure <130, or >180 mm Hg; 3) disease or condition that would preclude exercise; 4) untreated depression or anxiety disorders; 5) severe respiratory disease; 6) disease of the eye; 7) refractive error > 6 diopters or +6 diopters.

C.3.2. Study Design. Participants will undergo testing at; Baseline, after 4-week washout period, and after 10 weeks of exercise intervention (Table 1). The washout period will serve to minimize non-specific effects prior to baseline measurements.

Table 1. Study Design

	Baseline	**End of 4-week Washout**	**Post 10 week-exercise Intervention**
ECG & VO_2 max	X		X
Blood draw	X	X	X
Cognitive battery	X	X	X
OCT-A	X	X	X

C.3.2.1 Pre-Intervention Assessments. (Data collected across 2 visits within 7 days before the start of intervention). All participants must pass an exercise fitness test (VO_2 max) with 12 lead ECG and blood draw conducted under the supervision of an exercise physiologist and nurse practitioner. Well-established neurocognitive tests with published age-adjusted norms, will also be administered. Retinal scans OCT-A will be conducted at the Callahan Eye Hospital at UAB.

- **VO_2max:** Maximum oxygen consumption: Potential participants must pass a graded exercise stress test on a stationary cycle with 12-lead ECG conducted at the UAB Center for Exercise Medicine's Clinical Exercise Facility (UCEM) at UAB. The exercise test will continue to maximum, and expired gases will be collected throughout the test to monitor O_2 consumption and CO_2 expiration. We define maximum or test termination as either voluntary exhaustion, or the achievement of 2/3 physiologic criteria: 1) heart rate = 220 - age; 2) respiratory exchange ratio >1.15; 3) leveling off of oxygen consumption with increasing workload. The participant's perceived effort is monitored at each test stage via the

standard 6-20 rating of perceived exertion (RPE) scale. During the test, the 12-lead ECG and blood pressure (BP) will be monitored by a UCEM nurse practitioner. The graded test may be terminated prior to achieving maximum effort if: abnormal BP, such as an increasing diastolic pressure; ECG abnormality; or participant voluntarily stops the test.

- **Blood Collection.** Serum growth factors will be collected by a UCEM nurse practitioner. The samples for growth factors will be held for 30 minutes at room temperature before being placed on ice for 30 minutes. Then, samples will be spun at 3000 RPM for 10 minutes and then aliquoted (0.5 cc) and labeled with study name, participant ID, Date, and time of collection, and stored at -85 C at UCEM. Blood samples will be delivered to Dr. Barbara Gower's lab at UAB for analyses at the end of the study. The following growth factors will be analyzed (Table 2). This pilot study presents an opportunity to explore the role of the eye as a surrogate marker for changes in the brain. To that end, serum levels of BDNF and VEGF, which are highly linked to neurogenic and cognitive changes, [52 53 73] will be also measured for exploratory purposes.

Table 2. List of growth factors.	
Growth Factor	**NAME**
VEGF	Vascular Endothelial Growth Factor
IGF-1	Insulin-like Growth Factor 1
BDNF	Brain Derived Neurotrophic Factor

- **Standardized neuropsychological tests** have been selected to assess processing speed, memory, attention, and executive function, all of which have been shown sensitive to diffuse effects of cardiogenic, cerebral hypoperfusion. All tests have published aged-adjusted norms. The battery takes approximately 50 minutes. Specific tests include: Trail Making A & B, Digit Span; Rey Complex Figure; Digit Symbol; Controlled Oral Word Association (verbal fluency); Hopkins Verbal Learning Test; Boston Naming Test; Center for Epidemiologic Studies-Depression Scale, and the Brief Visual Memory Test, and will be administered by a psychology assistant blinded to all other study data.
- **OCT-A** Standardized OCT-A scan protocols [68] at Callahan Eye Hospital at UAB will be used to obtain our microvascular density outcome measures. Each participant will undergo 3 OCT-A scans on the Optovue Avanti system (AngioVue, Optovue, Inc., Fremont, CA, USA), which is a time efficient modality that does not require eye dilation.[74-76] OCT-A imaging of the posterior pole of the retina will comprise two sequential high-density scans, the first will be a 6mm-wide raster scan centered in the fovea; the second, a 6mm-wide raster scan centered in the optic nerve head. Centering of the scan is performed manually at baseline-visit and automatically at follow-up thanks to the retina eye-tracking system. Automatic repositioning allows for precise longitudinal monitoring of the functional and morphological retina parameters. The two scans are then automatically merged to compose a wide-field scan of the posterior pole of the eye (Angio Montage), yielding images that will be electronically transported to the Dr. Wang's imaging laboratory at the University of Miami for the calculation of retinal artery density. On an exploratory basis, we will simultaneously collect intraocular pressure, central corneal thickness, axial length, ocular pulse amplitude and systemic blood pressure which correlate with retinal vascular perfusion. All imaging at UAB will be performed by an ophthalmic photographer with over 20 years of experience in ocular imaging.

C.3.2.2. Exercise Intervention. In response to the COVID-19 research environment, participants will be asked to exercise independently 4 days/week for 10 weeks using an outlined HIIT protocol (Table 3). Sessions can be conducted at home or at a gym facility with access to a cycle ergometer. Each participant will undergo 2 supervised training sessions at UCEM to learn the HIIT protocol (exercise sessions 1 and 17). These sessions will allow researchers to supervise sessions directly and modify the protocol as needed to allow for maximal adherence to prescribed intensities. To record heart rate, session duration, and time at each exercise intensity, participants will be provided with an H10 Polar ™ heart rate chest strap monitor, and a Polar Beat™ account will be established for each individual. Participants will be asked to download the Polar Beat ™ smart phone application (available for iOS and Android devices), which will record each exercise session. Data from Polar Beat™ will allow the researcher to conduct remote monitoring of the intensity, duration, and frequency of exercise sessions, which will be used to provide participants with feedback to enhance adherence and participation. [77-79] Exercise sessions will entail 1 minute of high intensity exercise, followed by a short rest period (1 or 2 minutes) of lower intensity exercise. This cycle will be repeated for a total of 10 intervals per session. Intensity will be determined using heart rate max (HR_{max}= 220–age). Preliminary data from our lab confirms the feasibility and efficacy of an 8-week HIIT protocol in improving cardiorespiratory fitness in individuals 60-75 years of age (unpublished data). An increase in relative VO_2max has generalized clinical significance because studies show that each 3.5 mL/kg/min improvement in VO_2 max is associated with a 19% reduction in risk of cardiovascular disease mortality. [80] Finally, the research staff will log into the Polar Beat account associated with each participant and download the data for each session. Research staff will contact participants twice per week to provide feedback and guidance, as needed.

Table 3				
Exercise Protocol	**Study Week**			
Intervention Week	**1-3**	**4-5**	**6-8**	**9-10**
Work/Rest Ratio	1:2	1:1	1:2	1:1
Intensity (%HR_{max})	70-80	70-80	80-90	80-90

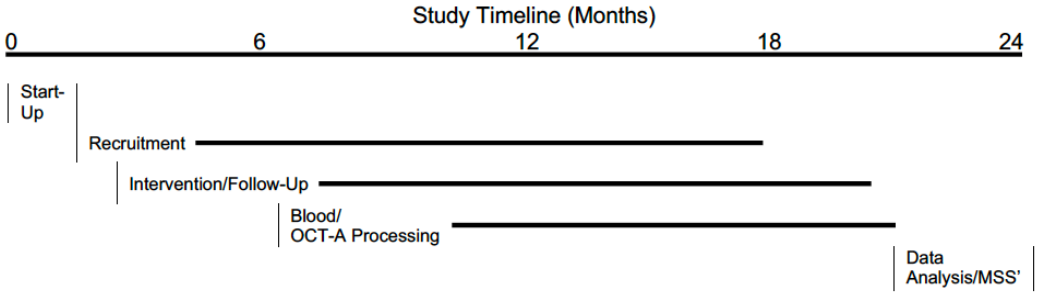
C.3.2.3. Post-Intervention Assessment. All pre-intervention measures (VO_2max, blood draws, cognitive assessments and OCT-A) will be repeated within 7 days following completion of the exercise intervention.

C.3.3. Sample Size Justification and Analysis Plan. We will summarize continuous variables (age, cognitive score, etc) using sample means and variances. We will summarize categorical variables using proportions. To test the effect of intervention, we will calculate paired differences for each individual and utilize a two-sample t-test to measure mean change in GF, as our primary outcome and MVD as our secondary outcome. We will use Pearson correlations to correlate changes in our outcome variables. We will use normal probability plots to examine the normality assumption for these procedures. If we observe evidence of non-normality, we will estimate effect sizes utilizing nonparametric procedures. Within this study, we will examine the pre-intervention relationship between MVD and composite cognitive Z-scores and analyze the effects of an exercise intervention on the relationship between increases in MVD with improvements in cognitive function, and the within person variances of these effects. These estimates are essential to serve as preliminary data for a larger, controlled study. Within this pilot, it would be premature to assume effects exist that could be declared statistically significant with adequate power using a sample size of 30 subjects. However, if the effect is sufficiently large (a Cohen's D of 1.06 or greater), we will have 80% power to detect such a difference with 30 individuals and a two tailed Type I error of 0.05.

D. MULTI-SITE MBI COLLABORATION

This application leverages the combined strengths of two Evelyn F. McKnight Brain Institutes: The University of Alabama at Birmingham (UAB) and the University of Miami (UM). UAB has expertise in exercise medicine and in neurocognition, with the resources of the Callahan Eye Hospital in obtaining OCT-A and in the analysis of growth factors in the NIH-funded laboratory of Dr. Barbara Gowers. UM has the world-renowned Bascom Palmer Eye Institute, with an R01-funded neuro-ophthalmology investigator, Jianhua Wang, MD, PhD, who specializes in the analysis of OCT-A images. Drs. Lazar and Rundek were colleagues at Columbia for more than a decade and are currently jointly funded by the NINDS for the "Family Study of Atherosclerosis and Vascular Cognitive Dysfunction" (3R01NS040807-15S1). Data will be stored in a secured REDCap database at UAB, and data transmission from UM to UAB will take placed on an encrypted platform already developed for world-wide clinical trials, such as CREST-2. The Research Subjects Review Board (RSRB), which serves as the UAB institutional review board, is credentialed to serve as the central IRB for both institutions. Biostatistical analyses will be conducted at UAB by faculty from the School of Public Health. If this project successfully confirms its hypotheses, the other two MBI's from the University of Florida and the University of Arizona will be invited to participate in a larger application.

E. TIMELINE AND FUTURE DIRECTIONS



Future Directions: The proposed study will provide critical information to guide future studies. 1) The current intervention will inform us regarding the effects of HIIT in reversing MVD 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. [81] 2) While we aim to recruit both men and women, our relatively small sample size will not be adequately powered to examine sex-specific effects. Studies with larger samples would permit secondary analyses directed at examining sex influences on MVD and cognition. Such a study would be supported by current evidence that women generally maintain higher IGF-1 levels[82 83], and lower blood pressure than men of the same age[81], suggesting sex-mediated influences on MVR. 3) In order to assess the effects of HTN and exercise on our outcome variables, future studies will require the inclusion of carefully matched controls of non-hypertensive older adults, and no exercise groups.

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BUDGET

A. Detailed Budget (By Year)

Yr1							
UAB							
PERSONNEL YEAR 1	**11/1/2020-10/31/2021**			**Fringe**	**Total**	**Total**	**Year 1**
NAME	**ROLE IN PROJECT**	**Effort**	**Base Salary**	**%**	**Salary**	**FB**	**TOTALS**
Ronald M. Lazar	Principal Investigator	1%	197,300	24.70%	1,973	487	2,460
Amani Norling	Project Coordinator	9%	40,000	32.30%	3,600	1,163	4,763
Terina Myers	Clinical Coordinator	5%	50,000	32.30%	2,500	808	3,308
Susan Barber	Neurology Grants Administrator	1%	93,174	32.30%	2,795	900	3,695
			Total Yr 1 UAB Personnel		**10,868**	**3,358**	**14,226**
Non-Personnel Costs	**Number**	**Cost @**	**Total**				
OCT-A Scans	45	200	9,000				
Exercise Testing/ECG	30	175	5,250				
Polar Monitors	20	100	2,000				
Exercise Training Sessions	30	45	1,350				
Blood Draws/Analysis	45	101	4,545				
Participant Compensation	15	780	11,700				
Materials			850				
				Total Non-Personnel Costs			**34,695**
				Total Yr 1 UAB			**48,921**
Univ of Miami							
PERSONNEL YEAR 1	**11/1/2020-10/31/2021**			**Fringe**	**Total**	**Total**	**Year 1**
NAME	**ROLE IN PROJECT**	**Effort**	**Base Salary**	**%**	**Salary**	**FB**	**TOTALS**
Tatjana Rundek	Principal Investigator	1%	197,300	24.70%	1,973	487	2,460
Jiang Wang	Co-Investigator	1%	160,000	32.30%	1,600	517	2,117
TBA	Imaging Analyst	5%	40,000	32.30%	2,000	646	2,646
			Total Yr 1 Miami Personnel		**5,573**	**1,650**	**7,223**
				Project Yr 1 Total			**56,144**

Yr2							
UAB							
	11/1/2021-10/31/2022			**Fringe**	**Total**	**Total**	**Year 1**
NAME	**ROLE IN PROJECT**	**Effort**	**Base Salary**	**%**	**Salary**	**FB**	**TOTALS**
Ronald M. Lazar	Principal Investigator	1%	197,300	24.70%	1,973	487	2,460
Amani Norling	Project Coordinator	9%	40,000	32.30%	3,600	1,163	4,763
Terina Myers	Clinical Coordinator	5%	50,000	32.30%	2,500	808	3,308
Susan Barber	Neurology Grants Administrator	1%	93,174	32.30%	2,795	900	3,695
			Total Yr 2 UAB Personnel		**10,868**	**3,358**	**14,226**
Non-Personnel Costs	**Number**	**Cost @**	**Total**				
OCT-A Scans	45	200	9,000				
Exercise Testing/ECG	30	175	5,250				
Polar Monitors	20	100	2,000				
Exercise Training Sessions	30	90	1,350				
Blood Draws/Analysis	45	101	4,545				
Participant Compensation	15	780	11,700				
Materials			850				
				Total Non-Personnel Costs			**34,695**
				UAB Yr 2 Total			**48,921**
Univ of Miami							
	11/1/2020-10/31/2021	**Effort**		**Fringe**	**Total**	**Total**	**Year 1**
NAME	**ROLE IN PROJECT**	**%**	**Base Salary**	**%**	**Salary**	**FB**	**TOTALS**
Tatjana Rundek	Site Principal Investigator	1.00%	197,300	24.70%	1,973	487	2,460
Jiang Wang	Co-Investigator	1.00%	160,000	32.30%	1,600	517	2,117
TBA	Imaging Analyst	5.00%	40,000	32.30%	2,000	646	2,646
			Total Yr 1 Miami Personnel		**5,573**	**1,650**	**7,223**
				Project Yr 2 Total			**56,144**

				Total Project Costs			**112,288**

B. Budget Justification

UNIVERSITY OF ALABAMA, BIRMINGHAM

Ronald Lazar, PhD, FAHA, FAAN

Dr. Lazar holds the Evelyn H. McKnight Endowed Chair in Memory and Learning in Aging in the Department of Neurology and is the Director of the McKnight Brain Institute at the University of Alabama at Birmingham (UAB). He is also the Director of the Neuropsychology Division. His research focus is on neurocognitive function in neurovascular and cardiovascular disease. For more than 20 years, he has been funded from NINDS, NICHD, NHLBI, NIA and NIDDK to investigate effects of stroke, brain arteriovenous malformations, carotid artery disease, heart disease, and endocrine abnormalities on brain function, with special emphasis on potentially reversible forms of cognitive impairment. Because of this expertise, he is currently a PI (MPI) of the NINDS/ NINDS StrokeNet funded ARCADIA-CSI (1U01NS110728-01) and PI (MPI) on the UAB StrokeNet Regional Coordinating Center (U24NS107223) on which he is responsible for recovery and rehabilitation. He also is currently Co-I and Cognitive Core Leader of the parent CREST-2 trial (1 U01 NS080168-01A1), and PI (MPI) for the ancillary CREST-H study (R01NS097876). He is Co-I on Genetic Contribution to Brain Arterial Dilatation and its Role in Cognition and Dementia (PI: Gutierrez, R01 AG057709-01), and for the supplement project Family Study of Atherosclerosis and Vascular Cognitive Dysfunction (3R01NS040807-15S1). Dr. Lazar will serve as PI of this project, overseeing all scientific, logistical and regulatory aspects. He will supervise Ms. Norling with regard to the exercise protocol, and OCT-A and the transfer of imaging data to the Univ of Miami and Ms. Myers who will be conducting the neurocognitive assessments. He will also work closely with Drs. Rundek and Wang at the University of Miami to ensure timely analysis of retinal images and with Dr. David Redden, who will be performing the statistical analysis in this project. We are requesting 1% effort on this project.

Christopher Girkin, MD, MSPH, FACS

Dr. Girkin is the chairman of the University of Alabama at Birmingham (UAB) Department of Ophthalmology and Chief Medical Officer for the Callahan Eye Hospital. After residency at UAB he completed a fellowship in neuro-ophthalmology at the Wilmer Eye Institute and was a Heed Glaucoma Fellow at the Hamilton Glaucoma Center at the University of California, San Diego. He joined the UAB faculty and founded the Department's Glaucoma Service in 1999. Dr. Girkin has authored or coauthored over 160 journal articles and his research lab has been supported by Research to Prevent Blindness, Glaucoma Research Foundation, EyeSight Foundation of Alabama, the Center for Disease Control and the National Eye Institute. This research explores the mechanisms underlying the greater predilection to develop glaucomatous injury in individuals of African ancestry. Related hypothesis are explored through patient-oriented research, including morphometric and biomechanical studies of the lamina cribrosa and posterior sclera utilizing post-mortem human donor tissues along with in vivo imaging of the lamina cribrosa in the NEI-sponsored African Descent and Glaucoma Evaluation Study (ADAGES). His honors include being selected to the "Best Doctors in America" yearly from 2003 to 2016, the AAO Senior Achievement Award, two American Glaucoma Society Clinician-Scientist Awards, the Research to Prevent Blindness Clinician-Scientist Award, the EyeSight Foundation of Alabama Eminent Scholar Award and the Ronald Lowe Medal. Thus, Dr. Girkin will oversee the acquisition of the retinal OCT-A scans and insure timely transfer to Dr. Wang's image processing laboratory at Miami. No effort is being requested.

Marcas Bamman, PhD

Dr. Bamman is currently a Professor in the Departments of Cell Development & Integrative Biology; Medicine and Neurology at the University of Alabama at Birmingham (UAB). He is the director of the UAB Center for Exercise Medicine (UCEM). Dr. Bamman has been fostering and leading clinical and translational research focused on exercise medicine/rehabilitation and biology since the 1990s, and has maintained continuous federal research support (NIH, VA, DoD) as PI for 20+ years. Dr. Bamman is currently PI of a NIAMS Clinical Center for the NIH Common Fund MoTrPAC initiative. In addition, Dr. Bamman has directed several exercise clinical trials including randomized dose-response trials (e.g., NCT02442479), and is the overall PI or site PI of five, multi-site randomized exercise trials in various phases: (i) molecular transducers of exercise-induced health benefits (NIH U01AR071133, NCT04151199); (ii) total joint arthroplasty rehabilitation (NIH R01HD084124, NCT02628795); (iii) aging with mobility impairment (NIH R01AG046920, NCT02308228); (iv) Parkinson's disease rehabilitation (NIH U01NS113851); and (v) epigenetic determinants of exercise responsiveness (DoD ONR N000141613159, NCT03380923). All of our human studies are biologically driven with the goal of better understanding exercise-induced health benefits in disease prevention, treatment, and rehabilitation. Finally, Dr. Bamman has served on >80 federal grant review panels. For the current study, Dr. Bamman will supervise the implementation of the baseline and follow-up exercise testing, and design of the exercise protocol. No effort is being requested.

Other Personnel

Amani Norling, MA, 4th Year PhD Student in the UAB Behavioral Neuroscience Program (Psychology)
Ms. Norling will be responsible for recruitment, scheduling participant visits, collecting data, participation in data analyses and manuscript preparation. We are requesting 9% effort on this project, with other support coming from internal grants.

Terina Myers, BA, Clinical Research Coordinator II
Ms. Myers will be responsible for neuropsychological testing and entering data into the electronic data capture system based at UAB. We are requesting 5% effort on this project.

Susan Barber, BA. UAB Neurology Grants Administrator
Ms. Barber will serve as the administrative liaison between UAB and the Univ of Miami, and will be responsible for monitoring the study budget and paying all expenses. We are requesting 1% effort for this project.

Non-Personnel Costs

A. Protocol and Patient Expenses
Thirty (30) participants will be enrolled in this pilot study.

Optical Coherence Tomography Angiography (OCT-A)
Each of the study participants will undergo three (3) OCT-A scans at a cost of $200 per scan (Project Total: $18,000).

Blood Draws/Analyses
Each participant will undergo two (2) blood draws, which will be analyzed at a cost of $243/participant (Project Total: $7290).

Exercise Testing
Each participant will undergo two (2) exercise testing sessions and two, 12 lead ECG assessments as part of our safety protocol at a cost of $350 (Project Total: $10,500).

Exercise Training
Participants will engage in 2 supervised training sessions at the University Center for Exercise Medicine (UCEM) at a cost of $90 for each participant ($2,700 total).

Polar Heart Rate Monitors
40 Polar H10 heart rate monitors will be purchased at a cost of $100/strap (total= $4000). These devices will permit remote monitoring by the study team during exercise training that will take place either in the participants home or in a local gym.

Participant Compensation
Participants will receive up to $780 (total= $23,400) for completing all assessments and all 40 exercise sessions.

B. Other Direct Costs

Materials and Supplies
Funds are requested to cover the costs of research, such as record sheets, bottled water, and testing materials that will be purchased for the neuropsychological testing sessions ($100). Cryo supplies will be needed to store the samples including cryolabels, cryotubes, cryoboxes, and biohazard bags ($725). Supplies will be needed for biomarker and blood draws ($725). Study binders will be created $5 per subject (30 subjects x $10: $150).

UNIVERSITY OF MIAMI

Tatjana Rundek, MD, PhD
Dr. Tatjana Rundek is a Professor of Neurology, Epidemiology and Public Health with tenure, Executive Vice Chair of Research and Faculty Affairs, Scientific Director of the Evelyn F. McKnight Brain Institute, Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging, and a Director of Clinical Translational Research Division in the Department of Neurology of the Miller School of Medicine. She holds a secondary faculty appointment at the Department of Neurology at Columbia University in New York. Dr. Rundek is a neurologist, clinical researcher and principal investigator of several NIH/NINDS funded R01 grants on genetic determinants of atherosclerosis, stroke, and cognitive decline. Dr. Rundek was a recipient of a NINDS K24 mid-career development award. She participates in

large stroke genetic consortia including the NINDS Stroke Genetic Network and International Stroke Genetic Consortium. Dr. Rundek was the Fulbright Scholar and the recipient of the research awards from the Hazel K. Goddess and the Dr. Gilbert Baum Funds. Dr. Rundek serves on the editorial boards of several scientific journals including Stroke, Neurology, Journal of Ultrasound in Medicine and Cerebrovascular Diseases. She has published over 360 scientific publications, editorials, reviews, and book chapters. She is a fellow of the American Neurological Association, a member of the American Heart Association and American Academy of Neurology. She was President of the Neurosonology Communities of Practice of the American Institute in Ultrasound in Medicine, the largest professional medical ultrasound organization in the US. Dr. Rundek serves on the Intersocietal Accreditation Commission (IAC) Vascular Testing Board of Directors, a national organization that accredits clinical echocardiography, nuclear/PET, MRI, CT and Dental laboratories and carotid stenting programs. Dr. Rundek is co-Director of the KL2 and Translational workforce development programs at the NCATS Clinical Translational Science Institute of the University of Miami. She is a Director of an MS degree in Clinical Translational Investigation at the Miller School of Medicine. During the course of this project, Dr. Rundek will have scientific oversight at Miami, and work in collaboration with Drs. Lazar at UAB and Wang at Miami in the interpretation of data and preparation of manuscripts.

Jianhua Wang, MD, PhD
Dr. Wang, is the Scientific Co-Director of Experimental Imaging Laboratory for the Bascom Palmer Eye Institute, University of Miami. Dr. Wang is an Associate Professor of Ophthalmology and Electric and Computer Engineering. After MD training in China, Dr. Wang obtained his PhD in vision science at University of Waterloo, Waterloo, Canada. He came to the University of Miami in July, 2006 from the University of Rochester, Rochester, NY. Dr. Wang has established the advanced ophthalmic imaging laboratory at the Bascom Palmer Eye Institute and is working closely with a group of neuro-ophthalmologists to study vasculature in the eye and neurological disorders. His research focuses on imaging microvasculature and microstructure of the eye as a window of the central nerve system. Currently, he and his collaborators in the Evelyn F. McKnight Center for Age Related Memory Loss are working on ocular microvascular dysfunction in age-related dementia. The aim of the study is to determine whether microvascular dysfunction plays a role in age related memory loss. Dr. Wang will be responsible for the OCT-A imaging protocol development and will supervise imaging acquisition. In addition, Dr. Wang be responsible for OCT-A image post-processing and outcome analyses. We are requesting 1% effort on this project.

Other Personnel
Post-Doc Imaging Analyst (TBA). This individual will be receiving the OCT-A images from UAB and performing the calculations of microvascular density and transmitting these values back to UAB for our primary analyses. We are requesting 5% effort for this project.

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: Lazar, Ronald M.

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

POSITION TITLE: Evelyn F. McKnight Endowed Chair in Learning and Memory

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
New York University, University Heights, NY	BA	06/71	Psychology
Northeastern University, Boston, MA	MA	06/73	Psychology
Northeastern University, Boston, MA	PhD	05/77	Psychology
Memorial Sloan-Kettering Cancer Center	Fellow	06/83	Neuropsychology

A. Personal Statement

The purpose of this pilot project is to obtain data supporting the effectiveness of an exercise intervention in hypertensive individuals in attenuating age-related cognitive decline via its impact on growth factor release, improving angiogenesis, vascular resistance and blood pressure. Dr. Lazar holds the Evelyn F. McKnight Endowed Chair in in Learning and Memory in the UAB Department of Neurology and serves as the director of the UAB McKnight Brain Institute. For more than 20 years, funding from NINDS, NICHD, NHILBI, NIA and NIDDK has enabled Dr. Lazar to have a long and successful history of examining the cognitive effects of comorbidities and aging, including cognitive effects of stroke, carotid artery disease, heart disease, and endocrine abnormalities on brain function, with special emphasis on potentially reversible forms of cognitive impairment. Because of this expertise, Dr. Lazar is the PD/PI of the recently funded NINDS/NIA funded Cerebral Hemodynamics and Neurocognition in Severe Aortic Valve Disease (1R21NS096972-01A1) and he is Co-PI (MPI) on the newly-funded UAB StrokeNet Regional Coordinating Center (U24NS107223) on which he is responsible for recovery and rehabilitation. He also is currently Co-I and Cognitive Core Leader of the parent CREST-2 trial (1 U01 NS080168-01A1), and PI (MPI) for the ancillary CREST-H study (R01NS097876). He is Co-I on Genetic Contribution to Brain Arterial Dilatation and its Role in Cognition and Dementia (PI: Gutierrez, R01 AG057709-01), PI (MPI) on the recently NINDS-funded ARCADIA-Cognition and Silent Infarction study, and for the supplement project Family Study of Atherosclerosis and Vascular Cognitive Dysfunction (3R01NS040807-15S1). In his role at UAB McKnight, he is currently PI of an exercise protocol designed to determine whether exercise affects oxygen extraction by the cerebral arterial system. He is also a K02 mentor to Thomas Buford, PhD, Director of the UAB Center for Exercise Medicine, for the impact of exercise on cognition. He is therefore suited to serve as a Principle Investigator in this project.

B. Positions and Honors

Positions and Employment

1980-1984 Graduate Faculty, Neuropsychology and Learning Processes Programs, CUNY, NY
1980-1984 Assistant Professor of Psychology, Dept of Psychology, Queens College of CUNY, NY
1981-1983 Adjunct Attending Psychologist, Dept of Neurology, Memorial Sloan-Kettering Cancer Center, NY
1983-1984 Assistant Attending Psychologist, Dept of Psychiatry, New York Hospital, NY
1983-1984 Adj Assistant Professor of Psychology (Psychiatry), Cornell University Univ Medical College, NY
1983-1984 Assistant Attending Psychologist, Dept of Neurology, Memorial Sloan-Kettering Cancer Ctr, NY
1984-1993 Chief Psychologist and Director of Neuropsychological Services, Dept of Psychology, Kings County Hospital Center, Brooklyn, NY
1984-1993 Director, Neuropsychology Service, Dept of Neurology, State University Hospital of Brooklyn, NY

1984-1993 Assistant Professor of Neurology and Psychiatry, SUNY/Health Science Center at Brooklyn, NY
1993-1994 Asst Prof of Clinical Neuropsy, Dept of Neurol, Columbia Univ Coll of Physicians & Surgeons, NY
1994-1996 Assoc Prof of Clinical Neuropsychol, Dept of Neurol, Columbia Univ Coll of Physicians & Surgeons, NY
2003-2013 Professor of Clinical Neuropsychology, Depts of Neurology and Neurological Surgery (Tenured), College of Physicians & Surgeons, Columbia University, NY
1994-2017 Professional Neuropsychologist, Dept of Neurology, NY Presbyterian Hospital, NY
1994-2017 Director, Levine Cerebral Localization Laboratory, Stroke Division, Dept of Neurology, NY Neurological Institute, Columbia University Medical Center, New York, NY
2013-Pres Prof of Neuropsychology in Neurology and Neurological Surgery (Tenured) at the Columbia Univ Medical Center, NY
2017-Pres Evelyn F. McKnight Endowed Chair in Learning and Memory in Aging, Dept of Neurology, U of Alabama at Birmingham, Birmingham AL
2017-Pres Professor of Neurology, Dept of Neurology, U of Alabama at Birmingham, AL
2017-Pres Director, UAB McKnight Brain Institute, Dept of Neurology, Un of Alabama at Birmingham, AL
2017-Pres Director, Neuropsychology Division, Dept of Neurology, Un of Alabama at Birmingham, AL
2017-Pres Senior Scientist, UAB Comprehensive Neuroscience Ctr, U of Alabama at Birmingham, AL
2020-Pres Senior Scientist, UAB Center for Clinical and Translational Science, U of Alabama at Birmingham

Honors:

Psi Chi / Robert Formica Memorial Award, Department of Psychology, New York University, 1971
Andrew W Mellon Fellow, Dept of Neurology, Memorial Sloan-Kettering Cancer Ctr, 1982-1983
Fellow, American Psychological Association, 2000
Fellow, American Heart Association, 2005
Fellow, American Academy of Neurology, 2011
Fellow, American Neurological Association, 2012
Evelyn F. McKnight Endowed Chair in Learning and Memory (UAB), 2017

National Consensus Panels

1. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. Circulation. 2011:124:2158-2177. PMID: 21969010
2. Standardized Neurologic Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative (NeuroARC), J Am Coll Cardiol. 2017 Feb 14;69(6):679-691.PMID: 28183511
3. Defining Optimal Brain Health in Adults: A Presidential Advisory from the American Heart Association/American Stroke Association. Stroke. 2017 Oct;48(10):e284-e303. PMID: 28883125
4. Brain Health Science Subcommittee, American Heart Assn/American Stroke Assn (2019-Pres)

Federal Government Advisory Committees

2017 - Fogarty Global Brain Disorders Study Section ZRG1 BDCN-N (55) R, CSR, NIH
2009 – 2015 Chartered Member, Acute Neural Injury and Epilepsy (ANIE) Study Section, Center for Scientific Review (CSR), NIH
2002 – 2010 Permanent Member, Circulatory System Devices Advisory Panel, Medical Devices Advisory Committee, Center for Devices and Radiological Health, US FDA
2009-2010 ZRG1 BDCN-L (95) S Competitive Revisions; Clinical Neuroscience and Disease, NIH.
2019 - NINDS Advisory Committee for Common Data Elements 2.0 for Stroke Outcomes

C. Contribution to Science

1. As a clinical and research neuropsychologist with a background in biological mechanisms, my interests have been in the use of behavior as an index of disease severity and progression, pathophysiology and treatment efficacy, and the factors involving the cerebral blood supply that represent common threads among many cognitive syndromes. Our earliest studies focused on carotid artery disease in which we studied both acute models involving test balloon occlusions to determine the consequences of permanent loss of unilateral blood supply and chronic conditions involving long-term critical stenosis. We have begun to show that cognitive impairment is a more sensitive metric of perfusion failure than physical function, and that the brain appears both to be able to tolerate longer-term ischemia than originally thought, with potential for reversibility.

a. **Lazar, R.M.**, Pavol, M., Browndyke, J., Bormann, Dwyer, M.G., et al. Neurocognition and Cerebral lesion burden in High Risk Patients before Undergoing TAVR: Insights from the Sentinel Trial, JACC Cardiovasc Interv. 2018 Feb 26;11(4):384-392, PMID: 29397361
b. Marshall RS, Asllani I, Pavol MA, Cheung YK, **Lazar RM.** Altered cerebral hemodyamics and cortical thinning in asymptomatic carotid artery stenosis. PLoS One. 2017 Dec 14;12(12): PMID: 29240808

c. Norling, A.M., Gerstenecker, A.T., Buford, T.W., Khan, B., Oparil, S., **Lazar, R.M.** The Role of IGF-1 Deficiencies in Microvascular Rarefaction and Hypertension. GeroScience, 2020,42(1), 141-158, PMID: 31808026
d. Norling, A.M., Marshall, R.S., Pavol, M.A., Howard, H., Howard, V., Liebeskind, D., **Lazar, R.M.** Is Hemispheric Hypoperfusion a Treatable Cause of Cognitive Impairment? Current Cardiology Reports, 2019;21(1):4,1089-9. PMID: 30661122

We then began to pursue the matter of whole-brain alterations in perfusion, using patients with NYHA Stage 4 Heart Failure to explore the effects of long-term hypoperfusion as a chronic model and the effects of implantation of left ventricular assist devices (LVAD's) o determine potential reversibility. As with carotid disease, patients appeared to be able to tolerate long-term perfusion failure to the whole brain, which affected diffusely-represented cognitive functions such as processing speed, attention and working memory. The implantation of LVAD's were found both to increase stroke risk due to thromboembolism from the device and to result worsening cognitive function if outflow was too great relative to pre-LVAD levels, but that reducing LVAD output resulted in normalized cognition. These data have led to us propose an inverted u-shaped function, so that global hypo- and hyper-perfusion result in impaired cognition, which to date had not been demonstrated empirically in patients with the same disease. These findings led the FDA to draft new guidance on the need to assess neurological and neurocognitive on all new devices for mechanical circulatory support. We have subsequently begun similar with transaortic valve replacement for severe aortic stenosis.

a. Pavol, M.A., Willey, J.Z., Wei, Y., Yuzefpolskaya, M., Marshall , R.S., Marascalco, P.J., Harwood, J., **Lazar, R.M**., Does cognition improve following LVAD implantation? General Thoracic and Cardiovascular Surgery, 2018, Aug;66(8):456-463. PMID: 29796750
b. Willey, J.Z., Demmer, R.T., Takayama, H., Colombo, P.C., **Lazar, R.M.,** Cerebrovascular disease in the era of left ventricular assist devices with continuous flow: risk factors, diagnosis, and treatment, Journal of Heart and Lung Transplantation, J Heart Lung Transplant. 2014 Sep;33(9):878-87. PMID: 24997495.
c. Festa JR, Jia X, Cheung K, Marchidann A, Schmidt M, Shapiro PA, Mancini DM, Naka Y, Deng M, Lantz ER, Marshall RS, **Lazar RM**. Association of low ejection fraction with impaired verbal memory in older patients with heart failure. Archives of Neurology 2011;68:1021-1026. PMID: 21825237.
d. Lietz K, Brown K, Ali SS, Colvin-Adams M, Boyle AJ, Anderson D, Weinberg AD, Miller LW, Park S, John R, **Lazar RM**. The role of cerebral hyperperfusion in postoperative neurologic dysfunction after left ventricular assist device implantation for end-stage heart failure. The Journal of Thoracic and Cardiovascular Surgery 2009;137:1012-1019. PMID: 19327532.

3. Concurrently, we have been looking at specific measures of cerebral hemodynamics in order to better understand the factors, which may be contributing to alterations in neurocognition. This line of inquiry led to an R01 grant in which we are studying the effects of four measures in the cerebral circulation on neurocognition in asymptomatic carotid disease: cerebral blood flow and fMRI activation with ASL techniques, and vasomotor reactivity and dynamic cerebral autoregulation using transcranial Doppler. We are also exploring cerebral hemodynamics in the setting in the setting of severe aortic stenosis in an R21 project.

a. Kapadia, S.R., Kodali,, S., Makkar, R., Mehran, R., **Lazar, R.M.,** et al. Embolic Protection During Transcatheter Aortic Valve Replacement, Journal of the American College of Cardiology. 2017 Jan 31;69(4):367-377, PMID: 27815101
b. Gutierrez J, Marshall RS, **Lazar, RM.** Arterial stiffness as a predictor of cognitive performance in subjects with and without vascular disease. JAMA Neurol. 2015 Mar 1;72(3):309-15. PMID: 25599130.
c. Marshall, R.S., **Lazar, R.M**., Liebeskind, D.S., Connolly, E.S., Howard, G., Lal, B.K., Huston III, J., Meschia, J.F., Brott, T.G., on behalf of the CREST-H investigators, Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis – Hemodynamics (CREST-H): Study Design and Rationale. International Journal of Stroke, 2018 [Epub ahead of print]. PMID: 30132751
d. Marshall RS, Pavol MA, Cheung YK, Asllani I, **Lazar RM.** Cognitive Impairment Correlates Linearly with Mean Flow Velocity by Transcranial Doppler below a Definable Threshold *Cerebrovasc Dis Extra*. 2020;10(1):21–27 PMID: 32289771

4. Working in one of the largest stroke services in the world, we also face the need to address the goal of promoting stroke recovery when loss of perfusion results in irreversible infarction. We have been exploring both the neurotransmitter systems in human stroke that may be related to the restitution of function as well as the biological systems which may limit both the degree and time windows for optimal recovery. My lab was the first in the world to show experimentally in human stroke that glutamate/GABA systems may be critical for promoting/maintaining and inhibiting stroke recovery. This early work has led to ongoing, innovative pilot studies to re-purpose existing drugs with targeted actions to reduce post-stroke cortical inhibition. We have also studied the natural history of stroke recovery from the acute stroke period to 90 days, discovering that

individuals with mild – moderate initial deficits in motor and language function almost universally recovery 70% of their deficits by 3 months, which we have termed proportional recovery. This work has been replicated in several laboratories around the world, leading to new work attempting to modulate this biological process.

a. Schambra H, Martinez-Hernandez IE, Slane KJ, Boehme AK, Marshall RS, **Lazar RM**. The neurophysiological effects of single-dose theophylline in chronic stroke patients. Restorative Neurology and Neuroscience, 2016, 21;34(5):799-813. PMID: 27567756.
b. Kitago T, Liang J, Huang VS, Hayes S, Simon P, Tenteromano L, **Lazar RM**, Marshall RS, Mazzoni P, Lennihan L, Krakauer JW. Improvement after constraint-induced movement therapy: recovery of normal motor control or task-specific compensation? Neurorehabilitation and neural repair 2013;27:99-109. PMID: 22798152.
c. **Lazar RM**, Berman MF, Festa JR, Geller AE, Matejovsky TG, Marshall RS. GABAergic but not anti-cholinergic agents re-induce clinical deficits after stroke. Journal of the neurological sciences 2010; 292:72-76. PMID: 20172537.
d. Yaghi S, Cotsonis G, de Havenon A, Prahbakaran S, Romano JG, **Lazar RM**, Marshall RS, Feldmann E, Liebeskind DS.. Poststroke Montreal Cognitive Assessment and Recurrent Stroke in Patients With Symptomatic Intracranial Atherosclerosis. *J Stroke Cerebrovasc Dis*. 2020;29(4):104663. doi:10.1016 PMID: 32044220

5. Our lab has had a specific interest in aphasia recovery because of its obvious impact on quality of life. Studying language after stroke from the time of acute onset to 90 days, we have found much greater inter-individual variability in the time course of recovery, although those with mild to moderate initial aphasia syndromes tend to recovery 70% of the deficits. We have also found that we are unable to predict 90-day outcomes among those with severe initial aphasia syndromes, even with models that include lesion volume, lesion location and age. We are now looking at the evolution of deficits every day during the acute stroke period to determine whether there are predictive factors for later recovery.

a. Gerstenecker, A., **Lazar, R.M.** Language recovery following stroke. The Clinical Neuropsychologist, Clin Neuropsychol. 2019 Jul;33(5):928-947. PMID: 30698070.
b. **Lazar R.M**., Boehme, AK. Aphasia as a predictor of outcome after stroke, Current Neurology and Neuroscience Reports. 2017 Sep 19;17(11):83. PMID: 28929424.
c. Amelia K. Boehme AK, Martin-Schild S, Marshall RS, **Lazar RM**, The Effect of Aphasia on Acute Stroke Outcomes, Neurology, 2016, Neurology. 2016 Nov 29;87(22):2348-2354. PMID: 2776586.
d. Dunn, L.E., Schweber, A.B., Lendaris, A.R., Marshall, R.S**., Lazar, R.M.** Variability in Motor and Language Recovery during the Acute Stroke Period. Cerebrovascular Disease EXTRA. 2016 22;6(1):12-21. PMID: 27099611.

Complete List of Published Work in PubMed (H-Index = 57)
https://www.ncbi.nlm.nih.gov/pubmed/?term=lazar+rm

D. Research Support

1U01NS110728-01 (Lazar/Lansberg) 04/01/2019 - 03/31/2024
NIH/NINDS
ARCADIA CSI (Cognition and Silent Infarcts)
This ancillary study to the ARCADIA trial will determine whether aspirin or apixaban reduces the number of silent brain infarcts in patients with atrial cardiomyopathy, with the effect of mitigating cognitive decline.

U24NS107223 (Gropen, Lazar, Harrigan) 09/01/2018 – 08/31/2023
NIH/NINDS
Strokebelt StrokeNet
The goal of the StrokeBelt StrokeNet is to establish a Regional Coordinating Center to facilitate Stroke research in the Southeastern States of Alabama and Mississippi. This infrastructure will provide research opportunities in acute stroke treatment, primary and secondary prevention, and post-stroke rehabilitation for an underserved, high-risk stroke population.

R01 AG057709-01 (PI:Gutierrez) 7/1/2018 - 6/30/2023
NIH/NINDS
Genetic Contribution to Brain Arterial Dilatation and its Role in Cognition and Dementia
The goal of this project is to study the role of gene regulation in the dilatation of intracerebral arteries in response to systemic cardiovascular risk factors.
Role: Co-I (neurocognitive outcomes).

1 R01 NS097876-01A1 (Lazar, Marshall, Liebeskind, Connolly) 4/1/2017 – 3/31/2022
NIH/NINDS
Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial - Hemodynamics (CREST-H) The goal of this study is to determine whether patients with asymptomatic carotid stenosis who have cerebral hemodynamic compromise and cognitive impairment will improve after revascularization.

1 U01 NS080168-01A1 (Brott) 7/1/2013 – 6/30/2022
NIH/NINDS
CREST-2 Clinical Coordinating Center.
This goal of this project is to assess if contemporary medical therapy is not inferior to contemporary revascularization (carotid endarterectomy or carotid angioplasty/stenting) plus best medical therapy in patients with ≥ 70% asymptomatic carotid stenosis. The cognitive aim is to assess whether medical therapy alone is non-inferior to revascularization to maintain the level of cognitive function at 4 years of follow-up.
Role: Co-I/Cognitive Core PI.

U01 NS080165 (PI: G Howard) 3/15/14 – 2/28/22
NIH/NINDS
CREST-2 Statistical and Data Coordinating Center – (SDCC)
CREST-2 is a pair of randomized trials to assess potential stroke reduction: 1) carotid endarterectomy plus aggressive medical management versus medical management alone, and 2) carotid stenting plus aggressive medical management versus medical management alone. Each trial will have approximately 1,240 patients randomized and followed for up to 4 years for any stroke during a 44-day peri-procedural period plus ipsilateral stroke over a follow-up period extending 4 years. The study is being performed in approximately 150 clinical centers in the US and Canada
Role: Co-I

3R01NS040807-15S1 (Lazar, Site PI) 8/1/2019 – 7/31/2020 (NCE)
Family Study of Atherosclerosis and Vascular Cognitive Dysfunction
The parent study, Family Study of Dominicans investigate how the genetic and non-genetic factors affect vascular precursor phenotypes of stroke with its deep phenotyping, extensive behavioral and clinical assessments, and the rich genetic data from previous grant cycles. The supplement studies genetic, epigenetic and vascular risk of cognitive function and cognitive decline in the high-vascular risk Dominican families.

Completed Research Support (Last 3 years)

1R21NS096972-01A1 (Lazar) 8/1/2016 – 7/31/2019
NIH/NINDS/NIA
Cerebral Hemodynamics and Neurocognition in Severe Aortic Valve Disease.
The goal of this project is to determine whether severe aortic stenosis is associated with impaired cerebral hemodynamics and, in turn, impaired cognition, and whether valve replacement is associated with improved cerebral hemodynamics and improved cognition.

1 R01 NS076277-01A1 (Lazar/Marshall) 4/1/2012-3/31/2018
NIH/NINDS
Blood Flow and Cognition in Asymptomatic Carotid Artery Disease.
This project studies the relationship of four measures of cerebral hemodynamics and cognitive function in patients with asymptomatic carotid artery disease

5 U54 NS081765-02 (Ogedegbe/Williams) 10/1/2012 – 9/30/2017
NIH/NINDS
The goal of this grant is to establish a Center for Stroke Disparities Solutions among 3 academic institutions (NYU; Columbia; and SUNY Downstate); 5 stroke centers and a practice-based research network of primary care practices within NYC) Health and Hospital Corp; the Research Division of the Hebrew Home at Riverdale and the Visiting Nurse Service of NY. The target communities are Black and Hispanic residents of NYC.
Role: Co-I

BIOGRAPHICAL SKETCH

DO NOT EXCEED FIVE PAGES.

NAME: Christopher A. Girkin

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

POSITION TITLE: Professor and Chairman of Ophthalmology, Specialty: Glaucoma and Neuro-ophthalmology

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
Drury College, Springfield, Missouri	BS	05/1989	Chemistry & Biology
University of Arkansas for Medical Sciences	MD	05/1993	Medicine
University of Alabama at Birmingham	Residency	06/1997	Ophthalmology
Johns Hopkins University/Wilmer Eye Institute	Fellowship	06/1998	Neuro-ophthalmology
University of California at San Deigo	Fellowship	06/1999	Glaucoma
University of Alabama at Birmingham	MSPH	05/2004	Epidemiology

A. Personal Statement

I am a fellowship trained neuro-ophthalmologist and glaucoma specialist with formal training in biostatistics and epidemiology. My primary research explores the mechanisms underlying the greater predilection to develop glaucomatous injury in individuals of African ancestry and investigates the morphometry of the optic nerve head as a biomarker to predict the development and progression of glaucomatous optic neuropathy. *The overarching hypothesis is that variation in ONH morphometry and biomechanical properties are largely responsible for the increased in the susceptibility to IOP-related optic nerve injury associated with African ancestry.* Related hypotheses are explored through patient-oriented research, including: 1) structural and functional evaluation of the optic nerve in the NEI-sponsored African Descent and Glaucoma Evaluation Study (ADAGES I and II) cohort; 2) in-vivo studies imaging the lamina cribrosa, ADAGES IV; 3), ex-vivo morphometric studies of the lamina cribrosa and posterior sclera utilizing post-mortem human donor tissues in the Digital Optic Nerve Reconstruction study (DONOR); 4) biomechanical testing of the optic nerve in brain-dead organ donors in the Alabama Living Eye Project (ALEP) and 5) imaging-based health services research to improve care to underserved populations in the CDC-sponsored Eye Care Quality and Accessibility Improvement in the Community (EQUALITY) study. The current proposal will utilize many of the methods developed in the EQAULITY Study. I will participate in the clinical evaluation of the proposed telemedicine protocol along with assisting in with interpretation, analysis and preparation of the presentation of the results of the study. I will oversee tissue collection at UAB and will assist in analysis, design and communication of the data produced from the study.

a) **Girkin CA,** Fazio MA, Yang H, Reynaud J, Burgoyne CF, Smith B, Wang L, Downs JC. Variation in the Three Dimensional Histomorphometry of the Normal Human Optic Nerve Head With Age and Race: Lamina Cribrosa and Peripapillary Scleral Thickness and Position. Invest Ophthalmol Vis Sci. 2017;58(9):3759-69. doi: 10.1167/iovs.17-21842. PubMed PMID: 28738420; PMCID: PMC5525554.

b) **Girkin CA**, Nievergelt CM, Kuo JZ, Maihofer AX, Huisingh C, Liebmann JM, Ayyagari R, Weinreb RN, Ritch R, Zangwill LM; ADAGES Study Group. Biogeographic Ancestry in the African Descent and Glaucoma Evaluation Study (ADAGES): Association With Corneal and Optic Nerve Structure. Invest Ophthalmol Vis Sci. (IOVS) 2015 Mar 5;56(3):2043-9. doi: 10.1167/iovs.14-15719. PMID: 25744975.

c) **Girkin CA**, Sample PA, Liebmann JM, Jain S, Bowd C, Becerra LM, Medeiros FA, Racette L, Dirkes KA, Weinreb RN, Zangwill LM; ADAGES Group. African Descent and Glaucoma Evaluation Study (ADAGES): II. Ancestry differences in optic disc, retinal nerve fiber layer, and macular structure in healthy subjects. Arch Ophthalmol. 2010 May;128(5):541-50. doi: 10.1001/archophthalmol.2010.49. PMCID: PMC5525554.

B. Positions and Honors

Positions and Employment

1994-1997 Ophthalmology Residency, University of Alabama at Birmingham/Eye Foundation

Hospital 1997-1998 Neuro-ophthalmology Fellowship, Johns Hopkins Hospital, Wilmer Eye Institute
1998-1999 Glaucoma Fellowship, Hamilton Glaucoma Center, UCSD
1999-2002 Assistant Professor of Ophthalmology, UAB Dept. of Ophthalmology
2000-2017 Director, Glaucoma Service, Dept. of Ophthalmology, UAB/Eye Foundation Hospital
2000- Associate Scientist, UAB Vision Science Research Center
2001- Associate Scientist, UAB Center for Outcomes Research
2002- Associate Professor of Ophthalmology, UAB Ophthalmology
2004- Associate Scientist, UAB Center for Minority Health and Research
2004- Senior Scientist, UAB Center for Aging
2006- Professor of Ophthalmology – UAB, Dept. of Ophthalmology
2012- Chief Medical Officer – UAB, Callahan Eye Foundation Hospital
2012- Chairman – UAB, Department of Ophthalmology

Honors: Magna Cum Laude 1989, Southern Medical Association Scholarship 1991, Ilse Oates Scholarship 1992, Merck Award 1993, Chief Resident 1997, Alabama Lions Sight Conservation Association Award 1999, Association for Research in Vision and Ophthalmology (ARVO) Investigator travel Award 1999, Heed Fellowship 1999, American Glaucoma Society (AGS) Research Fellowship Award 2003, AGS Clinician- Scientist Award 2004, Chair, American Academy of Ophthalmology (AAO) Glaucoma Sub-Day 2005, AGS Clinician-Scientist Award 2005, Research to Prevent Blindness-Physician-Scientist Award, 2005, Eyesight Foundation (ESFA) Eminent Scholar, 2007. Ron Lowe Medal, 2008, Selected as one of the "The Best Doctors in America" 2003-2018, AAO Senior Achievement Award 2012, ESFA Endowed Chair in Ophthalmology 2012.

Professional Societies: **(8 of 23)** Alpha Omega Alpha, Society of Heed Fellows, AMA, AGS (Secretary 2012- 2014), AAO, Research to Prevent Blindness, Fellow of the American College of Surgeons, Fellow ARVO.

Extramural Committees (12 of 66): NEI and FDA Sponsored Glaucoma Clinical Trial Design and Endpoint Planning Group 2008, Member, Scientific Advisory Committee, Glaucoma Research Foundation 2006 -, NEI Brain Disorder and Clinical Neuroscience Integrated Review Group 2009, Chair, Glaucoma Section, Program Committee, ARVO 2011-2012, Board of Directors AGS 2006-2016, Chair, Program Committee, AGS 2014-2016. Chair, Glaucoma Section, Basic Clinical Science Course Committee, AAO 2012-2016.

C. Contribution to Science

My Bibliography (**186** Medline referenced articles, h-index = 53, i10-index=133):
http://www.ncbi.nlm.nih.gov/pubmed?term=Girkin+C&cmd=DetailsSearch&log$=activity
https://scholar.google.com/citations?user=u94DGFYAAAAJ&hl=en&oi=sra

My primary research explores the mechanisms underlying the greater predilection to develop glaucomatous injury in individuals of African ancestry and investigates the morphometry of the optic nerve head as a biomarker to predict the development and progression of glaucomatous optic neuropathy. *The overarching hypothesis is that variation in ONH morphometry and biomechanical properties are largely responsible for the increased in the susceptibility to IOP-related optic nerve injury associated with African ancestry.* Related hypotheses are explored through patient-oriented research, including: 1) structural and functional evaluation of the optic nerve in the NEI-sponsored African Descent and Glaucoma Evaluation Study (ADAGES I and II) cohort; 2) in-vivo studies imaging the lamina cribrosa, ADAGES IV; 3), ex-vivo morphometric studies of the lamina cribrosa and posterior sclera utilizing post-mortem human donor tissues in the Digital Optic Nerve Reconstruction study (DONOR); 4) biomechanical testing of the optic nerve in brain-dead organ donors in the Alabama Living Eye Project (ALEP) and 5) imaging-based health services research to improve care to underserved populations in the CDC-sponsored Eye Care Quality and Accessibility Improvement in the Community (EQUALITY) study (not shown).

1. ADAGES is a NEI-funded multicenter cohort study designed to evaluation the structural and functional progression of the optic nerve in glaucoma in individuals of European (ED) and African descent (AD). The study began based on my K23 grant awarded in 2001 and is now in its 12th year. The other operational sites are the University of California, San Diego and Columbia University. This collaboration has resulted in over 35 peer-reviewed

manuscripts and 59 abstracts. This work has been previously funded through foundation and NIH support (Research to Prevent Blindness, Glaucoma Research Foundation, American Health Assistance Foundation, EyeSight Foundation of Alabama, NIH K23: EY 13959-01, NIH U10: EY 14267-01, NIH U10: EY 14267-02, NIH RO1: EY019869-01)

Recent related publications:

a) **Girkin CA**, Sample PA, Liebmann JM, Jain S, Bowd C, Becerra LM, Medeiros FA, Racette L, Dirkes KA, Weinreb RN, Zangwill LM, Group A. African Descent and Glaucoma Evaluation Study (ADAGES): II. Ancestry differences in optic disc, retinal nerve fiber layer, and macular structure in healthy subjects. Arch Ophthalmol. 2010;128(5):541-50. PubMed PMID: 20457974; PMCID: PMC2910255. *This study was the first to define racial differences in the optic nerve, nerve fiber layer and macula using a multimodal imaging approach.*

b) **Girkin CA**, Liebmann J, Fingeret M, Greenfield DS, Medeiros F. The effects of race, optic disc area, age, and disease severity on the diagnostic performance of spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2011;52(9):6148-53. PubMed PMID: 21421879. *This study was the first to determine the effect of racial variation in ONH structure on diagnosis of glaucoma using SDOCT.*

c) **Girkin CA**, Nievergelt CM, Kuo JZ, Maihofer AX, Huisingh C, Liebmann JM, Ayyagari R, Weinreb RN, Ritch R, Zangwill LM, Group AS. Biogeographic Ancestry (BGA) in the African Descent and Glaucoma Evaluation Study (ADAGES): Association With Corneal and Optic Nerve Structure. Invest Ophthalmol Vis Sci. 2015;56(3):2043-9. PMCID: PMC4373542. *This study was the first study to utilize BGA testing in ophthalmology and determined that variation in BGA corresponded to structural differences in corneal, optic nerve and retinal anatomy within self-described racial groups.*

2. Using in-vivo imaging, we are evaluating structural biomarkers for glaucoma susceptibility within "deep" optic nerve structures visualized within SDOCT datasets. Our particular interest is in defining racial differences in the rate and mode of change in these structures over time to better understand potential differences in pathobiology and to better define progression of glaucomatous disease in this at-risk and underserved population. We have a developed particular focus on the deep optic nerve structures as they not only may serve as new disease biomarkers but also may have mechanistic involvement with the pathogenesis of axonal injury.

Recent related publications:

a) Johnstone J, Fazio M, Rojananuangnit K, Smith B, Clark M, Downs C, Owsley C, Girard MJ, Mari JM, **Girkin CA.** Variation of the axial location of Bruch's membrane opening with age, choroidal thickness, and race. Invest Ophthalmol Vis Sci. 2014 Mar 28;55(3):2004-9. PMID: 24595390. *This study demonstrated that Bruch's Membrane Opening (BMO) likely changes with age due to thinning of the peripapillary choroid. This is important as all measurement of deep optic nerve structures (i.e. the laminar cribrosa) are currently dependent on the position of this landmark.*

b) Rhodes LA, Huisingh C, Johnstone J, Fazio M, Smith B, Clark M, Downs JC, Owsley C, Girard MJ, Mari JM, **Girkin C.** Variation of laminar depth in normal eyes with age and race. Invest Ophthalmol Vis Sci. 2014 Nov 20;55(12):8123-33. PMID: 25414182. *This study used three-dimensional quantification of the lamina cribrosa from SDOCT datasets of ADAGES participants and demonstrated racial differences in the effect of aging on remodeling of the lamina cribrosa between participants of African and European descent.*

c) Fazio MA, Johnstone JK, Smith B, Wang L, **Girkin CA.** Displacement of the Lamina Cribrosa in Response to Acute Intraocular Pressure Elevation in Normal Individuals of African and European Descent. *Invest Ophthalmol Vis Sci* 2016;57:3331-3339. *This study demonstrated that there is a racial difference acute deformation of the laminar cribrosa in response to elevation of IOP providing the first in-vivo evidence of a racial difference in the biomechanical behavior of the optic nerve.*

3. We have developed a unique library of high-resolution three-dimensional reconstructions from human donor eyes with associated clinical records. Donor ocular tissues were fixed at physiologic and elevated pressures to mimic in-vivo loading conditions in order to enable accurate morphometric and biomechanical analysis. This database currently contains over 190 reconstructed donor pairs. Each reconstruction was develop using an episcopic fluorescent technique developed by Dr. Downs that produces high-fidelity reconstructions of the load-bearing connective tissues of the optic nerve head to a resolution of 1.5 cubic micron voxel. We are utilizing these unique digital reconstructions to test the hypothesis that variations in three- dimensional (3D) laminar architecture are critical in determining individual susceptibility to glaucomatous injury. Specifically, that variations in laminar 3D architecture and biomechanical behavior are associated with well-described risk

factors for glaucomatous disease such as increasing age and African ancestry. This work has been funded through the NEI and foundation support (RO1EY18926, RO1EY19333, Research to Prevent Blindness - Clinician Scientist Award, EyeSight Foundation Research Grant).

Recent related publications:

a) **Girkin CA,** Fazio MA, Yang H, Reynaud J, Burgoyne CF, Smith B, Wang L, Downs JC. Variation in the Three-Dimensional Histomorphometry of the Normal Human Optic Nerve Head With Age and Race: Lamina Cribrosa and Peripapillary Scleral Thickness and Position. Invest Ophthalmol Vis Sci. 2017;58(9):3759-69. doi: 10.1167/iovs.17-21842. PubMed PMID: 28738420; PMCID: PMC5525554. *This paper revealed substantial sectorial and racial differences in LC and scleral morphology using 3D morphometric measurements of episcopic reconstructions of the optic nerve head (ONH). Increasing LC depth and scleral thickness with age was also in the AD group, but not ED group. Results suggest greater age-related remodeling of the load-bearing ONH connective tissues in eyes from AD individuals that could explain, in part, the greater predilection to glaucomatous injury seen in aged AD populations.*

b) Yang H, Downs JC, **Girkin C**, Sakata L, Bellezza A, Thompson H, Burgoyne CF. 3-D histomorphometry of the normal and early glaucomatous monkey optic nerve head: lamina cribrosa and peripapillary scleral position and thickness. Invest Ophthalmol Vis Sci. 2007;48(10):4597-607. doi: 10.1167/iovs.07-0349. PubMed PMID: 17898283; PMCID: PMC2764532. *This paper defined the morphometric methods used to determine scleral and laminar morphology in episcopic reconstruction of the ONH of the primate.*

c) Downs JC, Yang H, **Girkin C**, Sakata L, Bellezza A, Thompson H, Burgoyne CF. Three-dimensional histomorphometry of the normal and early glaucomatous monkey optic nerve head: neural canal and subarachnoid space architecture. Invest Ophthalmol Vis Sci. 2007;48(7):3195-208. doi: 10.1167/iovs.07-0021. PubMed PMID: 17591889; PMCID: PMC1978199. *This paper defined the morphometric methods used to determine the neural canal geometry in episcopic reconstruction of the ONH of the primate.*

D. Research Support

Ongoing Research Support

R01 EY028284-01A1 (Girkin/Fazio) 08/01/2018 – 07/30/2022
NIH/NEI
Determinants of the Biomechanical Behavior of the Human Lamina Cribrosa
This project will define the critical properties of the scleral and ONH quantified by in vivo and ex vivo custom methods that analyze how corneoscleral biomechanics modulates the mechanical response of the ONH to increased intraocular and intracranial pressure measured in the living human eye of brain-dead organ donors. Additionally, we will determine how these factors are associated with clinically assessable ocular characteristics and how these factors vary with aging, with glaucoma and across racial groups of relatively high- (African descent) and low- (European descent) risk for the disease.

R01EY026574 (Multi-PI:Fazio/Girkin/Zangwill) 07/01/2017 - 6/30/2021
NIH/NEI
African Descent and Glaucoma Evaluation (ADAGES) IV: Alterations of the Lamina Cribrosa in progression
ADAGES IV will describe the SDOCT changes in the lamina cribrosa and deep optic nerve structure in the ADAGES cohort of glaucoma patients to define the role of chronic remodeling in the optic nerve in glaucoma.
Role: PD/PI

R01EY025331 (Dreer) 06/01/2015 – 05/31/2020
NIH/NEI
Enhancing Glaucoma Medication Adherence Among African Americans
The purpose of this project is to see if a culturally relevant, health promotion-based intervention improves glaucoma medication adherence among a high-risk segment of the population.
Role: Co-Investigator

K23EY025724 (Rhodes) 03/01/2016 – 02/28/2021

NIH/NEI
Using Telemedicine to Improve Glaucoma Care: An Emerging Eye Care Delivery Model
The overall goal of this project is to determine if a telemedicine-assisted glaucoma detection and management program that is performed in community clinics and then transmitted to a remote reading center can access at-risk minority populations at lower cost, as accurately as standard in-person care by a glaucoma specialist, and with a platform for eye health education designed to improve compliance with recommended care.
Role: Mentor

U01DP006441 (Rhodes) **09/30/2019 – 09/29/2024**
CDC
Using Telemedicine to Prevent Blindness in an at-Risk Rural Alabama Population - Component A
The main goal of this project is to improve the quality and accessibility of glaucoma detection and management among a vulnerable and at-risk segment of our population.
Role: Co-Investigator

R01EY025756 (Racette) **08/01/2017 – 07/31/2021**
NIH/NEI
Early detection of glaucoma progression using a novel individualized approach
The major goal of this project is to improve the detection of glaucoma progression by reducing the time needed to identify glaucoma progression. We will use different combinations of structural and functional data within the framework of an individualized model to improve our ability to detect and monitor glaucoma progression.
Role: Co-Investigator

Overlap: none

Relevant completed grants:
R01EY0023704 (Weinreb) **07/01/2013 - 06/30/2018**
African Descent and Glaucoma Evaluation (ADAGES) III: Contribution of genotype to glaucoma phenotype in African Americans
The main goal of this study is to conduct a Genome Wide Associate Study (GWAS) for primary open angle glaucoma (POAG) in African Americans. To apply genetic tools to the structural and function testing in order to improve understanding of the genetics of POAG in the African American population.
Role: Co-Investigator

R01EY019869 (Multi-PI: Zangwill/Girkin/Liebmann) **02/01/2010-**
01/31/2016 National Eye Institute/University of California (San Diego)
African Descent and Glaucoma Evaluation (ADAGES II): Glaucoma Progression
The goal of this project is to systematically assess progression of visual field and structural measurements of the optic nerve in participants followed in the ADAGES study.

R01EY018926 (Multi-PI: Downs/Girkin) **04/01/2008 - 03/31/2016**
National Institutes of Health, National Eye Institute
Age- and Race-related Changes in Optic Nerve Head (ONH) Structure and Biomechanics
This project will to determine age- and race-related differences in 3D ONH morphometry and biomechanics and will elucidate the role of age and African ancestry in the pathophysiology of glaucomatous damage.

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: Bamman, Marcas M

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

POSITION TITLE: Professor, Departments of Cell, Developmental, & Integrative Biology; Medicine; and Neurology. Director, UAB Center for Exercise Medicine. Director, Core Muscle Research Laboratory, Birmingham/Atlanta VA Geriatric Research, Education, and Clinical Center

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
Kansas State University, Manhattan, KS	BS	05/1989	Exercise Science
University of Alabama at Birmingham, AL	MA	08/1990	Exercise Physiology
University of Florida, Gainesville, FL	PhD	08/1996	Physiology

A. Personal Statement

I am very happy to collaborate with Dr. Lazar on his study, **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,** which is a collaborative proposal between two Evelyn F. McKnight Brain Institutes. As Director of the UAB Center for Exercise Medicine (UCEM, >215 members), I have been fostering and leading clinical and translational research focused on exercise medicine/rehabilitation and biology since the 1990s, and I have maintained continuous federal research support (NIH, VA, DoD) as PI for 20+ years. Currently I am PI of a NIAMS Clinical Center for the NIH Common Fund MoTrPAC initiative. I have directed several exercise clinical trials including randomized dose-response trials (e.g., NCT02442479), and I am the overall PI or site PI of five, multi-site randomized exercise trials in various phases: (i) molecular transducers of exercise-induced health benefits (NIH U01AR071133, NCT04151199); (ii) total joint arthroplasty rehabilitation (NIH R01HD084124, NCT02628795); (iii) aging with mobility impairment (NIH R01AG046920, NCT02308228); (iv) Parkinson's disease rehabilitation (NIH U01NS113851); and (v) epigenetic determinants of exercise responsiveness (DoD ONR N000141613159, NCT03380923). All of our human studies are biologically driven with the goal of better understanding exercise-induced health benefits in disease prevention, treatment, and rehabilitation. Finally, I have served on >80 federal grant review panels. **In summary, I am fully committed to this pilot study, and I will bring experience and skills that will help ensure its rigor and ultimate impact.**

B. Positions and Honors

Positions and Employment

1993-96 Research Physiologist, Exercise Countermeasures Project, NASA Johnson Space Center
1996-2001 Assistant Professor, Exercise Physiology, Department of Human Studies, UAB
2001-05 Assistant Professor, Department of Physiology and Biophysics, UAB
2001- Investigator, Birmingham/Atlanta VA Geriatric Research, Education, and Clinical Center, Birmingham VA Medical Center
2001- Director, Exercise Clinical Trials Facility and Core Muscle Research Laboratory
2005-10 Associate Professor with tenure, Department of Physiology and Biophysics, UAB
2010- Professor, Department of Cell, Developmental, and Integrative Biology
2011- Director, UAB Center for Exercise Medicine

UAB Center Memberships and Secondary Faculty Departmental Appointments

UAB Center for Exercise Medicine (Director); Center for Clinical and Translational Science; Comprehensive Center for Healthy Aging (Steering Committee); Comprehensive Cardiovascular Center (Steering Committee); Comprehensive Arthritis, Musculoskeletal, Bone, and Autoimmunity Center; Comprehensive Neuroscience Center; Comprehensive Diabetes Center; Nutrition Obesity Research Center; Vision Science Research Center; Diabetes Research and Training Center; Center for Biophysical Sciences and Engineering; Division of Geriatrics, Gerontology, and Palliative Care, Department of Medicine; Department of Neurology.

Other Experience and Professional Memberships

NIH CSR Skeletal Muscle and Exercise Physiology (SMEP) Study Section (2009-13); Associate Editor, *J Appl Physiol* (2017-19); Associate Editor, *Frontiers in Striated Muscle Physiology* (2010-); Over 80 NIH, VA, and NASA Grant Review Panels (2002-); American College of Sports Medicine (ACSM, 1990-); ACSM Board of Trustees (2019-2022); ACSM Science Integration and Leadership Committee (2011-); American Physiological Society (1998-); Gerontological Society of America (1999-2007); NSCA Certified Strength & Conditioning Specialist (1994-); American Society for Gravitational and Space Biology (1995-96); Regular reviewer for more than 20 scientific journals.

Honors

Gwendolyn L. Tinklin Academic Scholarship, Kansas State University (1985-6); Professionals in Human Movement Honorary, Kansas State University (1989); Outstanding Achievement Award, American College of Sports Medicine Texas Chapter (1995); Excellence in Science Award, KRUG Life Sciences, NASA Johnson Space Center (1996); Named New Investigator Award, Obesity Research Center, UAB (1998-2000); Outstanding Alumnus, Kinesiology Program, UAB (1999); Fellow, American College of Sports Medicine (2002); UAB Argus Awards, Best Course Director (Medical Physiology 2004, 2005, 2006, 2007) and Best Course (Medical Physiology 2004, 2005, 2006); President's Award for Excellence in Teaching, UAB (2005); UAB Healthcare Leadership Academy (2010-11); Graduate Dean's Mentorship Award, UAB (2013); *UAHSF Endowed Professor in Regenerative and Translational Medicine* (2019).

C. Contributions to Science

1. Exercise-induced prevention of skeletal muscle atrophy

Early in my training I became quite interested in the mechanism(s) underlying muscle atrophy caused by disuse or lack of sufficient loading, and in developing interventions to prevent atrophy during unloading (e.g., extended bed rest). As PI of a 14-day bed rest trial at NASA Johnson Space Center and UTMB-Galveston, I was the first to demonstrate that substantial myofiber atrophy (~20%) and reductions in muscle function could be completely abrogated with brief exposures to high-intensity contractions (resistance training). This work helped provide a basis for NASA's resistance training hardware development and current inflight exercise countermeasures.

- **Bamman MM**, MSF Clarke, DL Feeback, RJ Talmadge, BR Stevens, SA Lieberman, and MC Greenisen. Impact of resistance exercise during bed rest on skeletal muscle sarcopenia and myosin isoform distribution. *J Appl Physiol.* 84(1):157-163, 1998.
- Clarke MSF, **MM Bamman**, and DL Feeback. Decreased incidence of load-induced myofiber wounding and consequent wound-mediated FGF release during bed rest. *J Appl Physiol.* 85(2):593-600, 1998.
- **Bamman MM**, GR Hunter, BR Stevens, ME Guilliams, and MC Greenisen. Resistance exercise prevents plantar flexor deconditioning during bed rest. *Med Sci Sports Exerc*. 29(11):1462-1468, 1997.
- Ferrando A., K Tipton, **M Bamman**, and R Wolfe. Resistance exercise maintains skeletal muscle protein synthesis during bed rest. *J Appl Physiol.* 82(3):807-810, 1997.

2. Exercise rehabilitation in aging, and molecular regulation of skeletal muscle mass

In the early 2000s I transitioned my interest in muscle atrophy and exercise rehabilitation to human aging, and to mechanisms regulating muscle mass. By integrating exercise clinical trials with cellular and molecular studies, we investigated differential adaptations to resistance training in young and atrophied, older adults, and we were the first to apply K-means cluster analysis as a means of revealing molecular underpinnings of inter-individual response heterogeneity. These studies focused on mechanisms of muscle regrowth (i.e. hypertrophy following atrophy) involving the regulation of translation initiation signaling and muscle stem (satellite) cell activation, and led to research on ribosome biogenesis, as well as exercise prescription dose optimization.

- Stec MJ, Thalacker-Mercer A, Mayhew DL, Kelly NA, Tuggle SC, Merritt EK, Brown CJ, Windham ST, Dell'Italia LJ, Bickel CS, Roberts BM, Vaughn KM, Isakova-Donahue I, Many GM, **Bamman MM**. Randomized, four-arm, dose-response clinical trial to optimize resistance exercise training for older adults with age-related muscle atrophy. *Exp Gerontol*. 2017 Dec 1;99:98-109.
- Stec MJ, Kelly NA, Many G, Windham ST, and **Bamman MM**. Ribosome biogenesis may augment resistance training-induced myofiber hypertrophy and is required for myotube growth in vitro. *Am J Physiol Endocrinol Metab*. 310:E652-61, 2016. PMC4835943.
- Thalacker-Mercer A, Stec M, Cui X, Cross J, Windham ST, **Bamman MM**. Cluster analysis reveals differential transcript profiles associated with resistance training-induced human skeletal muscle hypertrophy. *Physiol Genomics*. 2013 Jun 17;45(12):499-507. PMC3680779.
- Mayhew DL, TA Hornberger, HC Lincoln, and **MM Bamman**. Eukaryotic initiation factor 2Bε induces cap-dependent translation and skeletal muscle hypertrophy. *J Physiol*. 589(Pt12):3023-37, 2011. PMC3139084.

3. Impact of skeletal muscle inflammation susceptibility

In pursuit of mechanisms regulating muscle mass and exercise adaptation, my laboratory was the first to characterize a hyper-inflammatory state in the skeletal muscle of some individuals that likely plays a key role in muscle atrophy and likely must be overcome to induce effective muscle regrowth. Because it is noted independent of circulating inflammatory cytokine levels, and is present in vitro in muscle satellite cells isolated from affected individuals, we named this condition *muscle inflammation susceptibility* (MuIS). We first noted MuIS in aging human muscle, and have since noted MuIS independent of age in some, but not all, total joint arthroplasty patients with end-stage osteoarthritis. MuIS provides the scientific basis for two current R01 exercise clinical trials – in aging and in total joint arthroplasty.

- Thalacker-Mercer A, LJ Dell'Italia, X Cui, JM Cross, and **MM Bamman**. Differential genomic responses in old vs. young humans despite similar levels of modest muscle damage after resistance loading. *Physiological Genomics*. 2010 Feb 4;40(3):141-9. PMC2825766.
- Merritt EK, Stec MJ, Thalacker-Mercer A, Windham ST, Cross JM, Shelley DP, Tuggle SC, Kosek DJ, Kim JS, **Bamman MM**. Heightened muscle inflammation susceptibility may impair regenerative capacity in aging humans. *J Appl Physiol*. 2013 Sep;115(6):937-48. PMC3764621.
- **Bamman MM**, Ferrando AA, Evans RP, Stec MJ, Kelly NA, Gruenwald JM, Corrick KL, Trump JR, Singh JA. Muscle inflammation susceptibility: a prognostic index of recovery potential after hip arthroplasty? *Am J Physiol Endocrinol Metab*. 2015 Apr 15;308(8):E670-9. PMC4398830.
- Yarar-Fisher C, Bickel CS, Oster R, and **Bamman MM**. Heightened TWEAK-NF-kB signaling and inflammation-associated fibrosis in paralyzed muscles of men with chronic spinal cord injury. *Am J Physiol Endocrinol Metab*. 2016 May 1;310(9):E754-61. PMC4888537.

4. Parkinson's disease: Impact of exercise rehabilitation on neuromuscular plasticity

Since 2012 we have been investigating the impact of high-intensity exercise rehabilitation on both motor and non-motor symptoms of Parkinson's disease and its progression. We revealed a novel skeletal muscle histopathological phenotype in Parkinson's disease indicative of extreme denervation—reinnervation motor unit remodeling, and we are the first group to demonstrate remarkable neuromuscular plasticity consequent to high-intensity exercise training, accompanied by clinically meaningful improvements in both motor and non-motor symptoms. In our current trial, we are testing the impact of this intervention on neuroplasticity in the brain, focusing on networks that regulate cognition, sleep, and motor control.

- Lavin KM, Ge Y, Sealfon SC, Nair VD, Wilk K, McAdam JS, Windham ST, Kumar PL, McDonald MN and **Bamman MM**. Rehabilitative impact of exercise training on human skeletal muscle transcriptional programs in Parkinson's disease. *Front Physiol*., 17 June 2020. doi.org/10.3389/fphys.2020.00653
- Lavin KM, Sealfon SC, McDonald MN, Roberts BM, Wilk K, Nair VD, Ge Y, Lakshman Kumar P, Windham ST, **Bamman MM**. Skeletal Muscle Transcriptional Networks Linked to Type I Myofiber Grouping in Parkinson's Disease. *J Appl Physiol*. 2020 Feb 1;128(2):229-240. doi: 10.1152/japplphysiol.00702.2019
- Kelly NA, Hammond KG, Bickel CS, Windham ST, Tuggle SC, **Bamman MM**. Effects of aging and Parkinson's disease on motor unit remodeling: influence of resistance exercise training. *J Appl Physiol*. 2018 Apr 1;124(4):888-898. PMC5972459.

- Kelly NA, Ford MP, Standaert DG, Watts RL, Bickel CS, Moellering DR, Tuggle SC, Williams JY, Lieb L, Windham ST, **Bamman MM**. Novel, high-intensity exercise prescription improves muscle mass, mitochondrial function, and physical capacity in individuals with Parkinson's disease. *J Appl Physiol*. 2014 Mar 1;116(5):582-92. PMC4073951.

5. The future of research in exercise medicine and biology

For the past several years I have had the pleasure of collaborating with outstanding, interdisciplinary teams populated by leaders in the field, in an effort to help define the major knowledge gaps and future research priorities that will reveal mechanistic underpinnings and further propel the evidence base for exercise as front-line medicine in both prevention and disease treatment. Many of these efforts have led to white papers.

- Lavin KM, Roberts BM, Fry CS, Moro T, Rasmussen BB, **Bamman MM**. The importance of resistance exercise training to combat neuromuscular aging. *Physiology (Bethesda)*. 2019 Mar 1;34(2):112-122. doi: 10.1152/physiol.00044.2018
- **Bamman MM**, Cooper DM, Booth FW, Chin ER, Neufer PD, Trappe S, Lightfoot JT, Kraus WE, Joyner MJ. Exercise biology and medicine: innovative research to improve global health. *Mayo Clin Proc*. 2014 89(2):148-53. PMC3972063.
- Neufer PD, **Bamman MM**, Muoio DM, et al. Understanding the cellular and molecular mechanisms of physical activity-induced health benefits. *Cell Metab*. 2015 Jul 7;22(1):4-11.
- Ashish N, **Bamman MM**, Cerny FJ, et al. The clinical translation gap in child health exercise research: a call for disruptive innovation. *Clin Translational Sci*. 2015 Feb;8(1):67-76. PMC4324404.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/marcas.bamman.1/bibliography/41141751/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

U01NS113851 Corcos (PI) 09.25.2019 – 07.31.2024
NIH NINDS
Study in Parkinson Disease of Exercise Phase 3 Clinical Trial: SPARX3
The study objective of this 29-site, international, single-blind Phase III exercise dose-response trial is to establish the efficacy of high-intensity endurance exercise as first-line therapy for recently diagnosed people with Parkinson's disease (PD).
Role: Site PI

FA8650-19-C-7944 Broderick (PI), Bamman (subaward PI) 09.25.2019 – 09.24.2023
DoD DARPA
Peerless Biologic Aptitude
The overarching goal is to develop a disruptive training platform that integrates revolutionary high-information density molecular expression circuits, predictive models and real-time in vivo sensors to increase the biologic aptitude of elite special forces operators and units.
Role: Leader of Technical Area 1: Expression Circuits

U01AR071133 Bamman, Goodpaster, Trappe (MPI) 12.06.2016 – 11.30.2022
NIH NIAMS
The Exercise and Physical Activity Collaborative Team: A Proposed MoTrPAC Clinical Center
The goals are to help lead the NIH Common Fund Molecular Transducers of Physical Activity Consortium (MoTrPAC) as one of six adult clinical centers conducting a large-scale, randomized, controlled trial (RCT) of resistance vs. aerobic exercise training vs. control, accompanied by acute response studies in RCT participants and athletes to generate molecular maps that reveal underpinnings of exercise-induced health benefits.
Role: Contact Principal Investigator

R01HD091155 Sandroff (PD/PI) 02.08.2018 – 01.31.2024
NIH NICHD/NCMRR
Treadmill Walking Exercise Training Effects on Cognition and Brain Function in Multiple Sclerosis: A Systematically-Developed Randomized Controlled Trial
The overarching purpose is to addresses the important and understudied problem of novel interventions for improving cognition and brain health in cognitively-impaired persons with multiple sclerosis (MS).

Role: Co-Investigator

P2CHD086851 Bamman (PD/PI) 09.17.2015 – 06.30.2020 NCE
NIH NICHD/NCMRR, NINDS
National Rehabilitation Research Resource to Enhance Clinical Trials (REACT)
The overarching purpose is to catalyze high-impact, interdisciplinary clinical trials nationally via specialized expertise, core resources, study design and support services, training, education, and pilot funding.
Role: Program Director / Principal Investigator

3P2CHD086851-S1 Bamman (PD/PI) 02.01.2016 – 06.30.2020 NCE
NIH NICHD/NCMRR, NINDS
National Coordinating Center – Medical Rehabilitation Research Resource Network
The purpose is to oversee, coordinate, promote, and help evaluate the national network of six P2C centers that provide access to collaborative expertise particularly relevant to medical rehabilitation research.
Role: Program Director / Principal Investigator

R01HD084124 Bamman, Bridges (MPI) 04.15.2015 – 02.28.2020 NCE
NIH NICHD/NCMRR
Overcoming TWEAK Signaling to Restore Muscle and Mobility after Joint Replacement
The randomized clinical trial tests the hypothesis that progressive resistance training plus adjunctive functional mobility training after THA/TKA will more effectively restore muscle and mobility function to healthy standards than usual care. The aims are grounded on muscle inflammation susceptibility (e.g. TWEAK signaling).
Role: Contact Principal Investigator

N000141613159 Bamman (subaward PI) 09.01.2016 – 08.31.2021
Department of Defense, Office of Naval Research
Precision High-Intensity Training Through Epigenetics (PHITE)
The purpose of this multi-site, dose-response clinical trial is to better understand epigenetic regulation of molecular and physiological processes that drive exercise training adaptations.
Role: UAB Principal Investigator (Contact PI: T. Broderick, Boonshoft Sch. Medicine, Wright State University)

I01RX002745 Bamman (PI) 08.01.2018 – 01.31.2021
VA Rehabilitation R & D Service
Genetics of Osteoarthritis and Joint Replacement Recovery: Key to Precision Rehabilitation
This Gamma project in the VA Million Veterans Project (MVP) will leverage the rich MVP resource to test the overarching hypothesis that genetic variants explain a meaningful proportion of osteoarthritis prevalence, progression to end-stage disease leading to total hip or knee arthroplasty, and recovery success.
Role: Principal Investigator

UL1TR003096 Kimberly (PI) 05.06.2019 – 04.30.2024
NIH NCATS
UAB Center for Clinical and Translational Science
The mission is to address disparities and diseases disproportionately represented within the Deep South as we accelerate discovery to improve human health.
Role: Co-Investigator

R01NS092651 King (PI) 04.01.2016 – 03.31.2021
NIH NINDS
Smad Signaling in Skeletal Muscle as a Biomarker of Disease Progression in ALS
The goal is to characterize the Smad axis of signaling as a muscle biomarker of disease progression in ALS.
Role: Co-Investigator

T32HD071866 Bamman (PD/PI) 09.04.2012 – 04.30.2022
NIH NCMRR
Interdisciplinary Training in Pathobiology and Rehabilitation Medicine
The goal is to develop burgeoning scientists into future leaders in translational rehabilitation research.
Role: Program Director / Principal Investigator

UAB center grant Bamman (PI) 10.01.2019 – 09.30.2024
UAB Center for Exercise Medicine
The primary mission is to cultivate interdisciplinary research approaches that will form the biological basis underlying optimal exercise treatment strategies for specific diseases and disorders.
Role: Center Director

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: **Tatjana Rundek**

eRA COMMONS USER NAME (credential, e.g., agency login): **TR89XX**

POSITION TITLE: Professor of Neurology and Public Health Sciences, Vice Chair of Clinical Research, Director of Clinical Translational Research Division, University of Miami Miller 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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of Zagreb, Croatia	BS	09/1979	06/1983	Applied Mathematics
Medical School U of Zagreb, Croatia	MD	09/1984	06/1989	Medicine
Medical School U of Zagreb, Croatia	MS	08/1989	06/1991	Epi/Bioinformatics
Ludwig-Maximillian U, Munich, Germany	PhD	08/1991	05/1995	Neuroscience
Medical School U of Zagreb, Croatia	Residency	06/1991	06/1994	Neurology
Grossharden Spital Munich, Germany	Fellow	07/1994	07/1995	Stroke
Columbia University, New York, NY	Fellow	01/1998	06/2000	Stroke/Epidemiology

A. Personal Statement

I will serve as a site PI for this pilot proposal with a primary function of study oversight and liaison between the UAB and UM Evelyn F. McKnight Brain Institutes. The study will leverage the resources and infrastructure of the Evelyn F. McKnight Brain Institutes (MBI) at both UAB and UM as well as close collaborations between the directors of the MBIs, Dr. Ron Lazar at the UAB and Dr. Rundek as scientific MBI director at UM. I will provide my leadership and expertise in brain vascular hemodynamics and vascular contribution to cognitive impairment. As Scientific Director of the Evelyn F. McKnight Brain institute (MBI), I will utilize imaging and analytical infrastructure and resources of MBI needed for this project. I am a neurologist, neuroscientist and epidemiologist with an extensive experience in vascular neurology and neuroimaging studies. I serve as Executive Vice Chair of Research in neurology and direct Clinical Translational Research Division. At the institutional level, I am Director of MS in Clinical Translational Investigation, co-Director of CTSI KL2 and Translational workforce development, and co-Director of AlzSTARS education program of 1FL ADRC together with Dr. Smith at UF. I have a 25+year track record of NIH funding as PI, collaborative investigator, and research mentor. I have been conducting cross-disciplinary research in aging and brain health and disease for the past 20 years using neuroimaging. I have been a productive investigator with over 400 publications in the area of atherosclerosis and cognitive decline in aging populations. I am a true team scientist and clinical researcher with established extensive collaborations on the large NIH-funded studies with multiple national and international research groups. My current clinical translation research portfolio focuses on vascular biomarkers of age-related cognitive decline. I believe my expertise, skills, and qualifications make me well suited to participate in this project.
I have extensively collaborated and published with Dr. Jay Wang, my UM collaborator on this project, and these four peer reviewed publications highlight our collaborations and my experience relevant for this project:

1. 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. PMC3628415
2. 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.
3. Fleysher R, Lipton ML, Noskin O, Rundek T, Lipton R, Derby CA. White matter structural integrity and transcranial Doppler blood flow pulsatility in normal aging. Magn Reson Imaging. 2018 ;47:97-102. PMC5828865
4. 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.

B. Positions and Honors

Positions and Employment

1994-96	Assistant Professor of Neurology	Dept. of Neurology, University of Zagreb, Croatia
1994-00	Stroke Attending	Department of Neurology, University of Zagreb, Croatia
1996-98	Associate Professor of Neurology	Dept. of Neurology, University of Zagreb, Croatia
2002-07	Assistant Professor of Neurology	Columbia University, New York, NY
2002-07	Director & Attending, Vasc Laboratory	Columbia University Medical Center, New York, NY
2007-11	Associate Professor of Neurology	Miller School of Medicine, Univ. of Miami, Miami, FL
2007-	Director, Clinical Translational Div	Miller School of Medicine, Univ. of Miami, Miami, FL
2010-	Vice Chair, Clinical Translational	Miller School of Medicine, Univ. of Miami, Miami, FL
2011-	Professor of Neurology (with tenure)	Miller School of Medicine, Univ. of Miami, Miami, FL
2014-	Director, MS Clinical Translational	Miller School of Medicine, Univ. of Miami, Miami, FL
2016-17	Interim Scientific Director, McKnight Brain Institute (MBI)	Miller School of Medicine, Univ. of Miami, Miami, FL
2018-	Scientific Director, MBI	Miller School of Medicine, Univ. of Miami, Miami, FL

Other Experience and Professional Membership

2009-14	President, the Neurosonology Community of Practice, Am Institute of Ultrasound in Medicine
2012-	Member, the Board of the Directors, Intersocietal Accreditation Committee (IAC)-Vascular
2012-	Consulting Editor of *Stroke*
2013-	Editorial Board Member of *Neurology, Cerebrovascular Disease, J of Ultrasound in Medicine*
2014-	Member, the Clinical Standards Committee, Am Institute of Ultrasound in Medicine (AIUM)
2015-	Secretary, the Executive Committee, Intersocietal Accreditation Committee (IAC)-Vascular
2015-	Reviewer, NIH sections ZHL1 CT-K (C1)1, NHLBI 21, NIH LRP
2016-	Intersocietal Accreditation Committee (IAC), Vascular Testing Board member
2019-	Intersocietal Accreditation Commission (IAC), President elect

Honors

1995	Humbolt Award, Neurosonology Laboratory, University of Ulm, Germany
1996	George Soros Scholarship, Neurology Seminars, University of Krems, Austria
1997-99	Fulbright Award and Scholarship, Neurological Institute, Columbia University, New York, NY
2006-	Nassau Women Physicians Foundation Award for Stroke Research in Women; Long Island, NY
2015	The American Heart Association Core Vitae Award for Stroke
2018-	The Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging

C. Contributions to Science

1. Epidemiology of stroke and stroke disparities. Over the past 25 years I have pursued multi-disciplinary research in stroke epidemiology and stroke heath care disparities. The central findings from this research include the discovery of novel stroke risk factors (e.g., insulin resistance, sleep duration, homocysteine, adiponectin, oral infection and inflammation) in minority populations. Some of these reports were among the first in the literature. We conducted the seminal epidemiological investigation on the role of PFO in stroke and migraine. Our group was the first to report that atorvastatin reduces the serum coenzyme Q10 levels linking it to muscle pain. I am a strong believer in team science and many of my research products are the results of multiple collaborations between various national and international research teams and institutions.

a. **Rundek T**, Gardener H, Xu Q, Goldberg R, Wright C, Boden-Albala B, Disla N, Paik M, Elkind MSV, & Sacco RL (2010). Insulin Resistance and Risk of Ischemic Stroke Among Nondiabetic Women from the Northern Manhattan Study. Arch Neurol**.** 67:1195-200. PMCID: PMC2954671.
b. **Rundek T**, Elkind MS, Di Tullio MR, Carrera E, Jin Z, Sacco RL, & Homma S (2008). Patent Foramen Ovale and Migraine. A Cross-Sectional Study from the Northern Manhattan Study. Circulation. 118:1419-24. PMCID: PMC2737546.
c. **Rundek T**, & Sacco RL (2011). Outcome following stroke. In "Stroke- Pathophysiology, Diagnosis, and Management". Editors: J.P. Mohr, D.W. Choi, J.C. Grotta, B. Weir, P.A. Wolf; Fourth edition, Churchill Livingstone, Elsevier Inc.; Chapter 2: 58-67.
d. **Rundek T**, Naini A, Sacco RL, Coates K, & DiMauro S (2004). Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. Arch Neurol. 61:889-892. PMCID: PMC15210526.

2. Genetic contribution to atherosclerosis and stroke. I have been investigating genetic contribution to carotid disease for the past 10 years as PI of 2 NINDS R01 grants and a NINDS K24 award, and currently as PI of the

NINDS Family study of atherosclerosis, and a site PI of the NINDS SiGN (Ischemic Stroke Genetic Network). In one of my investigations I have taken the approach of extreme phenotypes by investigating genetic profile of individuals with a lot of risk factors but less atherosclerosis than expected as well as those with little to no risk factors but a lot of atherosclerosis. These investigations are now contributing novel findings on genetic and environmental determinants of atherosclerosis and stroke for targeted vascular therapies and prevention of CVD and stroke. I am also an active collaborative investigator of the large stroke consortia MEGASTROKE and others.

a. **Rundek T**, Elkind MS, Pittman J, Boden-Albala B, Martin S, Humphries SE, Hank Juo SH, Sacco RL. Carotid Intima-Media Thickness is Associated with Allelic Variants of Stromelysin-1, Interleukin-6 and Hepatic Lipase Genes: The Northern Manhattan Prospective Cohort Study. Stroke 2002; 333:1420-3. PMCID: PMC2692936.
b. Dong C, Della-Morte D, Wang L, Cabral D, Beecham A, McClendon M, Luca C, Blanton S, Sacco RL, **Rundek T.** Association of the sirtuin and mitochondrial uncoupling protein genes with carotid plaque. PLoS One 2011; 6(11):e27157. PMCID: PMC3210138.
c. Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, the Stroke Genetics Network (SiGN), and the International Stroke Genetics Consortium (ISGC). Identification of additional risk loci for stroke and small vessel disease: a meta-analysis of genome-wide association studies. Lancet Neurol. 2016;15(7):695-707. PMCID: PMC4943223
d. Meschia JF, Arnett DK, Ay H, Brown RD Jr, Benavente OR, Cole JW, de Bakker PI, Dichgans M, Doheny KF, Fornage M, Grewal RP, Gwinn K, Jern C, Conde JJ, Johnson JA, Jood K, Laurie CC, Lee JM, Lindgren A, Markus HS, McArdle PF, McClure LA, Mitchell BD, Schmidt R, Rexrode KM, Rich SS, Rosand J, Rothwell PM, **Rundek T**, Sacco RL, Sharma P, Shuldiner AR, Slowik A, Wassertheil-Smoller S, Sudlow C, Thijs VN, Woo D, Worrall BB, Wu O, Kittner SJ; NINDS SiGN Study. Stroke Genetics Network (SiGN) study: design and rationale for a genome-wide association study of ischemic stroke subtypes. Stroke. 2013; 44(10):2694-702. PMCID: PMC4056331.

3. Extracranial and intracranial imaging markers of carotid disease. Vascular imaging has been my primary tool to investigate atherosclerosis. I have been in the field of ultrasound for over 25 years. I was trained in ultrasound technologies by the inventor of transcranial Doppler (TCD) Dr. Rune Aaslid in early 80's and have been a part of an international brain hemodynamic research group since. I coauthored the first consensus document on carotid ultrasound imaging. I have been a part of large international collaborations on the progression of subclinical atherosclerosis (PROG-IMT, USE-IMT). I have applied arterial vessel wall principles to improve arterial compliance using a new technique of integrated power Doppler and changes of vessel wall diameter during cardiac cycle. In addition, I have helped advancing the field of brain circulation investigations using TCD to sleep breathing disorders, vascular cognitive impairment, memory loss and dementia. I am a Board member of IAC (Intersocietal Accreditation Commission), the largest US accreditation body that sets the standards for performance of clinical ultrasound, CT/MRI and cardiac Echo. I am president elect of IAC Vascular Testing Board. I have been an advocate for advancing quality of clinical ultrasound and improving access to high-quality clinical ultrasound in medicine.

a. **Rundek T**, Blanton SH, Bartels S, Dong C, Raval A, Demmer RT, Cabral D, Elkind MS, Sacco RL, & Desvarieux M. Traditional risk factors are not major contributors to the variance in carotid intima-media thickness. Stroke 2013; 44:2101-8. PMCID: PMC3738011.
b. **Rundek T**, Arif H, Boden-Albala B, Elkind MS, Paik MC, Sacco RL. Carotid plaque, a subclinical precursor of vascular events: the Northern Manhattan Study. Neurology. 2008; 70:1200-7. PMCID: PMC2831775.
c. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen TP, Sander D, Plichart M, Catapano AL, Robertson CM, Kiechl S, **Rundek** T, Desvarieux M, Lind L, Schmid C, DasMahapatra P, Gao L, Ziegelbauer K, Bots ML, Thompson SG; PROG-IMT Study Group. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet. 2012; 379(9831):2053-62. PMCID: PMC3918517.
d. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engström G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, **Rundek T**, Salonen JT, Sitzer M, Stehouwer CD, Witteman JC, Moons KG, Bots ML. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA. 2012; 308(8):796-803. PMCID: PMC4523149.

Complete List of Published Work in MyBibliography: https://www.ncbi.nlm.nih.gov/pubmed/?term=rundek

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

NIH/NINDS R01 NS 40807 Rundek (PI) 05/01/02-09/30/23
Family Study of Stroke Risk and Carotid Atherosclerosis
The major goal of this study is to evaluate heritability and genetic linkage of novel vascular risk factors such as carotid intima-media thickness among the families of high-risk Caribbean Hispanics.

NIA P30AG066506 Golde (PI) 06/15/20- 04/30/25
1Florida Alzheimer's Disease Research Center (1FL ADRC)
1FL AD Science Training to Advance Research Success (AlzSTARS) Rundek (Co-Director)
The major goal of program is to create and maintain a longitudinal clinical cohort of aging individuals with memory complains, detailed cognitive and brain MR imaging phenotypes, and infrastructure for further clinical research and research education in cognitive aging, MCI and AD.
Role: Co-Director of AlzSTARS Research Education Core (REC) and Co-Investigator of UM Clinical Core

FL DOH 9AZ25 Rundek (PI) 01/01/19-12/31/21
Brain Vascular Imaging Phenotypes, Vascular Comorbidities and the Risk for Alzheimer Disease: The Florida VIP Study of AD Risk (PI)
The major goal is to determine imaging and vascular phenotypes associated with increased risk of AD.

NIH/NINDS R37 NS 029993-11 Sacco (PI) 02/01/03-01/31/20
Stroke Incidence and Risk Factors in a Tri-Ethnic Region
The major goals of this project are to determine the effect of vascular risk factors on cognitive impairment and subclinical MRI findings in a prospective cohort study from 3 race-ethnic groups from Northern Manhattan.
Role: Co-Investigator

U54TR002736-01 Sacco (PI) 06/28/18-05/31/23
1KL2TR002737 Rundek (PI) 06/28/18-05/31/23
NIH/NCATS
Miami Clinical and Translational Science Institute
The goals of the Miami CTSI are to improve the quality and efficacy of clinical and translational research, advance team science and culturalized health sciences.
Role: Co-Director of Translational Workforce Development

NIH/NIMHD R01MD012467 Rundek, Sacco, Romano (MPI) 10/30/17-06/30/22
Disparities in Transition of Care after Acute Stroke Hospitalization
The objective of this study is to identify disparities in post-hospital stroke care among stroke patients hospitalized for acute stroke hospitalization and discharged to home in Florida and to develop effective initiative to reduce disparities in post-hospital stroke care.

NIH/NINDS U10 NS 077423 Benatar, Sacco (MPI) 09/30/11-08/31/18
University of Miami: Network of Excellence in Neuroscience Clinical Trials (NeuroNEXT)
The goals of this proposal are to enhance quality and efficiency of NIH trial implementation at the University of Miami and to leverage existing institutional strengths to enhance NeuroNEXT consortium activities.
Role: Training Director

NIH/NIA P01 AG003949 Lipton, Derby, Rundek (MPI) 07/1/11-06/30/20
The Albert Einstein Study Program Project in Aging
This is a Cerebral Hemodynamics Study of Aging of the AES program project aimed to study the vascular mechanisms of normal aging, MCI and dementia using TCD challenge test.
Role: PI of TCD Core

NIH/NINDS U10 NS086528 Romano (PI) 09/30/13-07/31/23
Miami Regional Coordinating Center for NINDS Stroke Trials Network
The major goal of this award is to function effectively as a Regional Coordinating Center for the NINDS stroke trials and to enhance quality and efficiency of NINDS stroke trial implementation at the Miami site.
Role: Training Director

NIH/NHLBI N01-HC65234 Schneiderman (PI) 06/01/14-05/31/24
Hispanic Community Health Study-Study of Latinos (HCHS-SOL) Miami Field Center

The HCHS/SOL is a multi-center epidemiologic study designed to determine the role of acculturation in disease prevalence and to identify health risk factors in Hispanics/Latinos.
Role: Adjudication Core Investigator

ARISTA-USA CV185-564 Rundek (PI) 01/04/17-12/31/20
BMS
Disparities in Stroke Outcomes and Care Delivery in Patients with Atrial Fibrillation: FLiPER-AF Study
This study will examine race-ethnic and sex disparities in health care delivered to stroke patients with AF and their outcomes after acute stroke hospitalization.

Completed Research Support

NIH/NIDA R01DA034589 Kumar (PI) 09/15/14-08/31/19
Predictive Biomarkers of CVD Risk in Diverse HIV-1+ Cocaine Abusers
Role: Co-Investigator

NIH/NGRI Columba GENIE (GENomic Integration with EHR) Weng (PI) 09/01/15-05/31/19
Role: Co-Investigator

NIH/NIDCR R01 DE 13094 Desvarieux (PI) 06/15/06-05/31/19
Oral Infections, Carotid Atherosclerosis and Stroke (INVEST)
Role: Co-Investigator

NIH/NINDS R01 NS084288-01A1 Romano (PI) 04/01/14-03/31/19
Mechanisms of Early Recurrence in Intracranial Atherosclerotic Disease (MyRIAD)
Role: Co-Investigator

AHA 15MM26340000 Rundek (PI) 07/01/15-06/30/18
NCRP Winter 2015 Mentor / AHA Mentee Award
This award supported Dr. Rundek's mentorship activities for 2 AHA fellows (from John Hopkins & UT Huston).

AHA14BFSC17690000 Sacco (PI) 04/01/14-03/31/18
AHA-ASA/Bugher Foundation Center of Excellence in Stroke Collaborative Research
Role: Training Director

NIH/NINDS U54 NINDS SPIRP U54NS081763 Sacco (PI) 01/01/13-12/31/18
Stroke Prevention/Intervention Research Program in Hispanics
Role: PI of Core C and PI of Supplement- Stroke Outcome in Women

NIH/NINDS R01 NS 065114 Rundek (PI) 07/01/10-06/30/17
Novel Factors for Unexplained Phenotypes of Subclinical Carotid Atherosclerosis

NIH/NINDS K24 NS 062737 Rundek (PI) 09/30/09-08/31/17
Genetic Determinants of Extreme Phenotypes of Subclinical Atherosclerosis

NIH/NINDS U01 NS 069208 Kittner (PI) 04/01/10-03/31/16
The NINDS International Stroke Genetics Consortium Study: Ischemic Stroke Genetics
PI: S. Kittner, U Maryland; T. Rundek, Site PI
Role: Site PI; Sign Publication Committee lead

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)	START DATE MM/YYYY	END DATE MM/YYYY	FIELD OF STUDY
Zhejiang Medical University, Hangzhou, Zhejiang	MD	09/1983	07/1988	Medicine
University of Waterloo, Waterloo, ON	MS	04/1999	06/2000	Vision Science
University of Waterloo, Waterloo, ON	PHD	07/2000	07/2003	Vision Science

A. Personal Statement

I have a broad background in vision research and electronic engineering, especially on advanced ophthalmic imaging and human studies. As an assistant professor at the University of Rochester, I have learnt 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 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 8 years, I have worked on vascular imaging of the eye and developed the methods and hardware to image microvasculature and microcirculation in the retina. 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 180 papers in top journals. Currently, I am the co-director of scientific experimental imaging laboratory at the Bascom Palmer Eye Institute and managing my own 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 in this proposed project.

1. Lin Y, Jiang H, Liu Y, Gameiro GR, Gregori G, Dong C**,** Rundek T, **Wang J.** Age-related alterations in retinal tissue perfusion and volumetric vessel density. Investigative Ophthalmology and Vision Research. 2019;60:685-693. PubMed PMID: 30786280; PubMed Central PMCID: PMC6383727.
2. Gameior GR, Jiang H, Liu Y, Deng Y, Sun X, Nascentes B, Baumel B, Rundek T, **Wang J**. Retinal tissue hypoperfusion in patients with clinical Alzheimer's disease. Eye Vis (Lond). 2018;17;5:21. PubMed PMID: 30140712; PubMed Central PMCID: PMC6097197.
3. 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 Focl Thinning of the Ganglion Cell-Inner Plexiform Layer in Patients with Mild Cognitive Impairment and Alzheimer's Disease J *Alzheimers Dis* 64(4):1261-127. PubMed PMID: 30040712.
4. Wei Y, Jiang H, Shi Y, Qu D, Gregori G, Zheng F, Rundek T, **Wang J**. Age-Related Alterations in the Retinal Microvasculature, Microcirculation, and Microstructure. Invest Ophthalmol Vis Sci. 2017 Jul 1;58(9):3804-3817. PubMed PMID: 28744554; PubMed Central PMCID: PMC5527847.

B. Positions and Honors

Positions and Employment

1988 - 1990 Resident, Department of Ophthalmology, Hangzhou First Hospital, Hangzhou
1991 - 1995 Ophthalmologist, Department of Ophthalmology, Hangzhou First Hospital, Hangzhou
1996 - 1999 Professional Affairs Manager, Johnson & Johnson Vision Products, China, Shanghai
2001 - 2001 Research Associate, University of Waterloo, Waterloo, ON

2003 - 2006	Research Assistant Professor, University of Rochester, Department of Ophthalmology, Rochester, NY
2006 - 2010	Assistant Professor, Bascom Palmer Eye Institute, University of Miami, Miami, FL
2008 -	Assistant Professor, 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
2010 - 2012	Associate Professor, Bascom Palmer Eye Institute, University of Miami, Miami, FL
2012 - 2020	Associate Professor (Tenured), Bascom Palmer Eye Institute, University of Miami, Miami, FL
2020 -	Professor (Tenured), Bascom Palmer Eye Institute, University of Miami, Miami, FL

Other Experience and Professional Memberships

1999 -	Member, Association for Research in Vision and Ophthalmology (ARVO)
2001 -	Fellow, American Association of Optometry (FAAO)
2001 -	Member, American Association of Ophthalmology (AAO)
2002 -	Member, Contact Lens Association of Ophthalmologists (CLAO)
2003 -	Fellow, International Association of Contact Lens Research (IACLE)
2005 -	Member, International Society of Contact Lens Research (ISCLR)

Honors

2000	Irvin M. & Beatrice Borish Student Travel Fellowship Award, American Academy of Optometry
2001	Travel award, International Society of Contact Lens Research
2003	Best Paper in Session, American Society of Cataract & Refractive Surgery
2003	Travel award, International Society of Contact Lens Research
2004	Pearson Medal for Creative Research, University of Waterloo

C. Contribution to Science

1. Through my more than 15 years of career development, I significantly contribute 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 clinic 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 PMID: 26030106; 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 PMID: 22191923; 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. Ke B, Mao X, Jiang H, He J, Liu C, Li M, Yuan Y, **Wang J**. The relationship between high-order aberration and anterior ocular biometry during accommodation in young healthy adults. Invest

Ophthalmol Vis Sci. 2017;58:5628-5635. PubMed PMID: 29094166; PubMed Central PMCID: PMC5667401.

b. 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 PMID: 22902211; PubMed Central PMCID: PMC3505244.

c. 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 PMID: 24787861; PubMed Central PMCID: PMC4083049.

d. 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 PMID: 26030106; 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 easily imaging the conjunctival microvascular network and small vessel blood flow velocity, which can be 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. Recent development of segmentation software enables automatic segmentation of 6 maps of retinal sub-layers. Furthermore, I adapted the RFI for the first time for imaging the retinal tissue perfusion and adapted OCT angiography to image volumetric vessel density.

   a. Lin Y, Jiang H, Liu Y, Gameiro GR, Gregori G, Dong C**,** Rundek T, **Wang J.** Age-related alterations in retinal tissue perfusion and volumetric vessel density. Invest Ophthalmol Vis Sci. 2019;60:685-693. PubMed PMID: 30786280; PubMed Central PMCID: PMC6383727.

   b. Gameior GR, Jiang H, Liu Y, Deng Y, Sun X, Nascentes B, Baumel B, Rundek T, **Wang J**. Retinal tissue hypoperfusion in patients with clinical Alzheimer's disease. Eye Vis (Lond). 2018;17;5:21. PubMed PMID: 30140712; PubMed Central PMCID: PMC6097197.

   c. Wei Y, Jiang H, Shi Y, Qu D, Gregori G, Zheng F, Rundek T, **Wang J**. Age-Related Alterations in the Retinal Microvasculature, Microcirculation, and Microstructure. Invest Ophthalmol Vis Sci. 2017 Jul 1;58(9):3804-3817. PubMed PMID: 28744554; PubMed Central PMCID: PMC5527847.

   d. Hu L, Shi C, Jiang H, Shi Y, Sethi Z, **Wang J**. Factor affecting microvascular responses in the bulbar conjunctiva in habitual contact lens wearers. Invest Ophthalmol Vis Sci. 2018;59:4108-4114. PubMed PMID: 30098199; PubMed Central PMCID: PMC6088803.

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 improve 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 PMID: 21060257; 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 PMID: 22496787; 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 PMID: 26047051; PubMed Central PMCID: PMC4457137.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/jianhua.wang.1/bibliography/48035987/public/?sort=date&direction=descendi ng

D. Additional Information: Research Support and/or Scholastic Performance Ongoing

Research Support

R01 R01NS111115A1 Detre and Wang (MPI) 08/15/2019-03/31/2024
NIH/NINDS
Novel Biomarkers of Small Vessel Contributions to Vascular Cognitive Impairment and Dementia (VCID) This project will investigate the biological and technical determinants of PVWM CBF and OCTA-derived microvascular density, associate changes in retinal microvasculature with brain WML and perfusion, and preliminarily show their predictive value in SVD by correlating baseline measures with longitudinal changes in healthy and clinical cohorts.

Florida Department of Health 20A05 Jiang (PI) 4/14/2020 – 6/30/2023
Ed and Ethel Moore Alzheimer's Disease Research Program
Retinal biomarkers for monitoring vascular contributions to Alzheimer's disease
This project investigates the retinal biomarkers for monitoring vascular contribution to AD. Role:
Co-investiagtor

Sun_UM_1, Sun Yat-sen University collaboration award Wang, Jianhua (PI) 10/01/15-09/30/20
Clinical applications of advanced ophthalmic imaging
The goal of this study is to develop and apply advance ophthalmic imaging for clinical research in ophthalmology.
Role: PI

Food UM 01, Global Healthcare Focus LLC Wang, Jianhua (PI) 01/01/17-12/31/20
Food supplement Ocufolin on retinal blood flow velocity in patients with vascular retinopathy
The goal of this study is to determine retinal blood flow velocity in patient with vascular retinopathy after taking food supplement Ocufolin for 6 months.
Role: PI

CR-5879 Johnson & Johnson Vision Care Jiang, Hong (PI) 03/1/2018-12/11/20
Lid-wiper microvascular response as an indicator of contact lens discomfort
The goal of this study is to characterize lid-wiper microvasculature in contact lens wear. Role:
Co-investigator

Imaging Research, Bausch & Lomb, CooperVision and Allergan Wang, Jianhua (PI) 01/01/06-12/31/23
Advanced ophthalmic imaging research
Unrestricted grants from Bausch & Lomb, CooperVision and Allergan for developing advanced ophthalmology imaging lab and clinical research.
Role: PI

Completed Research Support

NMSS, National Multiple Sclerosis Society Jiang, Hong (PI) 04/01/16-03/31/19
The Role of retinal microvascular impairment on Neurodegeneration in Multiple Sclerosis
The goal of this study is to determine the role of retinal microvascular impairment on neurodegeneration in MS. Role:
Co-Investigator

UM DBA 2019-3 Jiang, Hong (PI) 8/1/18-7/31/19
Novel retinal microvascular biomarker of vascular contribution to dementia The
goal is to run a preliminary study to bridge NIH grant application.

Role: Co-investigator

JJVC, Johnson & Johnson Vision Product Jiang, Hong (PI) 12/01/14-
12/31/16 Conjunctival microvascular characterization of contact lens wear
The purpose is to characterize conjunctiva microvascular in contact lens wearer
Role: Co-Investigator

UM SAC 2015-27R1, University of Miami Wang, Jianhua (PI) 01/01/15-06/30/16 Conjunctival Microvasculature and its association with tear protein biomarkers in dry eye syndrome
The purpose is to characterize conjunctival microvasculature in dry eye
Role: PI

NANOS, North American Neuro-Ophthalmology Society Jiang, Hong (PI) 04/15/15-10/15/16 Retinal microvascular alteration as a possible biomarker in Alzheimer's disease
The purpose of this project is to characterize the retinal microvascular dysfunction and optical properties of Retinal nerve fiber layer in AD patients.
Role: Co-Investigator

R21 EY021012-01 National Eye Institute (NEI) Wang, Jianhua (PI) 08/05/10-07/31/12 Magnetomotive optical coherence tomography for molecular imaging of the eye
The purpose of this project is to develop magnetomotive OCT for molecular imaging of the eye.
Role: PI

R03 EY016420-02 National Eye Institute (NEI) Wang, Jianhua (PI) 09/30/05-08/31/08 Characterization of Tear Dynamics
The purpose of this project is to characterize human tear dynamics using custom built optical coherence tomography
Role: PI

Allergan UM Contract, Allergan Wang, Jianhua (PI) 07/25/11-12/31/15 Tear dynamics after Restasis treatment in dry eye patients
This project is a clinical trial for further studying tear dynamics after treatment with Restasis in dry eye patients.
Role: PI

R21EY021336-01A1, National Eye Institute (NEI) He, Jichang (PI) 12/01/11-12/01/14 Optical coherence tomography equipped wavefront system for studying accommodation
The purpose of this project is to develop optical coherence tomography equipped wavefront system for studying accommodation
Role: Co-Investigator

1R21 EY019742-01A2, National Eye Institute (NEI) Wang, Michael (PI) 08/01/10-07/31/12 Optical reflectometry for tear film measurement
The purpose of this project is to develop a novel method called optical reflectometry for measuring human tear film in a nanometer scale.
Role: Co-Investigator

R03 EY016420-03 National Eye Institute (NEI) Wang, Jianhua (PI) 09/30/05-08/31/08 Characterization of Tear Dynamics
The purpose of this project is to characterize human tear dynamics using custom built optical coherence tomography
Role: PI

TATJANA RUNDEK, MD, PhD
Professor of Neurology and Public Health Sciences
Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging
Scientific Director of the Evelyn F. McKnight Brain Institute
Executive Vice Chair of Research and Faculty Affairs in Neurology
Director, Clinical Translational Research Division

Director, MS in Clinical Translational Investigation
Director, University of Miami CTSI KL2 Program
Miller School of Medicine, University of Miami
1120 NW 12th Street, CRB-1348, Miami, FL 33136
Tel: 305-243-7847; Fax: 305-243-7081
Email: trundek@med.miami.edu

July 23, 2020

Ronald M. Lazar, PhD, FAAN, FAHA
Evelyn F. McKnight Brain Institute at UAB
Department of Neurology
University of Alabama at Birmingham
rlazar@uabmc.edu

Dear Ron,

I enthusiastically support your application entitled ***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,*** which is a collaborative proposal between our two Evelyn F. McKnight Brain Institutes.

This an extremely important pilot study will investigate the effect of aerobic exercise on the relationship between age-related decline in insulin-like growth factor-1 (IGF-1) levels and greater microvascular rarefaction and vascular resistance in individuals with hypertension, which may considerably affects late-life cognitive decline. This pilot is very much needed to advance our research to the next level of understanding of cognitive performance in aging and provide basis for an effective lifestyle intervention to maintain cognitive function into old age.

As a Scientific Director of the University of Miami Evelyn F. McKnight Brain Institute, I will provide our institute infrastructure and resources needed to successfully complete this pilot, help with project oversight and liaison with Dr. Wang at the University of Miami Bascom Palmer Eye Institute. I will also participate in the data analyses and interpretations as well as in preparations of the presentations and publications resulting from this research. This pilot project will continue our long lasting research collaboration and strengthen the collaboration across our two McKnight Brain Research Foundation sites.

Thank you so much for including University of Miami Evelyn F. McKnight Brain Institute to this highly innovative and relevant pilot project. I am looking forward working with you and across our Institutes for successful and productive collaboration that will advance age-related cognitive research.

Kind regards,

Tatjana Rundek, MD, PhD

UNIVERSITY OF MIAMI

Office of Research Administration
1320 South Dixie Highway
Gables One Tower
Room #650, Locator Code 2960
Coral Gables, Florida 33146
305-284-3952

July 24, 2020

Ronald M. Lazar, PhD, FAHA, FAAN|UAB
Evelyn F. McKnight Endowed Chair
Professor of Neurology and Neurobiology
Director, Evelyn F. McKnight Brain Institute at UAB
Director, Division of Neuropsychology
Department of Neurology
The University of Alabama at Birmingham
SC 650K | 1720 7th Avenue South | Birmingham, AL 35294
Phone: 205-934-2334
FAX: 205-975-3094
E-mail: rlazar@uabmc.edu

Re: McKnight Brain Research Foundation Pilot Study "**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**"

Dear Dr. Lazar,

We are pleased to confirm the support and participation of Department of Ophthalmology at the University of Miami, Miller School of Medicine as a consortium contractor on your grant submission to the McKnight Brain Research Foundation entitled the "**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**".

By signing this letter, the University of Miami is certifying that we meet all requirements for receiving the grant. Consequently, this letter serves all required assurances. Dr. Jianhua Wang will serve as the Subcontract Principal Investigator here at UM and will perform all relevant services through his work on this contract.

We look forward to working with you on this new grant.

Sincerely,

K. Brandon Strickland, Executive Director
Office of Research Administration
University of Miami

Jianhua Wang, MD, PhD, Principal Investigator
Department of Ophthalmology
University of Miami

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: 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

Principal Investigator(s): Ronald M. Lazar, PhD

Institutions: University of Alabama at Birmingham (Prime Site), University of Miami

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:2

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

The proposed study would use a 10-week, remotely monitored, HIIT training on stationary cycle intervention in older adults with hypertension. The project would explore baseline associations between retinal microvascular density, GF, and cognitive function and the response of hypertension to this intervention. The proposed study is well positioned to provide pilot data for future, larger scale grant applications using exercise interventions to improve neurocognitive outcomes. The proposal is quite strong but could be improved if the link between OCT-A and WMH was strengthened, and the HIIT intervention was better justified. For example, a 1:1 ratio is not the most common work/rest ratio for HIIT and its justification is not clear. Finally, the requirements for equipment access, a cycle ergometer at home or gym and smart phone proficiency, may limit the diversity of the participants. Given the prevalence of hypertension in low SES and other underrepresented populations, methods to address this should be considered (e.g. a loaner ergometer).

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 significance is high. It is clear that effective means of impacting hypertention are important for improving neurocognitive outcomes. The use of OCT-A has the potential

to demonstrate microvasclular changes in response to intervention at a lower cost and in a more acceptable manner than MRI for WMH.

Weaknesses

-

2. Investigator(s):1

Strengths

- **No weakness**

Weaknesses

-

3. Innovation:3

Strengths

- The use of OCT-A is innovative in this context.

Weaknesses

-

4. Approach:2

Strengths

- The overall approach is sound and should serve the stated ojective of gathering pilot data for a future grant.

Weaknesses

- Given that OCT-A is functioning as something like a proxy for MRI derived WMH, it would have been useful to include baseline WMH measures. Understanding that this is a smaller budget proposal, would it not have been possible to recruit at least a subset of participants who had recent WMH measures?
- The HIIT approach is insufficiently justified. Again, 1:1 is not the most common approach and it is not clear if it was used in the preliminary data (the duration for this data is shorter than the proposed study, so they are clearly not the exact same protocols). While 1:1 has been called HIIT in the litriture, it has also been argued that the 1:2 is the minimium for “HIIT”. It would seem as though the short “rest” period would be more taxing. Further, the “work” periods are quite long for “HIIT”. Again, these choices may be fine, but are not sufficiently justified.
- Recruitment is likely to be biased towards already better represented populations given that participant access to stationary cycle is an enrolment requirement, as is smart phone proficiency sufficient to use polar app.
- Little consideration other than “Research staff will contact participants twice per week to provide feedback and guidance, as needed.” Is given to complince. This is likely to challenge.

- Technical challeges around Smart phone/Bluetooth paring may present additional challeges, has this been used in this population?

5. Environment:1

Strengths

- Excellent cites for the proposed study

Weaknesses

- none

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes:2

Strengths

- Both sites play integral roles.

Weaknesses

- It is not clear that the respective, and complementary, differences in individual sites recruitment potential are being fully exploited.

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

Strengths

- The impact potential is high, being an at home intervention with remote monitoring, that can be done at relatively modest cost.

Weaknesses

- Populations that may be otherwise suitable, and in need of such an interveiton, may be least able to meet the equipment/gym membership requirement.

3. Potential for future NIH funding of the research:2

- If results are pomising, I would expect the funding potential to be high.

MBRF Cognitive Aging & Memory Intervention Pilot Review

Application Title: 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

Principal Investigator(s): Dr. Ron Lazar and Dr. Tatjana Rundek

Institutions: University of Alabama and University of Miami

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

This is well designed pilot study based on premise that hypertension in older adults is partially mediated by growth factor deficiencies that result in abnormal microvascular retinal changes associated with hypertension and worsened cognition. To address this hypothesis, 30 adults with hypertension will undergo baseline assessments to assess relationship between microvascular retinal changes, growth factor, and cognition. This will be followed, after a 4 week washout period, by 10 weeks of at home intensive aerobic training, in order to learn whether improved cardiovascular fitness (VO2max) will influence growth facto, retinal microdensity and cognition. Although only a pilot, this study might benefit from a small nonhypertensive cohort. Strengths include sophisticated approach for measuring retinal microvasculature, the cognitive battery, clear inclusion/exclusion criteria, rationale for participant N, and clearly articulated aims and mapping of data onto these aims, with appropriate analyses. Strong synergy among the Mcknight investigators for completion of this project.

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

- Examination of role of GF deficiencies in microvascular density , hypertension, and cognition
- How exercise might potentially mediate this relationship

Weaknesses

- Prospectively, unclear how this information would be used other than as index or barometer

2. Investigator(s)

Strengths

- Exceptional team of researchers

Weaknesses

- None

3. Innovation

Strengths

- Use of sophisticated measures of retinal density (OCT-A) that provides high resolution 3-D imagesof microvascular density
- Examination of relationship between human growth factor, retinal density, and cognition

Weaknesses

-

4. Approach

Strengths

- Well designed study, rationale for sample size provided, including inclusion/exclusion criteria
- Well articulated procedures for obtaining indices of MVR & IGF
- Appropriate cognitive measures
- Sound design with wash out period
- Appropriate statistical approach that maps onto aims/hypotheses
- Awareness of weaknesses of their study

Weaknesses

- Concerns about cognitive practice effects, though the washout period may potentially be helpful.
- Lack of nonhypertensive control group
- My pull for higher SES participants given the demands of aerobic equipment for participation

5. Environment

Strengths

- Superb

Weaknesses

- None

Additional Criteria

1. Level of collaboration demonstrated between McKnight Brain Institutes

Strengths

- Capitalizes on strengths of UAB & UM (exercise science, cognition, neuro-opthamology)
- Participants will be run at UAB, with contribution of UM in terms of data interpretation/analyses.
- Builds on strength of academic relationships between Drs. Lazar and Rundek

Weaknesses

-

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

Strengths

- Potential is strong given interventional approach of aim 2;

Weaknesses

- Unclear how obtained knowledge would influence broad policy changes above and beyond reinforcing the importance of aerobic exercise

3. Potential for future NIH funding of the research

- Strong depending on results of this pilot study

January 6, 2021

Matthew Burns, MD, PhD
University of Florida College of Medicine
Department of Neurology
1149 Newell Dr.
Gainesville, FL 32610

Dear Dr. Burns,

Congratulations! You have been selected to receive a $150,000 2021 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. Your project dates are July 1, 2020-June 30, 2022.

You are invited to attend several events that will be held by the McKnight Brain Research Foundation, American Brain Foundation, and American Academy of Neurology during the duration of your award. More details will be provided as they become available.

The Senior Research Coordinator from the American Academy of Neurology Institute will be in contact with you shortly with more details and instructions to move this process forward. In the meantime, please feel free to contact Julia Miglets-Nelson, PhD, Grant Writing and Program Manager at the American Brain Foundation at jmiglets-nelson@americanbrainfoundation.org or 612-928-6315 with any questions.

Again, congratulations on being selected for this award. We look forward to seeing the results of your research.

Sincerely,

Michael L. Dockery, MD
Board of Trustees Chair
McKnight Brain Research Foundation

Jane B. Ransom
Executive Director
American Brain Foundation

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: Burns, Matthew Robert

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

POSITION TITLE: Clinical Fellow

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Oberlin College, Oberlin, OH.	B.A.	1996	2001	Physics
Oberlin College, Oberlin, OH.	B.A.	1996	2001	Religion
University of Illinois-Chicago College of Medicine, Chicago, IL.	M.D.	2005	2014	Medicine
University of Illinois-Chicago College of Medicine, Chicago, IL.	Ph.D.	2007	2014	Anatomy and Cell Biology
Northshore University Health System, Evanston, IL.	n/a	2014	2015	Internship, Medicine
University of Chicago Medical Center, Chicago, IL.	n/a	2015	2018	Residency, Neurology
University of Florida, Fixel Center for Neurological Diseases, Gainesville, FL.	n/a	2018	2020	Fellowship, Movement Disorders

A. Personal Statement

My long-term career goal is to translate my previous training in brain machine interface and electrophysiology, viral vectors, and neurodegenerative disease through K and R level extramural support into therapies for patients with movement disorders and dementia. I believe the outstanding support and expertise of my team of mentors, this training environment, and the APDA Cotzius Memorial Fellowship mechanism is the ideal combination to advance these goals.

Early in my scientific training I worked as a lab technician in the primate laboratory of Dr. Lee Miller performing single unit recordings in awake behaving monkeys of the primary motor cortex and cerebellum. The goal of this work was to understand the signaling properties of neurons that control movement, and use that understanding to implement neuronal ensemble-controlled prosthesis. This training provided exposure to electrophysiology as well as the scientific questions surrounding brain-machine interface and neuronal control of movement.

During medical school, my interest in the pathogenesis of neurodegeneration grew as a close family friend struggled and ultimately succumbed to complications of Parkinson's disease. Motivated by this experience, I took a leave from medical school to pursue a Ph.D. in the molecular mechanisms of neurodegeneration. I worked in the labs of Drs. Scott Brady and Gerardo Morfini, internationally recognized experts in axonal transport and neurodegeneration with long-standing records of NIH funding and trainee support. I developed expertise in microscopy and biochemistry of the squid giant axon at the Marine Biological Laboratory in Woods Hole, MA., as well as molecular, biochemical, and cell biology techniques. Finally, I established and developed expertise in viral vectors, using a lentiviral vector to develop a monoclonal cell line model of Hereditary Spastic Paraplegia (HSP). Using these techniques, I challenged the loss-of-function model of mutations in HSP by showing that mutations in one isoform of the gene SPAST result in a pathogenic gain-of-function activation of the kinase CK2 and a dysregulation of axonal transport. This work resulted in a first author publication, a first author review, and a book chapter. My graduate work also provided rigorous training in manuscript and grant writing and editing, as well as conference presentation and public speaking skills.

I have also completed clinical training in neurology at The University of Chicago Department of Neurology, where I published a first author manuscript, a review, and twice won outstanding resident presentation at the Barry G. W. Arnason Research Symposium. I completed residency in June of 2018 and have completed fellowship training in movement disorders at the internationally recognized Fixel Center for Neurological Diseases at The University of Florida (UF), where I was awarded the Parkinson's Foundation Institutional MDS Fellowship for the academic years 2018-2020, a Mangurian Foundation research award, and am currently a Pepper Foundation Scholar through the UF Institute on Aging.

I hope to pursue further translational research at the McKnight Brain Institute at The University of Florida with the ultimate goal of winning K and subsequent R level support. Sufficient protected time for research beyond the fellowship period makes support essential. I have assembled an internationally recognized group of mentors with specific expertise in the techniques, pathophysiology, and scientific questions in this proposal as well as strong records of successful K and R grant recipient mentorship. I hope this support will be the foundation of a career as a physician scientist and research into better care and new treatments for patients with neurodegenerative disease.

1. ***Burns MR**, McFarland N*. Current Management and Emerging Therapies in Multiple System Atrophy. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics. Accepted, 2020;
2. ***Burns MR**, Chiu SY, Patel B, Mitroponopolis SG, Wong JK, Ramirez-Zamora A*. Advances and Future Directions of Neuromodulation in Neurological Disorders. Neurology Clinics. Accepted, 2020;
3. *Okromelidze L, Tsuboi T, Eisinger RS,* ***Burns MR,*** *Charbel M, Rana M, Grewal SS, Lu CQ, Almeida L, Foote KD, Okun MS, Middlebrooks EH*. Functional and Structural Connectivity Patterns Associated with Clinical Outcomes in Deep Brain Stimulation of the Globus Pallidus Internus for Generalized Dystonia. AJNR Am J Neuroradiol. 2020 Mar;41(3):508-514. doi: 10.3174/ajnr.A6429. Epub 2020 Feb 13. PubMed PMID: 32054614; PubMed Central PMCID: PMC7077906.
4. *Leo Lanfranco*, Carina Weissman*,* ***Matthew Burns*,*** *Yuyu Song, Minsu Kang, Scott Brady, Peter Baas†, Gerardo Morfini†*, Mutant spastin proteins promote deficits in axonal transport through an isoform-specific mechanism involving casein kinase 2 activation, Human Molecular Genetics (2017). *co-first-authors.

B. Positions and Honors

Positions and Employment

2001-2002	Math, physics, and music teacher, St. Gregory The Great High School, Chicago, IL.
2002-2004	Lab Technician, Laboratory of Dr. Lee Miller, Feinberg School of Medicine
2004-2005	KAPLAN test prep teacher, MCAT and GRE
2008	Neuroanatomy teaching assistant, UIC College of Medicine Dept. of Anatomy and Cell Biology
2011-2013	Adjunct Professor of Neuroscience, Liberal Arts Dept., School of the Art Institute of Chicago
2016-2018	MERITS Program Scholar, University of Chicago Pritzker School of Medicine
2018-2020	Parkinson's Foundation Institutional MDS Fellowship Award recipient.

Other positions and Professional Memberships

Honors

2005-2006	Illinois State Senate General Assembly Medical School Tuition Scholarship
2006	American Academy of Neurology Medical School Student Summer Research Fellowship
2006-2007	Elected UIC Medical School Class Secretary
2016	Outstanding PGY-II Presentation, Barry G. W. Arnason Research Symposium
2018	Outstanding PGY-IV Presentation, Barry G. W. Arnason Research Symposium

Memberships in Professional Societies

2008-present American Society for Neurochemistry

2010-present Society for Neuroscience
2014-present American Academy of Neurology
2018-present International Parkinson and Movement Disorders Society

C. Contributions to Science

1. **Early Career:** My research career began with work in an undergraduate applied quantum mechanics seminar that produced a review of formulations of quantum mechanics for which I contributed the review of the Feynman Path Integral formulation. I then took the quantitative skills I developed in the electrophysiology lab of Dr. Lee Miller. I trained primates to play "center-out task" video games to assess motor cortex and cerebellum control of limb and hand movement, designed and built 2D robot arm training device for primate use, performed data acquisition for brain-machine interface optimization experiments, designed epidural electrode array for implantation and recording from motor cortex, and assisted in motor cortical electrode array implantation surgeries for primate subjects.
   a. *Styer DF, Balkin MS, Becker KM,* ***Burns MR****, Dudley CE, Forth ST, Gaumer JS, Kramer MA, Oertel DC, Park LH, Rinkoski MT, Smith CT, and Wotherspoon TD* (2002). 9 Formulations of Quantum Mechanics. Am. J. Phys. **70** (3).

2. **Graduate Career:** Completed doctoral research in the labs of Drs. Scott Brady and Gerardo Morfini; Designed and executed experiments to understand the role of fast axonal transport in neurodegenerative diseases including the hereditary spastic paraplegias; Developed expertise in cellular, mouse, and squid models of neurodegenerative disease in part through work at The Marine Biology Labs in Woods Hole, MA; Optimized and regularly applied lentiviral gene therapy and antibody-based techniques; Presented laboratory data and new developments in the field at lab meetings, departmental seminars, and national and international conferences; Contributed to manuscript, RO1, and private foundation grant writing, editing, and submission.
   a. *Leo Lanfranco*, Carina Weissman*,* ***Matthew Burns*,*** *Yuyu Song, Minsu Kang, Scott Brady, Peter Baas†, Gerardo Morfini†*, Mutant spastin proteins promote deficits in axonal transport through an isoform-specific mechanism involving casein kinase 2 activation, Human Molecular Genetics, (2017). *co-first-authors.
   b. *Morfini GA,* ***Burns M****, Binder LI, Kanaan NM, LaPointe N, Bosco DA, Brown RH Jr, Brown H, Tiwari A, Hayward L, Edgar J, Nave KA, Garberrn J, Atagi Y, Song Y, Pigino G, Brady ST*. Axonal transport defects in neurodegenerative diseases. J. Neurosci. 2009 Oct. 14; 29(41) :12776-86.
   c. ***Matthew R. Burns****, Brian Rogers, Peter Baas, Scott Brady, and Gerardo Morfini* (2010) Pathogenic Spastin Inhibits Fast Axonal Transport through a kinase-dependent mechanism. Society for Neuroscience 40th annual meeting, San Diego, CA. November 13th-17th, 2010.
   d. ***Matthew R. Burns****, Joanna M. Solowska, Shirley Rainier, Scott T. Brady, Peter Baas, John K. Fink, and Gerardo Morfini* (2009) Development and Optimization of Bicistronic Lentiviral Vectors Expressing Spastin Isoforms and Mutations**.** Society for Neuroscience 39th annual meeting, Chicago, IL. October 17th – 21st, 2009.

3. **Postdoctoral Career:** Since completing my graduate work, I have continued my research interest in mechanisms of neurodegeneration with a specific focus on cognitive and behavioral symptoms of Parkinson's disease and dementia. I have also pursued work in the area of neuromodulation and recently received internal funding to support development of a high field MR-compatible microfluidics optrode for experimental electrophysiology, optogenetics, and imaging in rodent models of parkinsonisms and dementia. Finally, I am a sub-investigator on a randomized, double-Blind, placebo-controlled multiple dose study to assess efficacy, safety, tolerability, and pharmacokinetics of ABBV-8E12 in Progressive Supranuclear Palsy as well as sub-investigator on the NIH funded 'Human Thalamocortical Network in Tourette Syndrome' trial.
   a. *Barry Setlow, Shelby L. Blaes,* ***Matthew R. Burns,*** *R. Joseph Dragon, & Caitlin A. Orsini*. Using rodent models to understand interactions between gambling and substance use, in submission, 2019

b. *Bonnie M. Scott, Robert S. Eisinger,* ***Matthew R. Burns****, Michael S. Okun, Aysegul Gunduz & Dawn Bowers*. Co-occurrence of apathy and impulse control disorders in Parkinson's disease**,** in submission, 2019.
c. *Elkouzi A, Tsuboi T,* ***Burns MR,*** *Eisinger RS, Patel A, Deeb W*. Dorsal GPi/GPe Stimulation Induced Dyskinesia in a Patient with Parkinson's Disease. TremorOther Hyperkinet Mov. 2019; 9. doi: 10.7916/tohm.v0.685

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1zg5bwYlhRLkP/bibliography/40400733/public/?sort=date&direction=ascending

D. Additional Information: Research Support

Pepper Scholars award (Burns: PI) 11/1/2020 – 11/1/2022
Mesocorticolimbic dysfunction and modulation of cognitive and behavioral impairment in a rat model of aging and synucleinopathy.
Role: PI

Mangurian (Burns: PI) 01/01/2020-12/31/2020
UFF Project
Modulation of Synuclein Pathology Through Induction of Gamma Band Oscillations in a Mouse Model of DLB
We hypothesize that treatment of a synucleinopathy mouse model with multisensory gamma stimulation will slow disease progression as measured through imaging and histopathology.
Role: PI

SPECIFIC AIMS: Aging is the single greatest risk factor for neurodegenerative disorders like Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). These *age-related* disorders are associated with loss of dopamine mediated reciprocal projections between deep brain nuclei to cortex and other forebrain targets[1-4] leading to brain-wide network dysfunction.[5-11] Such dysfunction induces motor symptoms including tremor, slowness, and stiffness, but can also cause cognitive and behavioral impairments in working memory, executive functions, and motivation which patients rate as debilitating and undertreated.[12-16] The explicit role of dopamine depletion and aging in the pathogenesis of these cognitive and behavioral symptoms remains poorly understood.

Deep brain stimulation (DBS) is a highly effective treatment for motoric symptoms in PD but benefit in cognition has been lacking. DBS targeting for cognition thus far has lacked detailed mechanistic guidance, and the chosen anatomic targets have failed to show clear benefit. In addition, DBS programming of cognitive symptoms would be challenging. The efficacy of DBS depends upon the ability to tune stimulation parameters to individual needs. Motor symptoms such as rigidity or tremor can be quickly and accurately assessed during a clinic visit, allowing for rapid identification of effective DBS settings to remediate these symptoms. Applying this approach to cognitive symptoms is a more challenging problem, however, because repeatedly asking patients if they feel more or less impulsive, apathetic, or mnemonically compromised is unlikely to be clinically useful. Moreover, most cognitive assessments do not have the sensitivity or test-retest validity to be useful during a single visit, and repeated cognitive testing is often prohibitively burdensome on patients.

Despite these challenges, however, recent clinical trials suggest DBS modulation of the mesocorticolimbic network, in which the dopaminergic ventral tegmental area (VTA) modulate a set of targets including prefrontal cortex (PFC), has been successful in improving depression and impulsivity.[8,17,18] Evidence suggests VTA dopamine (DA) signaling is compromised in normal aging[19-24] and that DA depletion in brain regions such as prefrontal cortex (PFC) can induce cognitive deficits.[25-29] As such, DBS may hold potential to promote cognition in conditions in which DA signaling is compromised. It is necessary, however, to (1) determine the role of aging and dopaminergic network dysfunction in cognition, (2) identify the key mechanistic network targets for neuromodulation that can modulate cognition and (3) develop biomarkers that provide accurate signatures of network function and cognitive ability that can be used for optimizing DBS parameters to effectivity treat cognitive deficits.

Imaging biomarkers of network dysfunction hold great promise as neural signatures of cognitive and affective symptoms in aging and disease.[30,31] Such biomarkers may be useful to identify appropriate brain sites for neuromodulation of cognitive deficits as well as response to chronic stimulation. VTA outputs have a different pattern of projections from the nigrostriatal substantia nigra.[32] The VTA DA neurons modulate several cortical networks that drive cognition and behavior, and in particular can modulate PFC, a brain region which supports executive functions that are compromised in both aging and PD.[25-29] **The objective** of this proposal is to use a well-characterized aged rodent model to determine the roles of aging and functional loss of mesocorticolimbic DA network changes detectable by fMRI that align with behavioral deficits, and whether stimulation of PFC can remediate such imaging and behavioral dysfunction. Our **rationale** is that these experiments will provide pre-clinical verification that brain stimulation is a useful treatment for cognitive symptoms. These experiments will evaluate the PFC as a target for therapeutic neuromodulation, as well as define imaging and behavioral biomarkers of network-specific cognitive dysfunction needed to quantify therapeutic benefit in future studies. **I hypothesize** that age- and experimentally induced loss of DA neurons will induce characteristic changes in brain-wide network activity that strongly associate with behavioral deficits, and that such deficits will be rescued by stimulating neuronal activity in PFC.

Aim 1: To determine how both normal aging and dopamine depletion in aging alter brain-wide network activity, and whether such alterations are rescued by prefrontal cortex stimulation.

Resting state fMRI can be used to characterize brain-wide patterns of neural activity that are characteristic of a range of neuropsychiatric conditions and aging.[33,34] We will use resting state fMRI in rats to determine the brain-wide patterns of neural network activity that are characteristic of young, aged control, and aged VTA-lesioned rats. At the same time, we will determine whether optogenetic stimulation of PFC can restore network activity in aged rats to a "young-like" state, and/or restore activity in aged lesioned rats to an aged control-like state.

Aim 2: To determine how both normal aging and dopamine depletion in aging alter executive function and motivation, and whether such alterations are rescued by prefrontal cortex stimulation.

Rats from Aim 1 will be tested in behavioral tasks assessing working memory, executive functions and reward motivation, all of which are altered in normal aging as well as neurodegenerative conditions including PD and DLB.[35,36] Optogenetic stimulation of PFC will be conducted in each behavioral task to determine whether such stimulation reverses age- and lesion-induced behavioral alterations. Both behavioral alterations and the effects of PFC stimulation will be linked to the patterns of brain-wide activity determined under Aim 1.

BACKGROUND: My mentors have successfully established a currently available aged rat model[35-38] that is amenable to targeted VTA lesions, providing a platform to understand how both normal aging and mesocorticolimbic DA pathology interact to influence cognitive and behavioral symptoms characteristic of human aging and PDD. My mentors have also successfully implemented *in vivo* optogenetic approaches in aged rats, and have used these approaches to define temporally distinct contributions of PFC to cognition.[37] Optogenetics is a well-established experimental model of DBS stimulation,[39,40] and affords compatibility with high field MRI.

A foundational goal in neuroscience is to understand how behavior and disease are 'encoded' in distributed brain networks. Pathological patterns of brain-wide network activity and their behavioral correlates are poorly understood but could be useful as markers of disease and efficacy of clinical interventions. CNS networks of higher cortical functions such as complex movements, memory, and executive function are orchestrated by deep brain structures.[41-43] Indeed, cortical dysfunction and behavioral deficits seen in both aging and PDD result from degeneration of deep brain nuclei. Beyond PDD, DBS is increasing being recognized as an approach that can benefit behavioral outcomes in a number of other disorders.[41,44-47] Intriguingly, network dysfunction as measured by fMRI is disrupted in aging and is associated with cognitive decline.[34,48] Nevertheless, relatively little attention has been given to the possibility that DBS could offer cognitive benefits in older populations, including those with age-associated disorders such as PDD and those with non-dementia-related cognitive deficits.

Although PDD is often characterized by degeneration of DA substantia nigra neurons, this disease also includes degeneration of DA neurons in ventral tegmental area (VTA).[1] Moreover, disruptions of VTA DA signaling in aging and experimental models can impair cognition and motivation.[19-24] Specifically, the VTA participates in the mesocorticolimbic network with projections to ventral striatum and PFC.[26,28,49-53] Loss of VTA input to PFC is thought to alter and impair these functions,[54-58] and electrical stimulation of VTA has been shown to modulate PFC.[59]

Despite initial optimism for treatment of cognitive impairment with DBS, the results of clinical trials to date have been mixed.[60-62] Notably, these studies have largely targeted the degenerating node in the network instead of affected downstream nodes. This approach is akin to targeting the substantia nigra to treat PD motor symptoms rather than downstream targets such as subthalamic nucleus or pallidum that yield the greatest efficacy. The VTA DA neurons project to PFC and there is initial data to indicate that DBS modulation of PFC-associated circuits can influence depression and impulsivity.[8,17,18] Together, these data suggest that neuromodulation for cognitive and behavioral deficits in aging and PDD warrant rigorous evaluation and offer substantial translational potential.[8,17,63-66]

APPROACH:

Aim 1: Experiments will employ young and aged Fischer 344 x Brown Norway F1 hybrid rats. The rats will undergo surgery to receive sham or dopamine-specific lesions of VTA through stereotactic injection of 6-OHDA as in previous work.[67,68] During the same surgery, rats will receive bilateral injections into the prelimbic portion of the medial PFC (the rodent homologue of human dorsolateral PFC)[36,69] of viral vectors containing channelrhodopsin (AAV-CaMKIIα-hChR2-mCherry) or a control construct (AAV-CaMKIIα-mCherry), with optic fibers targeting the same region for light delivery, as in my mentors' previous work.[37,70] Group sizes (for each of the three groups (young sham control, aged sham control, and aged VTA lesioned) X ChR2 vs. control construct; n=8/group, N=48 total) were chosen based on our labs' previous experience with similar group comparisons for both neuroimaging[71-73] and the behavioral tasks to be used in Aim 2.[35,74,75] All rats, stereotaxic surgical training, viral vectors, imaging time, and equipment for optogenetics will be provided through mentors' support. After surgical recovery and sufficient time for viral expression, rats will be evaluated during resting state 11.7T fMRI as in previous work from the Febo lab[72,73,76,77] to compare network activity between sham and lesioned animals, both in the presence and absence of optogenetic PFC stimulation. Note that the design of fMRI experiments will allow testing of multiple stimulation parameters in the same rats, to allow comparison of the effects of different stimulation frequencies.

Analysis. Resting state networks will be assessed using methods previously published by the Febo lab.[71-73] Briefly, fMRI datasets for each subject will be averaged to increase signal to noise, fitted to a 'boxcar' (on/off) model function of hemodynamic response, then first pass t-test (cluster-size corrected) will be used to determine response brain regions. A mixed effects linear model analysis (with familywise error correction) will then be used to determine statistical significance between lesioned and sham control animals, under both PFC stimulation and non-stimulation conditions.

Expected Results. I expect a blunted fMRI BOLD signal in PFC as well as PFC-associate network nodes such as ventral striatum and dorsal anterior cingulate cortex in aged and aged-VTA lesioned rats as compared to young controls. This would suggest reduced somatodendritic activity in the region, which would reduce output to downstream targets.[78] I further expect that with optogenetic stimulation of VTA neurons, PFC BOLD signal

responses will increase in magnitude in aged and aged-VTA lesion animals. This is turn will increase BOLD activity in downstream targets in ventral striatum and dorsal anterior cingulate.

Aim 2: Evidence suggests that degeneration of the VTA contributes to non-motor symptoms of PD, and that they participate in a forebrain circuit including PFC that regulates cognitive and executive functions and motivation. The relationship of pathology in these nuclei to specific behavioral impairments and the ability of circuit modulation to rescue these impairments has been little-studied in the context of aging. To address this issue, the same rats used for Aim 1 will be tested sequentially for working memory (delayed response task), impulsivity (intertemporal choice task) and motivation (progressive ratio task) as conducted previously in our lab.[35,37,74] In each task, rats will be tested in both the presence and absence of optogenetic PFC stimulation. The design of these experiments allows for extended within-subjects testing, to enable comparison of the effects of multiple stimulation parameters. Response latencies in each task and open field activity will be used to assess potential motoric effects of the lesion/PFC stimulation. Following completion of experiments, rats will be euthanized for histological assessment of lesions and optic fiber placements as in our labs' previous work.[37,70,79,80]

Analysis. Data from each task will be analyzed using multi-factor ANOVA, with age/surgical condition as a between-subjects variable and PFC stimulation condition (on or off) as a within-subjects variable.

Expected Results. On the basis of my mentors' previous work in aged rats,[35,36,38] I predict that aged-sham rats will exhibit modest deficits in working memory and reward motivation, as well as reduced impulsivity, compared to young-sham rats. On the basis of data in PD patients, I predict that aged-lesioned rats will exhibit further deficits in working memory and reward motivation compared to aged-shams, as well as greater impulsivity. Finally, I predict that PFC stimulation will rescue deficits in both aged-sham and aged-lesioned rats, and that the magnitude of this rescue will be greater in aged-lesioned rats.

STRENGTHS AND LIMITATIONS: The proposed techniques have analogues in patients, providing a guide to more focused, hypothesis-driven future clinical work with similar functional network imaging and behavioral assessments, as well as experimental DBS targeting. All techniques are available and optimized at the University of Florida, and well-established through peer-reviewed publications by those mentors' long-standing and productive collaborations. The involved mentors have committed all the necessary resources. In addition, the toxin-induced lesion model is well-accepted, with robust and rapid onset pathology producing loss of neuronal projections analogous to anatomical degeneration observed in PDD and allowing for a rapid time to data collection. A unique strength of this proposal is the immediate availability of aged animals without the need to wait to age the animals for this project, as ongoing work in the lab currently uses these animals. Age represents a fundamental risk factor among neurodegenerative diseases but is largely unrepresented among commonly used animal models. Behavioral assays in working memory, impulsivity, and motivation in rat models provide robust assessment of these cognitive symptoms and have been optimized by my mentors.[35,37,38,79,81,82] Moreover, targeted lesions of VTA allow for isolated assessment of the contribution of dopamine networks in cognitive dysfunction without the confounding motor impairment that accompanies substantia nigra lesions.

Limitations include the relative simplicity of the VTA lesion model and the single node (PFC) targeting for stimulation. One of the limiting factors of fMRI is that the signal arises from hemodynamic mechanisms that are modulated by VTA dopamine. To confirm hemodynamic effects of VTA lesions we will test subsets of rats using a CO2 challenge (mock BOLD response).[83] Future experiments under this project can employ more sophisticated models of synucleinopathies (in collaboration with the Center for Translational Research in Neurodegenerative Disease at University of Florida), and target additional nodes in the networks supporting cognitive/motivational functions impaired by aging and disease (such as ventral striatum and cingulate cortex). Finally, as this proposal represents translational neuroscience research into both PD and dementia, in addition to the McKnight fellowship, I request to be considered for the Neuroscience Research training scholarship, both Parkinson's disease scholarships, as well as the Katzman scholarships, at the committee's discretion.

POTENTIAL FOR FUTURE WORK:

The proposed experiments will lay the foundation for determining the roles of aging and dopamine loss in cognitive impairment, and combining DBS with fMRI to optimize stimulation targets and parameters for addressing cognitive and non-motor sequelae of aging and disease. They will also provide a framework for future, more detailed and cell-specific mechanistic questions directed toward the circuitry of cognitive/motivational dysfunction. Further work will also focus on cingulate orbitofrontal, and ventral striatal targets for neuromodulation. Finally, this work will provide the foundation and preliminary data necessary for a K application to expand the hypothesis that DA tone in aging drives characteristic changes in brain wide network activity that define pathologic changes in behavior and fMRI network activity and can be rescued by optogenetic stimulation of downstream network nodes.

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January 6, 2021

Wai-Ying Yau, MD
Mass General Brigham
Department of Neurology
Mailcode: WACC 8-835
55 Fruit Street
Boston, MA 02114

Dear Dr. Yau,

Congratulations! You have been selected to receive a $150,000 2021 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. Your project dates are July 1, 2020-June 30, 2022.

You are invited to attend several events that will be held by the McKnight Brain Research Foundation, American Brain Foundation, and American Academy of Neurology during the duration of your award. More details will be provided as they become available.

The Senior Research Coordinator from the American Academy of Neurology Institute will be in contact with you shortly with more details and instructions to move this process forward. In the meantime, please feel free to contact Julia Miglets-Nelson, PhD, Grant Writing and Program Manager at the American Brain Foundation at jmiglets-nelson@americanbrainfoundation.org or 612-928-6315 with any questions.

Again, congratulations on being selected for this award. We look forward to seeing the results of your research.

Sincerely,

Michael L. Dockery, MD
Board of Trustees Chair
McKnight Brain Research Foundation

Jane B. Ransom
Executive Director
American Brain Foundation

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: Wai-Ying Wendy Yau

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

POSITION TITLE: Neurology Resident

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
Brigham and Women's Hospital and Massachusetts General Hospital		Expected 06/2021	Residency in Neurology
Brigham and Women's Hospital		06/2017	Internship in Medicine
University of Pittsburgh	M.D.	05/2017	Medicine
University of Michigan	B.S.	08/2009	Biopsychology and Cognitive Science

A. Personal Statement

My AAN proposal aims to quantify the role of white matter injury and tau accumulation in vascular contributions to cognitive aging, and to delineate whether amyloid burden differentially affects these pathways. I have extensive research experience and the technical expertise to successfully carry out the proposed work. I have over a decade of experience in neuroimaging research, with expertise in using structural and functional imaging techniques to study development and aging in normal and disease populations. In particular, my work at UCSD used advanced MRI volumetric techniques to quantify white matter disease burden and found a significant relationship with midlife hypertension in cognitively normal individuals, which sparked my initial interest in vascular risk and its impact on brain health. In a separate project in eating disorders, I used diffusion tensor imaging (DTI) and found persistent alterations in white matter microstructure in individuals recovered from anorexia nervosa. These projects illustrate my readiness to use volumetric and new DTI methods to quantify white matter injury in the current proposal. During medical school, I successfully competed for a Howard Hughes Medical Institute (HHMI) medical research fellowship, where I studied the longitudinal changes in PET and MR imaging markers in autosomal dominant Alzheimer's disease under the mentorship of Dr. William Klunk, a leading expert in PET imaging. This work was published in a first-author manuscript in The Lancet Neurology, highlighting my potential to design, carry out and publish high impact research. In addition, I gained important skills in PET imaging and longitudinal statistical modeling, both of which strongly support my success in carrying out the current proposal. My recent work with Dr. Sperling studied the vascular and lifestyle modifiers of brain injury and cognitive decline, returning to my research interests in vascular impact on brain health while harmonizing with my clinical interests in cognitive neurology.

The proposed project and training plan will be a formative step in my career development as a cognitive neurologist-scientist. Based on the results from the current studies, I plan to submit a K23 proposal to further elucidate upstream mechanisms of vascular contributions to cognitive aging, with the dual objective of identifying earlier biomarkers, and to investigate potential protective mechanism of lifestyle modifiers. This will serve my ultimate career goal of promoting healthy brain aging and delaying cognitive decline and dementia.

1. **Yau WY**, Tudorascu DL, McDade EM, Ikonomovic S, James JA, Minhas D, Mowrey M, Sheu LK, Snitz BE, Weissfeld L, Gianaros PJ, Aizenstein HJ, Price JC, Mathis CA, Lopez OL, Klunk WE (2015). Longitudinal assessment of neuroimaging and clinical markers in autosomal dominant Alzheimer's disease: a prospective cohort study. *The Lancet Neurology*, 14(8), 804-813.
2. **Yau WY**, Bischoff-Grethe A, Theilmann RJ, Torres L, Wagner A, Kaye WH, Fennema-Notestine C (2013). Alterations in white matter microstructure in women recovered from anorexia nervosa. *International Journal of Eating Disorders*. 46(7): 701-8.
3. Rabin JS, Yang HS, Schultz AP, Hanseeuw BJ, Hedden T, Viswanathan A, Gatchel JR, Marshall GA, Kilpatrick E, Klein H, Rao V, Buckley RF, **Yau WW**, Kirn DR, Rentz DM, Johnson KA, Sperling RA, Chhatwal JP (2019). Vascular risk and β-amyloid are synergistically associated with cortical tau. Annals of neurology. 85(2):272-9.
4. Fennema-Notestine C, McEvoy LK, Notestine RJ, Panizzon MS, **Yau WY**, Franz CE, Lyons MJ, Eyler LT, Neale MC, Xian H, McKenzie RE, & Kremen WS (2016). White matter disease in midlife is heritable, related to hypertension, and shares some genetic influence with systolic blood pressure. *NeuroImage: Clinical.* 12:737-745

B. Positions and Honors

Positions and Employment

2003-2004	Research assistant, Laboratory of Dr. Terry Robinson, University of Michigan, Ann Arbor
2004-2010	Research technician, Laboratory of Drs. Jon-Kar Zubieta and Mary Heitzeg, University of Michigan, Ann Arbor
2010-2012	Research Associate, Laboratory of Drs. Christine Fennema-Notestine and Walter Kaye, University of California, San Diego
2012	Summer research fellow, Laboratory of Dr. Beatriz Luna, University of Pittsburgh
2013	Summer research fellow, Laboratory of Dr. William Klunk, University of Pittsburgh
2014-2015	Howard Hughes Medical Institute (HHMI) Medical Research Fellowship, Laboratory of Dr. William Klunk, University of Pittsburgh

Academic and Professional Honors

2004	Phi Beta Kappa Honor Society
2009	High Honors in Biopsychology and Cognitive Science, University of Michigan, Ann Arbor
2012	Physician Scientist Training Program (PSTP), University of Pittsburgh
2014	Howard Hughes Medical Institute (HHMI) Medical Research Fellowship
2016	Alpha Omega Alpha Honor Society
2017	American Academy of Neurology Medical Student Prize for Excellence in Neurology

C. Contributions to Science

I. The impact of vascular risk and lifestyle factors on brain injury and cognitive decline

There is increasing urgency to find modifying factors to slow cognitive decline and the onset of dementia. Consonant with a growing literature, my collaborative work at UCSD and the Sperling lab demonstrates the importance of systemic vascular risk and lifestyle factors on brain health and cognition. In Fennema-Notestine et al., we used multi-channel structural MRI to quantify the burden of white matter disease in a cohort of cognitively normal individuals 56 to 66 years of age. Despite a relative lower burden of white matter disease compared to prior studies in late life, we found a significant relationship between midlife hypertension and the burden of white matter disease, suggesting that white matter markers may be sensitive to early vascular risk related brain injury. My subsequent work in the Rabin et al. studies in the Sperling lab further demonstrates that in cognitively normal older individuals, higher vascular risk is associated with greater cross-sectional tau pathology and longitudinal gray matter atrophy, and that higher amyloid burden has a synergistic effect on these deleterious relationships. Similarly, lower physical activity was associated with increased gray matter atrophy and worse prospective cognitive decline in individuals with high amyloid burden. Collectively, these studies highlight the importance of vascular factors and their interaction with amyloid burden on

neurodegeneration and cognitive decline, and formed the inspiration for the current proposal in addition to highlighting its significance and urgency.

- Rabin JS, Klein H, Kirn DR, Schultz AP, Yang HS, Hampton O, Jiang S, Buckley RF, Viswanathan A, Hedden T, Pruzin J, **Yau WW**, Guzmán-Vélez E, Quiroz YT, Properzi M, Marshall GA, Rentz DM, Johnson KA, Sperling RA, Chhatwal JP (2019). Associations of Physical Activity and β-Amyloid With Longitudinal Cognition and Neurodegeneration in Clinically Normal Older Adults. JAMA neurology. Jul 16.
- Rabin JS, Yang HS, Schultz AP, Hanseeuw BJ, Hedden T, Viswanathan A, Gatchel JR, Marshall GA, Kilpatrick E, Klein H, Rao V, Buckley RF, **Yau WW**, Kirn DR, Rentz DM, Johnson KA, Sperling RA, Chhatwal JP (2019). Vascular risk and β-amyloid are synergistically associated with cortical tau. Annals of neurology. 85(2):272-9.
- Fennema-Notestine C, McEvoy LK, Notestine RJ, Panizzon MS, **Yau WY**, Franz CE, Lyons MJ, Eyler LT, Neale MC, Xian H, McKenzie RE, & Kremen WS (2016). White matter disease in midlife is heritable, related to hypertension, and shares some genetic influence with systolic blood pressure. *NeuroImage: Clinical.* 12:737-745

II. Longitudinal changes of neuroimaging and clinical markers in autosomal dominant Alzheimer's disease

There is growing consensus that the development of Alzheimer's disease (AD) begins with an extended preclinical stage lasting one to two decades before the onset of cognitive symptoms, presenting a potential window for disease-modifying treatments. The dynamic biomarker model proposed a sequence of amyloidosis, neurodegeneration and cognitive decline in the pathogenesis of AD, largely based on cross-sectional evidence. Our study presents the first within-individual verification of this biomarker model, using longitudinal, multi-modal neuroimaging and clinical data from individuals carrying mutations for autosomal dominant Alzheimer's disease (ADAD). Our pooled longitudinal data suggests a sequence of brain amyloidosis, followed by cerebral hypometabolism and hippocampal atrophy, followed by cognitive decline. Importantly, within-individual verification in mutation carriers with the longest follow-up (seven to eight assessments over six to eleven years) revealed sequential phases in ADAD development: 1) active amyloidosis without progressive neurodegeneration, 2) amyloid-plateau without progressive neurodegeneration, 3) amyloid-plateau with neurodegeneration and cognitive decline. Our data provides very strong support for amyloidosis as the earliest progressive component of the biomarker model and further suggest that amyloidosis is largely complete prior to the initiation of progressive neurodegeneration and cognitive decline. These findings support efforts to target early amyloid deposition as a means of secondary prevention in the ADAD population.

- **Yau WY**, Tudorascu DL, McDade EM, Ikonomovic S, James JA, Minhas D, Mowrey M, Sheu LK, Snitz BE, Weissfeld L, Gianaros PJ, Aizenstein HJ, Price JC, Mathis CA, Lopez OL, Klunk WE (2015). Longitudinal assessment of neuroimaging and clinical markers in autosomal dominant Alzheimer's disease: a prospective cohort study. *The Lancet Neurology*, 14(8), 804-813.

III. Alterations in white matter microstructure in women recovered form anorexia nervosa

Individuals suffering from anorexia nervosa (AN) have well-documented brain structural abnormalities including reduced global and regional white matter volumes and densities. More recently, a study using Diffusion tensor imaging (DTI) further showed that AN patients have deficits in microstructural integrity of white matter tracts. My project used DTI to investigate whether such alterations persist following long-term recovery of individuals who suffered from AN. While overall deficits in white matter integrity were not detected in recovered individuals, within group analysis suggested that more severe illness history was associated with worse white matter integrity after recovery. This indicates that severity of illness history may have long-term consequences, emphasizing the importance of aggressive treatment in AN. In addition, recovered AN patients showed lower mean diffusivity in white matter regions important for cognitive control, which was further associated with higher harm avoidance, a core behavioral trait in AN.

- **Yau WY**, Bischoff-Grethe A, Theilmann RJ, Torres L, Wagner A, Kaye WH, Fennema-Notestine C (2013). Alterations in white matter microstructure in women recovered from anorexia nervosa. *International Journal of Eating Disorders*. 46(7): 701-8.

In addition, I contributed to the following functional MRI studies on alterations in reward processing and executive control in adolescents with AN.

- Bischoff-Grethe A, McCurdy D, Grenesko-Stevens E, Irvine LE, Wagner A, **Yau WY**, Fennema-Notestine C, Wierenga CE, Fudge JL, Delgado MR, Kaye WH (2013). Altered brain response to reward and punishment in adolescents with anorexia nervosa. *Psychiatry Research: Neuroimaging*. 214(3): 331-40.
- Wierenga C, Bischoff-Grethe A, Melrose AJ, Grenesko-Stevens E, Irvine Z, Wagner A, Simmons A, Matthews S, **Yau WY**, Fennema-Notestine C & Kaye, WH (2014). Altered BOLD Response during Inhibitory and Error Processing in Adolescents with Anorexia Nervosa. *PloS one*, 9(3), e92017.

IV. Functional neurobiology of addiction risk in children of alcoholics

Children of alcoholics are at an elevated risk for developing alcohol and other substance use disorders. Drugs of abuse activate the mesolimbic reward circuitry in the brain, which is important in the development of addiction. My project used functional magnetic resonance imaging and a monetary incentive delay paradigm to investigate whether children of alcoholics show alterations in the mesolimbic reward circuitry. Our results indicated that children of alcoholics, specifically those who had not demonstrated any problem drinking behavior, showed reduced ventral striatum activation during anticipation of monetary reward and loss. In addition, there was a unique positive association among nucleus accumbens activation, precursive externalizing behavior and alcohol consumption in children of alcoholics. Our results suggest a blunted mesolimbic reward circuitry response to incentive anticipation in children of alcoholics potentially reflects a resilience mechanism and is associated with less alcohol use and behavioral problems. In addition, the close association between brain reward responses, alcohol consumption, and behavioral risk may, in part, underlie the addiction vulnerability in children of alcoholics.

- **Yau WY**, Zubieta J-K, Weiland BJ, Samudra PG, Zucker RA, Heitzeg MM (2012). Nucleus Accumbens Response to Incentive Stimuli Anticipation in Children of Alcoholics: Relationships with Precursive Behavioral Risk and Lifetime Alcohol Use. The Journal of Neuroscience. 32(7):2544-51.

In addition, I contributed to other functional MRI studies focusing on the reward, executive control and emotional regulation circuitries in the same children of alcoholics cohort, as reflected by the following selected co-authored publications.

- Villafuerte S, Heitzeg MM, Foley S, **Yau WY**, Majczenko K, Zubieta JK, Zucker RA, & Burmeister M (2011). Impulsiveness and insula activation during reward anticipation are associated with genetic variants in GABRA2 in a family sample enriched for alcoholism. Molecular Psychiatry. 17(5):511-9.
- Heitzeg MM, Nigg JT, **Yau WY**, Zucker RA, & Zubieta JK (2010). Striatal dysfunction marks preexisting risk and medial prefrontal dysfunction is related to problem drinking in children of alcoholics. Biological Psychiatry. 68(3):287-295.

V. Factors mediating inter-individual variability in placebo-induced analgesia

Activation of endogenous opioid neurotransmission has been shown to mediate placebo-induced analgesia. Substantial variation in the magnitude of these responses was observed between individuals. My project examined the contribution of various stimulus- and individual-related factors to the variability in the neurochemical responses to placebo administration. Our results showed that the affective qualities of pain, the individuals' pain sensitivity as well as internal affective state contributed to 40–68% of the variance in the regional endogenous opioid responses to placebo.

- Zubieta J-K, **Yau WY**, Scott DJ, Stohler CS (2006). Belief or Need? Accounting for individual variations in the neurochemistry of the placebo effect. *Brain Behavior and Immunity*. 20(1):15-26.

D. Additional Information: Research Support and/or Scholastic Performance

Completed Research Support

2014-2015 Howard Hughes Medical Institute (HHMI) Medical Research Fellowship

Quantifying Vascular Contributions to Cognitive Aging Mediated by White Matter Injury and Tau

Specific Aims

Growing epidemiological and neuropathological data indicates that systemic vascular risk factors and vascular injury are common and potent contributors to cognitive aging and emergence of clinically recognized cognitive impairment[1-3]. Recent work in our lab demonstrated that higher systemic vascular risk was associated with prospective cognitive decline in a group of clinically normal elderly[3]. Importantly, those with high vascular risk and concomitant elevated brain β-amyloid (Aβ) levels showed the steepest cognitive decline, consistent with the synergism between vascular and Alzheimer's disease (AD) pathologies in leading to cognitive impairment noted on neuropathological studies[4-6]. This interaction poses a significant threat to healthy cognitive aging, given the pervasiveness of vascular disease (>75% of US adults over age 60 suffer from hypertension alone[7]) and the increasing prevalence of Aβ pathology with age (up to 41% of cognitively normal 80 to 90 year-old by PET imaging[8]). However, the mechanisms underlying vascular contributions to cognitive decline remains unclear, limiting our ability to develop effective, targeted interventions to promote healthy brain aging.

While studies support a link between vascular risk and white matter (WM) pathologies[9], and between WM injury and cognitive impairment[10-12], longitudinal studies are lacking and none has delineated the role of longitudinal WM injury in context of Aβ burden. Interestingly, a recent study from our group showed that vascular risk score interacts synergistically with Aβ to promote cross-sectional tau burden[13]. This raises the possibly of a different pathway that relies on vascular risk interacting with Aβ to promote tau pathology and cognitive decline; however, verification with longitudinal tau data is critically needed. Moreover, while algorithmic cardiovascular risk scores are easy to implement and capture risk of cognitive decline, they do not identify distinct biological pathways that mediate vascular effects on cognitive aging. Accordingly, biologically-based markers, such as plasma markers with positive and negative effects on endothelial health, are needed to inform the underlying mechanisms. This project leverages longitudinal neuroimaging, cognitive, and clinical data, in addition to plasma samples from the Harvard Aging Brain Study (HABS), a community cohort of 298 cognitive normal elderly followed for up to 9 years, to elucidate the mechanisms underlying vascular contributions to cognitive aging. I will test my hypothesis that **WM injury and tau accumulation are distinct mechanisms underlying vascular contributions to cognitive decline, with WM injury acting independently from Aβ, while tau mediates the synergistic effects between vascular risk and Aβ**.

Aim 1: Determine the impact of systemic vascular risk on longitudinal WM injury and tau accumulation
Macro- and micro-structural WM injury will be respectively measured on MRI by WM hyperintensity (WMH) and peak width of skeletonized mean diffusivity (PSMD), a recently-developed diffusion tensor imaging (DTI) measure more sensitive to cerebral small vessel disease[14]. Tau pathology will be measured by ^{18}F-flortaucipir PET in two regions of interests (ROIs): 1) entorhinal cortex (ET), a region of earliest tau pathology in aging, and 2) inferior temporal cortex (IT), a region in which cerebral small vessel disease is associated with tau deposition in vascular cognitive impairment[15]. Systemic vascular risk will be measured by Framingham Heart Study general cardiovascular disease (FHS-CVD) risk score[16]. Using linear mixed-effects models, I will model FHS-CVD in relation to longitudinal WMH, PSMD, ET tau and IT tau, controlling for covariates and examining interactions with Aβ burden. Hypothesis 1: Higher FHS-CVD predicts increased longitudinal WM injury independently from Aβ, but acts synergistically with higher Aβ to predict increased longitudinal tau burden.

Aim 2: Define the relationship between novel vascular plasma markers, longitudinal WM injury and tau
Using ultra-high sensitivity immunoassays, we recently identified novel plasma markers from pro-angiogenic (VEGFR2 composite), anti-angiogenic (VEGFR1 composite), and endothelial dysfunction (ICAM/VCAM composite) pathways that independently predict prospective cognitive decline in clinically normal older adults, especially those with elevated Aβ (manuscript in preparation). I will model these vascular plasma composites in relation to longitudinal WMH, PSMD, ET tau and IT tau, along with interactions with Aβ. Hypothesis 2: Lower pro-angiogenic and higher anti-angiogenic and endothelial dysfunction plasma composites predict greater longitudinal WM injury independent of Aβ, and greater longitudinal tau accumulation only in those with high Aβ.

Aim 3: Quantify mediating mechanisms of vascular contributions to cognitive decline in aging
Using structural equation modeling (SEM) (Figure 1), I will quantify the combined effects of vascular risk and injury on longitudinal cognitive performance, examining white matter injury, tau accumulation, in addition to gray matter atrophy as potential mediators, and determine whether Aβ burden moderates these relationships. Hypothesis: WM injury and tau accumulation are independent mechanisms of vascular contributions to cognitive aging, with WM injury acting independently from Aβ, while tau pathway is synergistic with high Aβ.

Significance

While there is increasing recognition of the significance and burden of vascular contributions to cognitive aging, our ability to identify those most at risk and effectively target the underlying process is limited by our understanding of the mediating mechanisms. This proposal leverages up to 9 years of longitudinal imaging, cognitive and clinical data from a community cohort of normal elderly, a necessary but rare resource, to address the gap in knowledge of whether WM injury and tau accumulation are distinct mechanisms of vascular contributions to cognitive decline, and how Aβ moderates each pathway. It further incorporates novel plasma markers to improve on demographic and clinical information-based vascular risk scores to better capture vascular effects on cognition, inform the pathobiology of imaging markers, and shed light on protective and pathological mechanisms. If my hypotheses prove correct, WM injury and tau may be potential distinct targets for intervention in Aβ-negative and Aβ-positive individuals respectively, to prevent or reverse vascular contributions to cognitive aging. Promoting healthy brain aging will have magnified downstream effects of delaying cognitive impairment and dementia. Recent estimates suggest that delaying dementia onset by 5 years could reduce future prevalence by one third[17], carrying immense emotional and financial benefits for individuals, families, and health care systems. Additionally, increasing evidence points to the role of midlife vascular risk on development of late life cognitive decline[18,19]. While this presents an exciting window for intervention, it also highlights the need to identify early biomarkers sensitive to detect change within the short time frame of an intervention study, as change in cognition may not be evident for a decade or more. Thus, this proposal has the potential to help establish markers of WM injury and tau burden as candidate primary end points in future early intervention/prevention trials, and expedite testing of potential disease modifying strategies for both vascular and AD contributions to age-related cognitive decline.

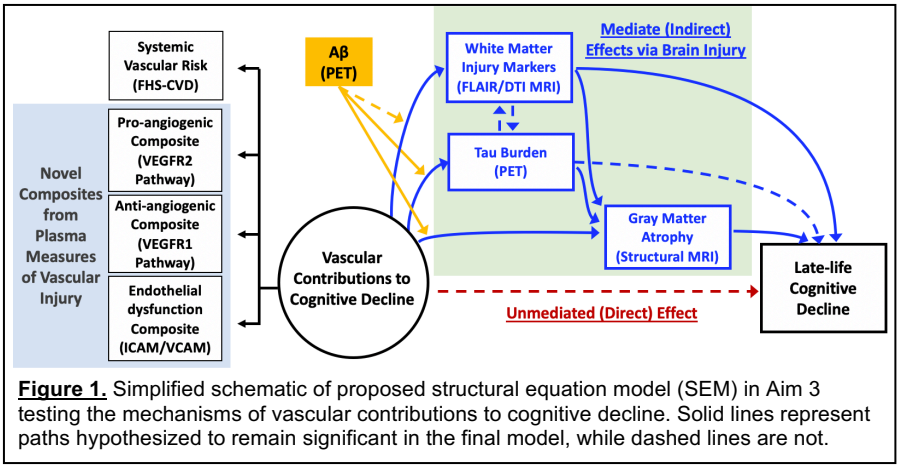

Figure 1. Simplified schematic of proposed structural equation model (SEM) in Aim 3 testing the mechanisms of vascular contributions to cognitive decline. Solid lines represent paths hypothesized to remain significant in the final model, while dashed lines are not.

Preliminary data: Figure 2 shows our prior finding of a synergistic interaction between higher FHS-CVD and Aβ burden on greater cross-sectional IT tau burden[13], supporting our hypothesis of a tau-mediated pathway in vascular contributions to cognitive decline that relies on synergistic interactions with Aβ. In contrast, our preliminary data showed that while higher baseline PSMD predicted greater prospective cognitive decline (p=0.02), there was no significant interaction with Aβ (p=0.99), providing support for a WM injury pathway that is independent from Aβ. Figure 3 shows that lower pro-angiogenic and higher anti-angiogenic plasma maskers are respectively synergistic with high Aβ to promote prospective cognitive decline (manuscript in preparation).

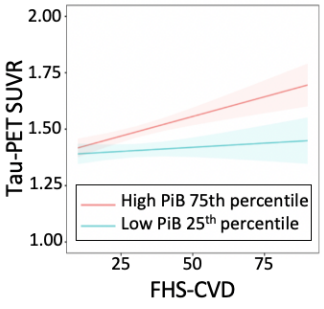

Figure 2. Significant interaction between FSH-CVD and Aβ burden on cross-sectional IT tau burden: higher FSH-CVD and higher Aβ was associated with higher cross-sectional IT tau.

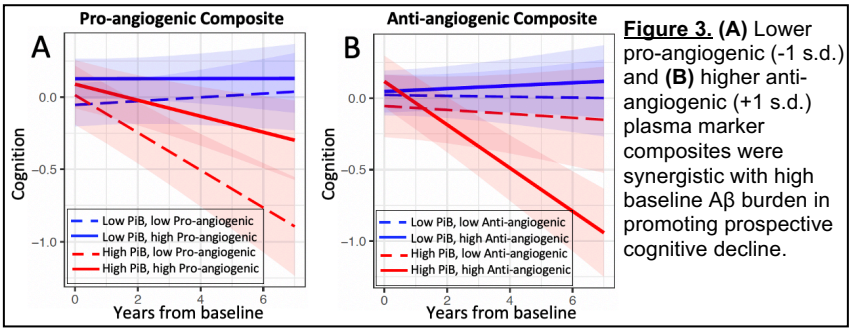

Figure 3. **(A)** Lower pro-angiogenic (-1 s.d.) and **(B)** higher anti-angiogenic (+1 s.d.) plasma marker composites were synergistic with high baseline Aβ burden in promoting prospective cognitive decline.

Research Design and Methods

Participants: The HABS cohort currently consists of 298 (ages 50-95, 62% female) participants who were cognitively normal at baseline, and followed longitudinally (for up to 12 years by end of this project) with annual cognitive assessment and serial brain imaging every 3 years. I expect to have >250 participants with three MRI and Tau PET scans by the start of my proposal, and >300 complete datasets by the end of the project.

Aim 1: WMHs are identified on MR FLAIR images using a well-validated automated algorithm (with manual quality checks)[20]. PSMD is calculated from DTI images using FMRIB Software Library (FSL)[14]. ET and IT tau burdens are quantified as standardized uptake value ratios within FreeSurfer-defined ROIs using published

methods[13]. Aβ burden is measured with ^{11}C-Pittsburgh Compound-B (PiB) at baseline and serially. Methods for image acquisition and processing are well detailed in recent publications[13,21,22]. I will use the software library R (The R Foundation)[23] to perform statistical analysis. All statistical models in Aims 1 to 3 will include baseline age, sex, and apolipoprotein E *(APOE*) ε*4* status as covariates. I will use linear mixed-effects models (nlme package) to assess whether baseline FHS-CVD predicts longitudinal WMH, PSMD, IT tau and ET tau respectively, and whether the interaction between FHS-CVD and baseline Aβ burden impacts this relationship.

Aim 2: Vascular markers are measured in baseline plasma using MesoScale Discovery V-PLEX Angiogenesis Panel 1 and Vascular Injury Panel 2 assays. Preliminary studies identified seven markers that predict prospective cognitive decline alone and/or interactively with Aβ burden (manuscript in preparation, see Figure 3). Through data-driven hierarchical clustering, these markers formed 3 clusters that recapitulate known biologic pathways: pro-angiogenic (VEGF-A, VEGF-C, bFGF), anti-angiogenic (soluble FLT1, PIGF) and endothelial dysfunction (VCAM-1, ICAM-1). I will use plasma marker composite (i.e. mean z-score of log-transformed marker levels) from each cluster in linear mix-effects models to determine their relationship with longitudinal WMH, PSMD, IT tau and ET tau respectively, and assess for any interaction with baseline Aβ.

Aim 3: I will use the lavaan package in R[24] to perform SEM as illustrated in Figure 1. I will estimate latent vascular contributions to cognitive decline from FHS-CVD and pro-angiogenic, anti-angiogenic and endothelial dysfunction plasma composites. I will then determine whether WMH, PSMD, tau and gray matter volume mediate the latent vascular effects on prospective cognitive decline, and whether Aβ burden moderates these relationships. Following the initial fit of the causal model, paths that are not significant will be eliminated to improve parsimony and degrees of freedom. The final model will be assessed using goodness of fit indices. Total gray matter volume is measured using FreeSurfer[22] using published methods. Cognition is measured using a well-published composite of Mini-Mental State Examination, Digit Symbol Coding, Logical Memory–delayed recall, and free recall plus total recall from the Free and Cued Selective Reminding Test[3].

Power analysis: Based on a sample of 300 participants with 3 imaging time points, we estimated minimal detectable effects with 80% power at family-wise error corrected $\alpha<0.05$ (two-tailed) for Aims 1 and 2. Slopes were extracted from linear mixed effects models to calculate longitudinal power using conventional linear models. Prior work suggests that ET tau will be the weakest predictor in the primary analyses. Accordingly, we used ET tau as the example imaging marker, and anticipate greater power for the other imaging measures. With these assumptions, we have sufficient power to detect an association of $r_{partial}>0.21$ for FHS-CVD and ET tau, and $r_{partial}>0.23$ for each plasma composite and ET tau, as well as their respective interaction with Aβ.

Potential pitfalls: We chose to use a single well-validated cognitive composite in Aim 3 to improve parsimony with our prior studies and to reduce multiple statistical comparisons. However, it is possible that decline in different cognitive domains may be mediated by different mechanisms. We will further perform exploratory analyses by generating composite measures of processing speed, executive function and episodic memory using published methods[20], and model these domains separately to assess for differential mediating mechanisms. Gaining statistical expertise in causal modeling is critical to the success of Aim 3, and will be a major component of my training as detailed under Coursework Description section. In addition, I will work closely with Dr. Lori Chibnik, an experienced biostatistician on my mentoring team, to ensure the statistical integrity of my hypothesis testing and to troubleshoot and refine my statistical models. While I hypothesize that there will be complete mediation of the vascular effects on cognitive decline by the proposed imaging markers (WM injury, tau burden and gray matter atrophy), if I find instead a remaining significant direct effect in the causal model, it would indicate that there are additional mechanisms not currently accounted for in my proposed model. I will further investigate other potential mechanisms in future studies as discussed below.

Future Directions

Based on results of this proposal, I will expand my work into additional aging datasets and apply new imaging techniques to further elucidate upstream mechanisms of vascular contributions to cognitive aging, and identify even earlier imaging biomarkers. For example, I will examine whether functional neurovascular impairments such as reduced cerebral blood flow[25] and vascular reactivity[26,27] are mechanisms through which vascular risk leads to WM injury and tau accumulation, and how they relate to plasma markers of vascular health. A second direction of future work will study whether and by what mechanisms specific pharmacological (e.g. statins) or lifestyle (e.g. physical activity) modifiers are protective against vascular contributions to cognitive aging. These investigations will form the basis of my K23 application and facilitate my transition to an independent clinician scientist career to elucidate contributors to cognitive decline and promote successful brain aging.

References

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2. Vemuri, P. *et al.* Age, vascular health, and Alzheimer disease biomarkers in an elderly sample. *Ann. Neurol.* **82,** 706–718 (2017).
3. Rabin, J. S. *et al.* Interactive Associations of Vascular Risk and β-Amyloid Burden With Cognitive Decline in Clinically Normal Elderly Individuals: Findings From the Harvard Aging Brain Study. *JAMA Neurol* (2018). doi:10.1001/jamaneurol.2018.1123
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5. Zekry, D. *et al.* Degenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly. *Acta Neuropathol.* **103,** 481–487 (2002).
6. Kapasi, A., DeCArli, C. & Schneider, J. A. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol.* **134,** 171–186 (2017).
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McKnight Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss
Scholars and Mentors
January 2021

2018 Scholars and Mentors

Brice McConnell, MD, PhD (Scholar – University of Colorado, Denver)
brice.mcconnell@ucdenver.edu
Benzi Kluger, MD, MS (Mentor – University of Colorado, Denver)
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Kimberly Albert, PhD (Scholar – Vanderbilt)
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Paul Newhouse, MD (Mentor – Vanderbilt)
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2019 Scholars and Mentors

Christian Camargo, MD (Scholar – University of Miami)
ccamargo@med.miami.edu
Richard Wurtman, MD (Mentor)
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Farzaneh Sorond, MD, PhD (Mentor – Northwestern)
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2020 Scholars and Mentors

Bryan Baxter, PhD (Scholar – Massachusetts General/Harvard)
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Dara Manoach, PhD (Mentor – Massachusetts General/Harvard)
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Sarah Getz, PhD (Scholar – University of Miami)
Sarah.getz@med.miami.edu
Bonnie Levin, PhD (Mentor – University of Miami)
blevin@med.miami.edu

2021 Scholars (Mentors' Names Requested)
CONFIDENTIAL UNTIL PUBLIC ANNOUNCEMENT SPRING 2021

Matthew Burns, MD, PhD (Scholar – UF College of Medicine)
Mattburns50@hotmail.com
Barry Setlow, PhD (Mentor – UF College of Medicine)
Setlow@ufl.edu

Wai-Ying Wendy Yau, MD (Scholar – Mass General Brigham)
wyau@partners.org
Reisa Sperling, MD (Mentor – Mass General Brigham)
Reisa@bwh.harvard.edu

CONTRIBUTION AGREEMENT

The parties to this Contribution Agreement ("Agreement") are the American Brain Foundation ("ABF"), located at 201 Chicago Avenue, Minneapolis, MN 55415 and the McKnight Brain Research Foundation ("Donor" or "MBRF"), located at c/o SunTrust Bank, Inc., 200 South Orange Avenue, Orlando, FL 32801.

Donor, a Florida Section 501(c)(3) private foundation, hereby makes a grant to the ABF to fund ten (10) McKnight Clinical Translational Research Scholarships in Cognitive Aging and Age-Related Memory Loss (each, a "CTRS").

ABF, a Minnesota nonprofit Section 501(c)(3) public charity, accepts MBRF's grant for the purpose and subject to the restrictions specified in this Agreement.

Therefore, in consideration of the mutual covenants and agreements herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties agree as follows:

1. Purpose. Donor hereby grants $1.65 million to ABF to be used to fund ten (10) CTRS's in Cognitive Aging and Age-Related Memory Loss for the selected recipients ("Recipient"), to be funded by the Donor, and which will be further provided to the American Academy of Neurology Institute ("AANI"), a Minnesota nonprofit Section 501(c)3 public charity, pursuant to an agreement between ABF and AANI (the "AANI Grant Agreement"), and further provided to each Recipient pursuant to agreements between AANI and each Recipient ("Recipient Agreement"). References herein to Purpose shall be to the funding of the ten (10) CTRS's.

The ABF agrees to use all of the Grant and income earned on the Grant, if any, only for the purposes and in the manner permitted in this Agreement. Specifically, the Grant shall be used to fund and administer a portion of each CTRS and not for any other purpose.

2. Name. The name of each CTRS will be the "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," unless otherwise mutually designated by MBRF and ABF.

3. Timing and Number of CTRS. ABF will award ten (10) CTRS as follows:

2023 – 2 CTRS awards

2024 – 2 CTRS awards

2025 – 2 CTRS awards

2026 – 2 CTRS awards

2027 – 2 CTRS awards

The total payment to ABF for each CTRS will be $165,000. Each CTRS will be for $150,000 and will be paid over a two year period. ABF will be paid $15,000 for each CTRS for administering the CTRS program.

4. Funding. The aggregate amount of the Grant is $1.65 million. MBRF will make the following payments to ABF:

$330,000 by June 1, 2023
$330,000 by June 1, 2024
$330,000 by June 1, 2025
$330,000 by June 1, 2026
$330,000 by June 1, 2027

If no Recipient is identified for a CTRS (pursuant to the selection process described below), or if funding for the second year is not approved, or if funds are returned for a CTRS, the ABF will then return to MBRF the portion of the returned funds that are attributable to the Grant or will work collaboratively with Donor to identify another use of the funds that is as close as possible to the Donor's original intent, as expressed in this Agreement.

5. Selection & Administration.

a) ABF Obligations.

The ABF will assure:

i. Promotion of the availability of the CTRS's, and request for applications

ii. Compilation of a list of qualified recipients via peer-reviewed competition

iii. Distribution of funds to the Recipients' institutions, and

iv. Collection of annual progress reports and expenditure reports as set out in this Agreement.

b) Recipient Selection and Monitoring.

Recipient selection will be conducted as follows:

i. The Research Program Subcommittee ("Subcommittee") and ad hoc reviewers staffed by the AANI, will participate in reviewing applications of potential recipients

ii. Donor may designate up to three (3) physicians/scientists to serve as reviewers until Recipients for each CTRS is selected

iii. **Each application will be reviewed by three reviewers**

iv. The Subcommittee and ad hoc reviewers will identify the top applications in rank order that merit funding and will identify the recommended recipients of the CTRS's.

v. The Science Committee will have final review of the recommended applications for receipt of the CTRS's.

vi. The ABF will share the name of the recipients with the Donor before notifying the recipients. Donor will have 7 days from that time to provide approval. Upon request, the ABF will share the recommended recipient's full application and any reviewer comments with the Donor. Upon request, the ABF will share the applications which were not recommended for funding and any reviewer comments with the Donor.

vii. The ABF will send a letter jointly signed with Donor to each recipient notifying them that they have been selected. ABF will provide a draft of each letter to Donor for review/approval.

ABF will provide annual and final research progress and financial reports to Donor as provided by each Recipient, for information only.

The original three reviewers will assess performance of each CTRS based on the first annual report; funding for the second year of each CTRS is contingent upon the approval of this report by the original three reviewers. The final report of each Recipient will be reviewed by the subcommittee. If funding is not approved or amounts are repaid pursuant to this paragraph, ABF will return payments received from the Recipient as described in Section 3.

6. Term of Agreement; Termination for Material Breach. This Agreement goes into effect on the date on which both parties sign below. In the event of a material breach of this Agreement by either party, which such breach is not cured within 60 days of receipt of written notice of the breach, the non-breaching party may terminate this Agreement by written notice to the breaching party, effective upon receipt, in which case no further funding will be made under this Agreement.

7. Research Products. The Recipients may develop inventions, products, publications, processes, know-how, formulae, and the like, from the research funded by the Grant, whether or not capable of protection under copyright, trade secret or patent protections (the "Research Products"). Donor and ABF will have no rights in or to the Research Products that are conceived or reduced to practice in the performance of each CTRS, regardless of whether the invention is patented or copyrighted.

8. Licensure of Names and Marks. Solely for the purpose of performing their obligations under this Agreement and for acknowledging each party's support for each CTRS, MBRF and ABF grant to each other, and the American Academy of Neurology Institute, the non-exclusive revocable right and license to reproduce, store, display,

distribute and transmit the names and marks of the American Brain Foundation and the McKnight Brain Research Foundation, in each case as approved by the applicable party, on and in connection with each CTRS. Such use will only be in accordance with all of the terms and conditions of this Agreement, and not for any other purposes without the express written permission of each party.

9. Physician Payments Sunshine Act. The Physician Payments Sunshine Act ("PPSA") requires applicable pharmaceutical and device manufacturers ("Manufacturer") to report to the Centers for Medicare and Medicaid Services ("CMS") certain payments or transfers of value made to physicians or teaching hospitals, including payments made through third parties. If either party's support of any of the CTRS's is funded in whole or in part from a payment or transfer of value from a Manufacturer, the Manufacturer may be required under the PPSA to report the funding to the Recipients to CMS. If a party's support of any of the CTRS's is funded in whole or in part from a payment or transfer of value from a Manufacturer, such party will notify the other party and may notify potential Recipients of this fact.

10. Liability. Donor is not responsible for any claim, judgment, award, damages, settlement, negligence or malpractice arising from the funded CTRS's.

11. Relationship of the Parties. The relationship of ABF and Donor does not constitute a partnership, joint venture, or any other type of business organization. Neither party shall have any authority to act on behalf of or obligate the other party.

12. General Provisions.

a) Amendments. This Agreement will not be amended or modified except by a writing signed by both parties and identified as an amendment to this Agreement.

b) Assignment. No party will assign this Agreement or its obligations, duties and liabilities without the prior written consent of the other party.

c) Binding Effect. This Agreement will be binding upon and inure to the benefit of the parties, their successors and permitted assigns.

d) Waiver. The failure of either party to complain of any default by the other party or to enforce any of such party's rights, no matter how long such failure may continue, will not constitute a waiver of the party's rights under this Agreement. The waiver by either party of any breach of any provision of this Agreement will not be construed as a waiver of any subsequent breach of the same or any other provision. No part of this Agreement will be waived except by the further written agreement of the parties.

e) Entire Agreement. This Agreement constitutes the entire Agreement among the parties with respect to this subject matter, and there are no representations, understandings, or agreements that are not fully expressed herein. No amendment, change, waiver, or discharge will be valid unless in writing and signed by both parties.

f) Severability. In the event any provision of this Agreement is held to be invalid or unenforceable, the remainder of this Agreement will remain in full force and effect as if the invalid or unenforceable provision had never been a part of the Agreement.

IN WITNESS WHEREOF, the undersigned have executed this Agreement on the dates specified below.

AMERICAN BRAIN FOUNDATION

_____ _____

Jane Ransom Date
Executive Director

MCKNIGHT BRAIN RESEARCH FOUNDATION

_____ _____

Signature Date

_____

Printed Name

_____

Title

Report on Outreach to Possible Partners for the Mid-Career Research Award

Jan. 21, 2021

Active Prospects:

1) AARP

Dr. Lee Dockery secured a phone meeting that took place on Monday, January 11, with Ms. Sarah Lock, Sr. VP Policy & Brain Health for AARP, and Executive Director, Global Council on Brain Health (GCBH). Amy joined in the call. Dr. Dockery explained the mid-career research award program directing Ms. Lock's attention to the attached white paper. Dr. Dockery shared the various ways the AARP could partner with the MBRF, including by providing matching funding, partial funding, and/or providing staff to manage the call for applications, the review process and management of the grant. (He offered that staff might be fully funded by AARP or MBRF might share that cost.) All options were put on the table.

Next Step: Ms. Lock will discuss the program informally with a few trusted AARP colleagues and will share their views with us after those discussions. She values the prestige, scientific credibility, and visibility this program would bring to the GCBH and the AARP Foundation. **If we don't hear from Ms. Lock by February 1, we will reach out again.**

2) **American Federation for Aging Research (AFAR)**

This prospect was recommended by Dr. Patricia Boyle. Dr. Boyle's contact there is Mike Hodin, PhD, a member of their Board of Directors. Dr. Boyle and Amy agreed that the contact needs to be with the Executive Director. From the AFAR website: *"Since its founding, AFAR has granted close to $184 million to 4,240 talented researchers, physicians, and medical students to conduct research and to help them begin and further careers in aging research and geriatric medicine. AFAR awards 35 – 40 grants and scholarships each year. They are selected through a rigorous review process led by expert committees."* Information about AFAR and its grant programs is at https://www.afar.org.

Next Step: Amy sent an email and white paper on Jan. 21 to Stephanie Lederman, Executive Director of AFAR, asking for a phone appointment for Dr. Thambisetty and herself. Amy invited Ms. Lederman to connect on Linked-In and she accepted the invitation. **Wait for response from Ms. Lederman.**

3) The Glenn Foundation for Medical Research

Dr. Thambisetty forwarded the link https://glenfoundation.org. After looking at the website, it looks as though Kevin Lee, PhD, Sr. Scientific & Programmatic Advisor, may be the appropriate person to reach out to. Of note, the homepage says "The Glenn Foundation supports many programs through the American Federation for Aging Research."

Next Step: Amy sent the email and white paper on Jan. 21 to Dr. Kevin Lee to request a phone meeting for Dr. Thambisetty and Amy. **Wait for a response from Dr. Kevin Lee.**

4) National Science Foundation (NSF)

Amy reached out to Dr. Joanne S. Tornow, Assistant Director NSF, who connected her with Dr. Donal Manahan, Division Director for Integrative Organismal Systems. Dr. Tornow noted that the program as described might not be appropriate for the NSF, but that the NSF might be able to suggest changes that would align with the MBRF's vision and goals for the program.

Amy followed up with Dr. Manahan on January 18, copying Dr. Tornow, asking for a phone appointment for herself and Madhav. Dr. Manahan responded that he was in discussion with his neuroscience team.

Next Step: **Wait for Dr. Manahan's response.**

5) Patient-Centered Outcomes Research Institute (PCORI)

Dr. Lee Dockery reached out to Dr. Nakela Cook, MD, MPH, Executive Director of PCORI. Dr. Dockery was connected to Dr. Steve Clauser, Program Director, Healthcare Delivery and Disparities Research, and Mr. Greg Martin, Chief Engagement and Dissemination Officer. A call took place on Friday, Jan. 15.

PCORI is interested in funding research to improve patient care outcomes for either a specific disease or a specific population. They referred us to their funding announcement. They might be open to proposals from individual researchers at the MBIs but they very nicely suggested that the mid-career award is not in alignment with PCORI's congressionally-mandated mission.

Next Step: **Dr. Thambisetty will review the funding announcement and provide feedback on any possible approach we might make**. **Should none be appropriate PCORI will move to the No Further Action Required category;** however, Amy will reach out periodically to Dr. Clauser and Mr. Martin and will consider possibilities with PCORI that might be appropriate with the MBIs**.**

6) Buck Institute

This organization was recommended by Dr. Allison Brashear. On their website https://www.buckinstitute.org, the Buck Institute refers to themselves as "pioneers in the study of the biology of aging." Dr. Eric Verdin is President and CEO of the Buck Institute.

Next Step: **Amy will ask the Research Committee for feedback on approaching Dr. Verdin.**

7) The Kavli Foundation

Dr. Thambisetty forwarded the website for The Kavli Foundaiton.
https://www.kavlifoundatioin.org/about-foundation

Next Step: **Amy to send email and white paper to them.**

8) The Grass Foundation

Dr. Thambisetty forwarded the website for The Grass Foundation.
https://www.grassfoundation.org

Next Step: **Amy to send email and white paper to them.**

9.) Retirement Research Foundation

This organization was a partner in funding the IOM Study. Dr. Lee Dockery forwarded the website for the Retirement Research Foundation.
https://www.rrf.org

Next Step: **Amy to send email and white paper to them.**

No Further Action Required:

1) **Howard Hughes Medical Institute (HHMI)**

Madhav forwarded the email and bio for Dr. Erin O'Shea, President of the HHMI. Amy developed a draft email and sent to Madhav for his edits and additions. Amy sent the approved draft to Dr. O'Shea and received a response with a few hours. The HHMI is focused on their current support for researchers and will be launching a few of their own new projects this year. There is no interest from the HHMI.

Next Step: **No further action required.**

2) The John D. and Catherine T. MacArthur Foundation

Looking at the website at https://www.macfound.org there doesn't appear to be a fit. The homepage says they "support creative people, effective institutions, and influential networks building a more just, verdant, and peaceful world. "

Next Step: The MacArthur Foundation does not appear to be a prospect for the MBRF Mid-Career Award Program. **No further action required.**

3) **Veterans Administration (VA)**

Amy reached out by email to Dr. Carolyn Clancy, Assistant Under Secretary for Health for Discovery, Education and Affiliate Networks and Dean of the Veterans Health Administration. Dr. Clancy expressed interest in the program on behalf of the VA. She contacted the VA's lawyers who advised that the MBRF could partner with one of the not-for-profit groups working on behalf of the VA.

Later the lawyers advised Dr. Clancy that at least one grant would have to be awarded to a researcher at the VA . Amy discussed this with Dr. Lee Dockery, deciding this would be unacceptable. Amy wrote to Dr. Clancy to thank her and to let her know this would not be of benefit to the MBRF.

Next Step: **No further action required.**