Age-related Memory Loss (ARML) Program and Cognitive Aging and Memory (CAM) Program

2014 Annual Report

UF Evelyn F. & William L. McKnight Brain Institute
UNIVERSITY *of* FLORIDA

Prepared for the McKnight Brain Research Foundation by the University of Florida McKnight Brain Institute and Institute on Aging

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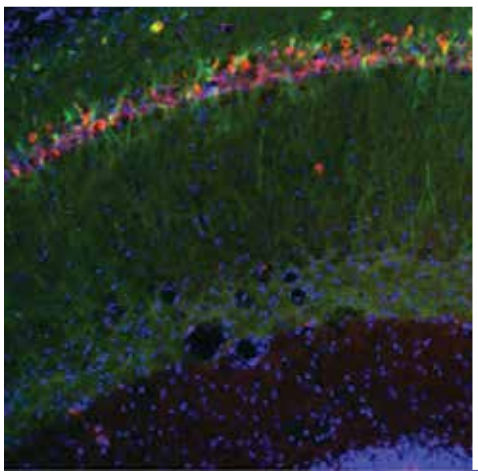

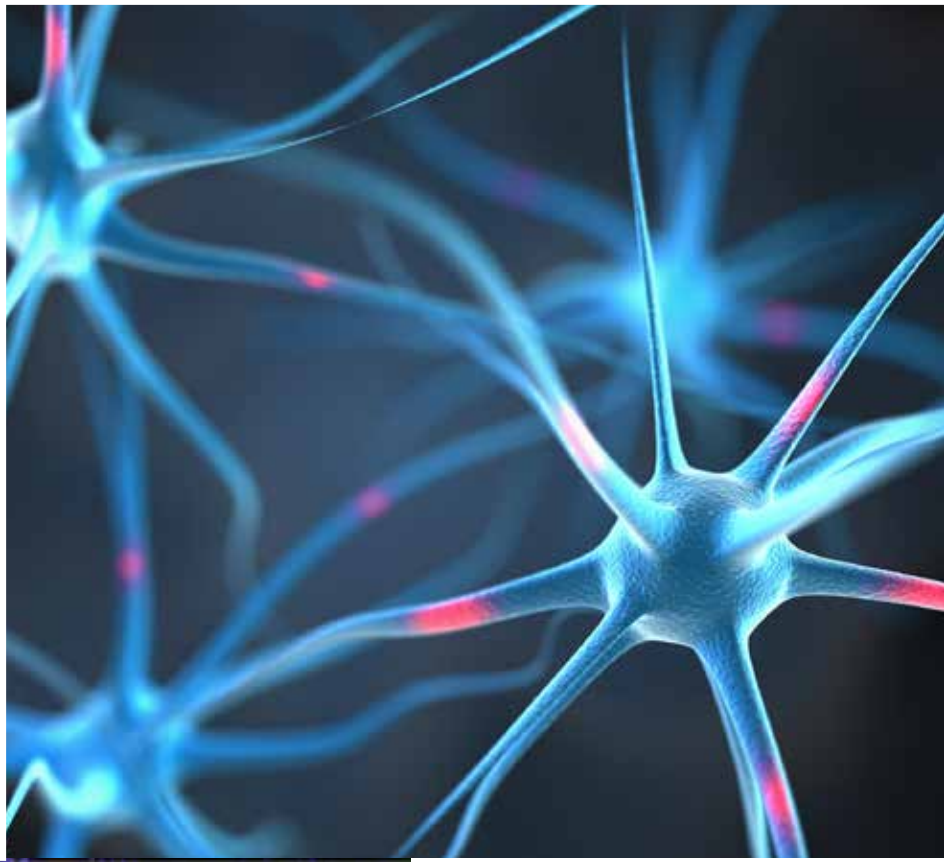

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January 9, 2015

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Dear Trustees:

UF Health and the UF College of Medicine would like to express our continued appreciation for the ongoing support and partnership of the McKnight Brain Research Foundation. The past year has seen significant growth of our Age-related Memory Loss (ARML) Program and the Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP), led by Drs. Thomas Foster and Ronald Cohen, respectively.

Accomplishments over the last twelve months include:

- Hosting the very successful 7th Annual McKnight Inter-institutional Meeting,
- Strengthening cross institutional collaborations with the establishment of several core initiatives at UF: the cognitive aging, neuroimaging, and epigenetics cores.
- Increased extramural funding for key faculty in the programs, along with promising pilot studies and grant submissions.
- A growing number of publications in prominent journals and talented trainees in the fields of cognitive aging and memory loss.

As we begin 2015, we are excited by the prospects for novel discovery, increased NIH funding, a physician recruitment to CAM-CTRP, and overall expansion of both programs.

The continued contribution and partnership with the McKnight Brain Research Foundation is fundamental in the success of these programs and initiatives. Thank you again for this support.

Sincerely,

David S. Guzick, M.D., Ph.D.
Senior Vice President, Health Affairs
President, UF Health

Thomas A. Pearson, M.D., Ph.D.
Executive Vice President, Research & Education,
Health Science Center
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Michael L. Good, M.D.
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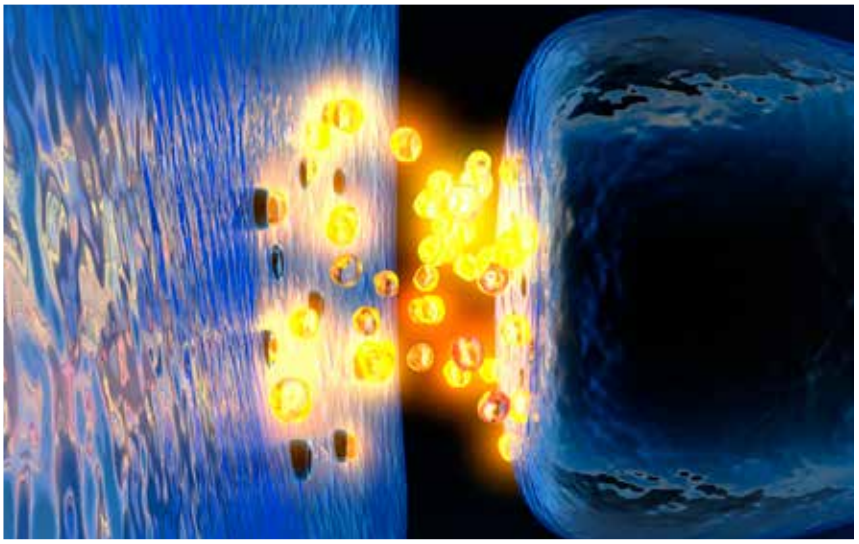
Age-related Memory Loss (ARML) Program

2014 Progress Report



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January 15, 2015

Dear Trustees of the McKnight Brain Research Foundation:

It is a great pleasure to present this report to Trustees of the McKnight Brain Research Foundation (MBRF). This report describes the accomplishments of the Age-Related Memory Loss (ARML) Program and the Cognitive Aging and Memory-Clinical Translational Research Program (CAM-CTRP) in 2014. The ARML Program has made important progress towards understanding the biological mechanism of memory loss in aging while the CAM-CTRP has focused on translational works toward prevention or alleviation of cognitive loss associated with aging. These programs also played leadership roles in the advancement of interinstitutional, collaborative research involving investigators from the four McKnight Brain Institutes (University of Florida, University of Arizona, University of Alabama Birmingham and University of Miami). We are extremely grateful for the MBRF for the support of these inter-institutional research programs. Specifics of these progresses are described in detail in this report and are summarized in the letters from Dr. Thomas Foster for the ARML Program and Drs. Ronald Cohen and Marco Pahor for the CAM-CTRP.

Briefly, Dr. Jennifer Bizon of the ARML Program has explored the mechanistic role of GABAergic signaling in memory loss associated with aging in rats. Impressive results of her work are being translated into the development of novel GABAB receptor antagonists as therapeutic agents that can be used in human clinical trials. Dr. Sara Burke, who moved from the University of Arizona to the MBI over a year ago, has successfully established her productive laboratory. She has published five papers on age-related memory loss, including three in the Journal of Neuroscience in 2014. Dr. Andrew Maurer is a new faculty member who brought cutting-edge electrophysiological technologies to study functions of cells in hippocampus and entorhinal cortex, which are critical for understanding the mechanism of memory loss in aging. Drs. Brandi Ormerod, Jason Frazier and Leonid Moroz have finished their research projects funded by the ARML program. Dr. Moroz continues to be active in the interinstitutioonal epigenetic project. Dr. Thomas Foster, Director of the ARML Program, directed these research activities. Dr. Thomas Foster, who is also Professor and Chair for Research on Cognitive Aging and Memory, continues to be one of the top international researchers of cognitive aging, and his accomplishments led to a renewal of the NIH Merit Award. He identified impaired acquisition of episodic spatial information as a hallmark of early cognitive loss associated with aging, and the redox/calcium-mediated impairment of the NMDA receptor function contributing to an early stage of senescence hippocampal neurons. Dr. Foster also initiated a new study to examine the role of systemic inflammation in age-related cognitive decline as a project aiming at translational applications. Furthermore, Dr. Foster led the effort to establish the University of Florida Bio-Informatics Core as a part of the inter-institutional collaboration to facilitate the understanding of the role of epigenomics in cognitive aging.

The highlight of the report of the CAM-CTRP includes the second site visit of the External Advisory Board. The Board praised the Program's accomplishments and strongly supported continuation of the Program. Clinical projects including the WISE BRAIN Study, ACTIVE BRAIN study and a dozen pilot projects are in progress in the CAM-CTRP. The CAM-CTRP supports variable part of efforts of multiple faculty members involved in these studies. Additionally, three new studies, i.e., ENIGMA-HIV, ARCH and U-TRACK, have been started. Dr. Ronald Cohen, Director, CAM-CTRP, played a major role in the development of the McKnight Inter-institutional Neuroimaging Initiative. Drs. Cohen and Woods made further development of the research infrastructures for the CAM-CTRP, including Neuroimaging Processing and Data Analysis Lab, connection between the CAM-CTRP and the University HiPerGator computing system, a ^{31}P-^{1}H phosphorous MRS whole brain coil for cerebral metabolic spectroscopy, a DTI system to assess neuroinflammation, the Brain Wellness Program, the Human Electrophysiology Lab, and more. These progresses have been made under the auspice of Dr. Marco Pahor, Director of the Institute on Aging.

These two programs have made important advances and developed strong initiatives for the training of early investigators. However, there were also challenges. For the CAM-CTRP, we were fortunate to encounter Dr. Michael Nitsche, Professor at the University of Cologne, Germany, as an M.D. candidate for the CAM-CTRP. Unfortunately, it would not be easy for Dr. Nitsche to obtain his Florida medical license without completing his residency in the US, although he would otherwise fulfill recommendation of the External Advisory Committee. For the ARML Program, Dr. Kevin Felsenstein, who had been playing a key role of pharmacological biochemist in translational projects, had to take extended medical leave. However, the team has overcome the difficulty by arranging a contractual collaboration with the Sanford Burnham High Throughput Screening Program.

In summary, the funds generated from the MBRF endowment haveallowed investigators to develop impressive, basic translational and clinical research programs at the University of Florida. We are sincerely grateful for the generosity and strong support of the MBRF and keenly aware of the ultimate goal to develop preventive and therapeutic interventions for cognitive loss associated with aging. All members of the ARML Program and CAM-CTRP are fully committed toward this goal. Best regards, Tetsuo Ashizawa, M.D. Executive Director, McKnight Brain Institute Melvin Greer Professor of Neurology

Best regards,

Tetsuo Ashizawa, M.D.
Executive Director, McKnight Brain Institute
Melvin Greer Professor of Neurology

AGE-RELATED MEMORY LOSS PROGRAM (ARML):

The ARML program consists of researchers dedicated to understanding and alleviation of age-related cognitive decline. MBRF sponsored support of ARML researchers is overseen by the ARML Program committee consisting of Drs. Tom Foster (Evelyn F. McKnight Chair for Research on Cognitive Aging and Memory and ARML Committee Chair), Tetsuo Ashizawa, (Executive Director, McKnight Brain Institute and Melvin Greer Professor and Chair of Neurology), Lucia Notterpek (William T. and Janice M. Neely Professor and Chair of the Department of Neuroscience) and Christiaan Leeuwenburgh (Chief, Division of Biology of Aging at the Institute on Aging and Leader of the Metabolism and Biomarkers and Research Career Development Cores).

Major goals of the ARML program include support for collaboration and communication among researchers and nurturing scientists dedicated to the exploration and innovative research in the understanding and alleviation of age-related memory loss. The ARML fund partially supports the faculty salary of Drs. Thomas Foster (43% FTE) and Jennifer Bizon (70%FTE), as well as two new hired faculty, Drs. Sara Burke (100% FTE) and Andrew Maurer (100% FTE). Drs. Burke and Maurer are expected to receive external funding to offset a significant portion of their FTE supports in the next five years. Other faculty who participated in the ARML Program supported their salaries from other sources. The following is a summary of activities towards these goals followed by recognition of some of the achievements of ARML researchers.

Promoting Collaboration and Communication across MBRF Institutes

A high point for the year has to be the gathering of scientists and clinicians in Gainesville for the 7th Inter-Institutional Meeting of the Evelyn F. McKnight Brain Research Foundation (April 23-25, 2014). Dr. Tom Foster at the University of Florida's McKnight Brain Institute and Chair of the ARML committee hosted the event and oversaw arrangements for this important and successful meeting. In addition, two sessions focused on the major themes and collaborations across the four institutes. Dr. Foster arranged for recognition of young investigators, with a scientific session enabling them to present their results on cognitive aging.

The ARML Program at UF has a prominent role in cross institute collaborations

1) **Cognitive Aging Core:**
   Based on the previous work of this core and the resulting published papers, a battery of behavioral tasks has been implemented by the Bizon, Setlow, & Foster labs such that groups of animals are tested on a series of cognitive tasks. The protocols for spatial episodic memory have also been adopted by the University of Arizona and animals are being tested across the institutions for use in cross institute epigenetic studies (see Epigenetic Core). The results indicate that the behavioral tests are reliable across institutes (figures are included in the Chairs report). In addition, we continue to interact with individuals involved in human testing and assessment across the four institutes to determine if the animal models are valid for examining changes in cognition across domains (memory, attention, sensory processing) in humans. This work will determine if cognitive decline is due to a single factor (e.g. equal impairment in all domains) or results from changes in discrete neural circuits that underlie specific cognitive processes. Finally, this battery of tasks forms a critical component for several grants that have recently been funded or received positive scores from study sections (see below).

2) **Neuroimaging Core:**
   Blood has been or will be collected from neuroimaging studies conducted by the CAM-CTRP and at other MBRF institutes as part of ongoing studies and the McKnight Inter-Institute Neuroimaging Initiative. One idea is to use samples for examining transcriptional markers in the blood. As part of this initiative, ARML Program researchers (Drs. Foster, Kumar, Moroz) are collaborating with T-Gen to examine RNA in the plasma. Protocols have been developed and samples have been acquired (2 protocols with four samples each). Currently, we are waiting on the results. It is hoped that the procedure will provide information, not only on systemic inflammation which contributes to brain aging, but also provide a glimpse into brain metabolism associated with cognitive function. Thus, this work is directed at providing a molecular link between Cognitive and Neuroimaging Cores.

3) **Epigenetics and Bio-Informatics Core:**
   This Core provides a shared Inter-institutional resource related to transcription, genomics, and epigenomics and acts as a catalyst for discoveries across all Evelyn F. McKnight Brain Institutes. We have made outstanding progress in setting up the infrastructure necessary to ensure that sequencing capability is available at UF. The details for the ARML Program at UF, which is directed by Drs. Foster and Moroz can be found in the Chair's Report.

   A study involving cross institute collaboration is directed at testing an epigenetic hypothesis of cognitive aging. Alabama, Arizona and Gainesville sites have provided tissue from cognitively characterized rodents (see **Cognitive Aging Core**). The transcriptome was analyzed at the separate sites, to test our ability to coordinate tissue sharing, to see how the different methods used at the different sites compare, and to evaluate the strengths and weaknesses of methodologies

proposed. The initial results were reported that the McKnight Social poster session at the Society for Neuroscience meeting (2014) and exceeded expectations such that the values were highly reliable across institutes and across different platforms (see figures in the Chairs Report). Differences related to cognitive status were noted and confirmed across institutes. Recently (12/2014) the first set of DNA methylation data was released from Alabama. A general finding is that there is an increase in methylation in older cognitively impaired animals. This has raised a lot for questions to be addressed before our next meeting in 2015. In the end we aim to design experiments to investigate transcriptional dysregulation in aging humans. As part of this we are examining RNA in blood samples (see **Neuroimaging Core**).

Collaborations within UF:

Several collaborative projects have received extramural funding in 2014:

1) **Signaling Cascades and Memory Deficits during Aging (Foster PI):** This NIA MERIT award was renewed in 2014 and examines the idea that a decline in synaptic plasticity signaling from the synapse to the nucleus contributes to the onset and progression of cognitive decline. Other researchers on this grant include Drs. Kumar and Bizon.

2) **Neural Mechanisms of Cognitive Decline in Aging (Bizon PI):** This project was funded in 4/2014 by NIA. The goal of this project is to determine the contributions of GABAergic and cholinergic basal forebrain projection neurons and their cortical targets to age-related cognitive decline. Other researchers on this grant include Drs. Setlow, Kumar, and Foster.

3) **A contract with Sanford Burnham (Bizon PI)**, the goal of which is to generate novel GABA(B)R antagonists with improved pharmacokinetic properties over the current generation of compounds. Since last year, we have generated strong preclinical data to indicate that several drugs from this class of compounds markedly improve multiple aspects of age-related cognitive decline. The contract with Sanford Burnham represents a significant advance towards a discovery program for treatment of age-related cognitive decline. While Dr. Bizon is the principle investigator, a research team of clinicians and basic scientists (Drs. Tetsuo Ashizawa, Glenn Finney, Kevin Felsenstein, Ron Cohen, Barry Setlow and Tom Foster) meet with her to help develop a tractable strategy for advancing a translational program to assess the use of GABA(B) receptor antagonists as cognitive enhancers in aged individuals.

Other collaborative projects facilitated by ARML funding in 2014:

The ARML program provides support for collaborations. A group of ARML researchers (Foster, Leeuwenburgh, Bizon, Setlow, Frazier, Ormerod) met to share their vision of factors that contribute to cognitive aging in order to develop plans for generating grant proposals. A major idea to emerge was the role of systemic inflammation in cognitive decline. A consistent observation of aging in humans and animals is a persistent low level increase in serum markers of inflammation and this pro-inflammatory phenotype is thought to contribute to age-related diseases, including cognitive decline. However, a clear understanding is lacking for how low-grade systemic inflammation, acting in the context of aging, compromises brain cells to influence the onset and progression of cognitive impairments. The ARML committee provided funding ($6,000) for a pilot project on the Role of Systemic Inflammation in Age-Related Cognitive Decline. The preliminary data was used for grants submitted to NIH. A proposal, *Modeling age-related memory-loss with chronic induced low-level inflammation*, was submitted by Dr. Ormerod. Another proposal submitted by Dr. Foster (Drs. Bizon and Kumar co-I), *Systemic inflammation in regulating the onset and progression of brain aging*, received a very good score and was ranked at the 12th percentile.

This pilot work has also generated a number of collaborations between ARML researchers and individuals at the Institute on Aging (Carter, Leeuwenburgh, Scarpace) and the Center for Translational Research in Neurodegenerative Disease (Drs Chakrabarty, Cruz, and Golde) to develop animal models in order to examine the effects of chronic systemic inflammation on aging and age-related diseases. It is hoped that this work will inform and integrate with pilot studies through CAM-CTRP that involve measures of inflammation including The ACTIVE BRAIN Study, Methotrexate study on systemic inflammation of older adults (ICE): (Anton, Woods), Proteomics and genomics of cognitive aging (Cohen, Leeuwenburgh, Moroz), Oxytocin Clinical Trial (Ebner, Woods, Porges, Cohen), and U-TRACK: (Woods).

Previous ARML funding contributing to current collaborations

Drs. Ormerod (2013-2014), Frazier (2011-2014) and Moroz (2011-2012) have received research funds from the ARML Program to conduct pilot projects that had been competitively selected by peer reviews. Dr. Brandi Ormerod received ARML funding for a pilot project to study neurogenesis during aging. During the current year, she received UF Opportunity Funding and recently submitted a NIH R03 grant. Both the proposals deal with neurogenesis in normal aging and are based on data from her pilot project. These projects involve collaborations between Drs. Ormerod, Burke, and Maurer (all three are co-PIs).

Dr. Jason Frazier received ARML funding to study the role of Ca2+ in senescent physiology. Dr. Frazier continues to collaborate with Drs. Foster and Bizon and publish on senescent neurophysiology linked to cognitive decline. Importantly, Dr. Frazier just received a great score (8th percentile) on a grant dealing with *Novel Aspects of Central Oxytocin Signaling Relevant to Mood/Anxiety Disorders*. In

this regard, Dr. Ebner (CAM-CTRP member, mentored by Drs. Cohen and Foster) received CAM-CTRP funding to examine the role of oxytocin in regulating aging of cognitive processes including socioemotional processing, attention, and memory. It is hoped that these common interests can be leveraged for future studies of mechanisms of cognitive aging.

Dr. Leonid Moroz received funds to examine transcriptional markers of aging in single neurons. This work resulted in previous funding for several researchers (Moroz, Frazier, Foster). Dr. Moroz continues to collaborate closely with Dr. Foster and helps direct the Epigenetics Core at the University of Florida. In addition, he is collaborating with members of CAM-CTRP to examine the genomics of cognitive aging (Cohen, Leeuwenburgh).

The ARML Program supports the development of young scientists dedicated to the exploration and innovative research in the understanding and alleviation of age-related memory loss.

Dr. Sara Burke was hired as an Assistant Professor and provides a strong addition to the ARML research effort. Her research focus is on a cognitive process and a brain region that is different from that of the other ARML researchers. Furthermore, she brings new and technically advanced skills for examining the behavior associated activity of multiple neurons. These skills include in vivo electrophysiological recording of cell discharge activity in freely moving and behaving animals and the molecular histological techniques to determine the history of activated cells. Finally, her history of publications and association with the McKnight Brain Research Foundation insures that she is dedicated to the research aims of the ARML Program.

Dr. Andrew Maurer was hired as a Research Assistant Professor. His research examines mechanisms by which information is propagated within neural circuits and the role of inhibitory in neural computations. He offers expertise in understanding electrical waves, oscillations, and evoked potentials that are recorded in field electrical activity. Thus, he provides a link between studies of human EEG and animal studies that are able to localize the source electrical signals. During 2014, Dr. Maurer submitted 10 grant proposals and is currently collaborating with other ARML researchers (Drs. Burke, Bizon, Ormerod). In addition he is collaborating with and Dr. Jiang (Bioengineering) to obtain fMRI in freely moving animals.

Recognition of achievements

In addition to the new funding from extramural sources (Foster and Bizon), and several well scored proposals (Frazier, Foster), Dr. Joe McQuail and Dr. Caitlin Orsini, who are working in the Bizon laboratory received McKnight Brain Institute postdoctoral fellowships.

Dr. Moroz was awarded the title of Distinguished Professor, University of Florida, Gainesville, FL

Dr. Bizon accepted a position as a Section Editor for the Neurobiology of Aging, one of the premier journals for age-related cognitive decline.

Dr. Foster accepted a position as a sitting member of a NIH study section, Learning and Memory, which oversees much of the research proposals to examine age-related memory decline. In addition, he has accepted a position as a Member of the Steering committee for the Winter Conference on Neural Plasticity.

The members of the ARML program published 30 manuscripts in 2014. Of special note are the number of researchers that have published in top tier journals including Nature (Moroz) and the Journal of Neuroscience (Burke, Bizon, Frazier, Foster, Kumar, Maurer).

SUMMARY OF SCIENTIFIC ACHIEVEMENTS SINCE LAST REPORT: ARML PROGRAM FACULTY:

Jennifer Bizon, PhD

In the past year, my laboratory has substantially advanced our research program that is centered on elucidating the neural mechanisms of prefrontal cortical mediated cognitive decline in aging. Major accomplishments this year included ***five new grant awards***, including:

1. R01 renewal from NIA ($1,000,000 direct over 5 years) which received a near perfect score (Impact Score:11, Percentile: 3rd), awarded on May 15, 2014. The overarching goal of this R01 is to understand how age-related alterations in forebrain inhibitory circuitry affect executive functions, and to identify potential therapeutic targets that can be exploited to improve cognition in aged individuals. Our central hypothesis is that individual differences in prefrontal cortical GABAergic signaling underlie distinct forms of executive dysfunction within aging populations. Under this grant, we will 1) determine if individual differences in prefrontal cortical GABAergic signaling contribute to different forms of age-related executive dysfunction; 2) determine if compromised regulation and activation of prefrontal cortical interneurons contribute to age-related executive dysfunction; and 3) determine if altered GABAergic signaling and executive dysfunction in aging contribute to impairments in decision making.

2. NIA supplement to the R01 above ($95,000.00 total) to support the graduate training of Sofia Beas who will be conducting work under the award.

3. Two McKnight Brain Institute postdoctoral fellowships (total of $60,000.00 over 2 years), which will support training of Dr. Joe McQuail and Dr. Caitlin Orsini, who are working on projects related to age-related cognitive decline in my laboratory. Note that Dr. Orsini is also a finalist in the Thomas H. Maren award competition (which could provide an additional $50,000.00 for postdoctoral training over the next two years).

4. A contract with Sanford Burnham, the goal of which is to generate novel GABA(B)R antagonists with improved pharmacokinetic properties over the current generation of compounds. Since last year, we have generated strong preclinical data to indicate that several drugs from this class of compounds markedly improve multiple aspects of age-related cognitive decline. The contract with Sanford Burnham represents a significant advance towards a discovery program for treatment of age-related cognitive decline. I continue to meet monthly with a research team of clinicians and basic scientists (Drs. Tetsuo Ashizawa, Glenn Finney, Kevin Felsenstein, Ron Cohen, Barry Setlow and Tom Foster) to develop a tractable strategy for advancing a translational program to assess the use of GABA(B) receptor antagonists as cognitive enhancers in aged individuals.

5. A collaborative grant with Dr. Tom Foster (my effort is 20% as a co-I). Under this award, experiments are planned to investigate gene expression in relation to both hippocampal and prefrontal cortical dependent cognition in young and aged rats. A second grant with Dr. Foster on which I am also a co-I also recently received a promising score.

Publications and presentations

In addition to the success in generating new funding for our research, we have continued to be productive, and have published ***7 peer-reviewed manuscripts and 1 invited chapter***. These publications include one study (published in *The Journal of Neuroscience*) that was the subject of several press releases, including a front-page article in the *Gainesville Sun* during Brain Awareness Week). In this study, we present findings showing that GABAergic signaling alterations in prefrontal cortex critically contribute to age-related deficits in working memory abilities and demonstrate that working memory can be improved in aged rats by targeting prefrontal cortical GABA(B) receptors. In addition to these publications, members of my laboratory have made ***20 conference presentations at national and international meetings*** (including at the Society for Neuroscience annual meeting, American College of Neuropsychopharmacology annual meeting, the Association for Chemoreception Sciences annual meeting, and the International Behavioral Neuroscience Society annual meeting). Our visibility at such meetings is expected to continue in the upcoming year, as I will be participating in panel presentations in both the Winter Conference for Brain Research in Big Sky, Montana in January and the International Behavioral Neuroscience Society meeting next June in Victoria, Canada.

National Service

Last summer, I accepted the position of Section Editor for the Behavior, Physiology, and Cognition section of *Neurobiology of Aging*. This journal represents one of the leading outlets for experimental work on age-related cognitive decline (5 year impact factor 5.05).

Sara N. Burke, PhD

Since November, 2013, I have made significant progress in establishing a research program investigating the neurobiology of age-related memory loss. This includes the approval of two animal protocols and the implementation of a cognitive test battery. The behavioral tests that animals are currently participating in are designed to evaluate age-related deficits on tasks that involve different subregions of the medial temporal lobe, as well as how effectively these brain areas interact in support of behavior. We have already made the novel observation that aged rats are impaired at acquiring object-place associations, which rely on interactions between the perirhinal cortex and hippocampus. We are currently running another cohort of young and aged animals through this task and then we will be preparing these data for publication within the next several months.

As part of establishing my lab, I have also recruited personnel to assist with molecular, behavioral and electrophysiological studies. This includes an IDP graduate student, Sarah Burke, a student OPS employee, Nick Topper, who has expertise in software design and programmable microcontrollers, and eight undergraduate students. One of my undergraduate students, Jordan Reasor, was awarded an HHMI Science for Life Fellowship and another student, Jaren Bannerman, won a University Scholar Award from the College of Medicine. I also employed a first-year IDP graduate student over the summer, Abbi Rosen, who worked in my lab on a Board of Education Fellowship. Finally, I successfully recruited a postdoc, Sarah Johnson, who will began working with me on September 4, 2014.

As one of my areas of expertise involves high-channel count neurophysiological recordings, along with Andrew Maurer and Nick Topper, we have set up two physiology recording rigs and constructed micro-electrode arrays that are being implanted intracranially in rats to monitor cellular activity. We have now completed three implant surgeries that have provided pilot data for grant applications. One aspect of setting up the electrophysiology equipment involved developing a video tracking program that could easily be integrated with the recording hardware to synchronize neural and behavioral data. Under the mentorship of Andrew Maurer and myself, Nick Topper implemented a novel method to do this and we have written and submitted a paper entitled, "Multiple frequency audio signal communication as a mechanism for neurophysiology and video data synchronization" for publication in the *Journal of Neuroscience Methods*. In addition to the physiology, I have also set up a wet lab to begin labeling immediate-early gene expression using fluorescent in situ hybridization. Abbi Rosen presented data from our first successful *in situ* hybridization during her rotation seminar in October 2014.

Andrew Maurer, PhD

While I was hired full-time less than 5 months ago as a Reserach Assistant Professor, I am pleased to report that I was able to produce two peer-reviewed articles with University of Florida, McKnight Brain Research Foundation Affiliation. Moreover, between July 1st and November 24th of this year, I will have submitted over 10 grant applications, 6 of which are targeting the NIH or NSF. Finally, as of October 9th, I have a joint appointment in Biomedical Engineering, providing me with the opportunity to co-mentor Master's students should one be interested.

Currently, we are working towards understanding how information is propagated in the nervous system, from one region to another, and how these processes are altered by the aging process. In collaboration with Dr. Sara Burke, we have successfully acquired action potential and EEG data from a high-density electrophysiology array from the dentate gyrus, a region of the brain necessary for learning and memory. This brain region is quite unique as it is both vulnerable to the aging process and exhibits neurogenesis, the integration of new born neurons into the network across the lifespan. These recordings are part of a larger project involving Dr. Brandi Ormerod, a neurogenesis expert, with the over-arching goal of determining how the age-related decrease in neurogenesis affects information processing within the hippocampus.

Furthermore, in collaboration with Drs. Jen Bizon and Sara Burke, we are in the process of collecting preliminary data investigating how inhibitory neuron decline may underlie age-associated deficits in working memory. By recording from large populations of excitatory and inhibitory neurons during a working memory task, we hope to understand how information is "maintained across temporal delays" (one definition of working memory) and identify therapeutic targets of intervention. Based on Dr. Bizon's previous work, we will attempt to restore physiological and behavioral activity with GABA and NMDA receptor modulators.

Finally, in collaboration with Dr. Huabei Jiang, I am working on a novel and exciting research track that allows hemodynamic activity to be monitored in freely-behaving rats. Specifically, the blood-oxygen-level-dependent (BOLD) method in functional magnetic resonance imaging (fMRI) has emerged as a powerful tool for linking brain function to cognition. The application of this tool for probing neural-behavioral relationships in aged and clinical populations, however, is problematic because significant

metabolic and hemodynamic changes occur over the course of aging and disease. Without knowing the impact of these changes on neurovascular coupling and their relationship to the BOLD signal, direct comparisons of metabolic measures of brain activity between age groups is problematic. This can effectively delay the translation of laboratory findings to the clinic. Thus, a means to quantify the dynamics of the neurovascular unit across the lifespan and in disease is critical for connecting metabolic-based measures of brain activity to cognitive function. The overarching goal of this project is to generate integrated technology that provides an integrated measure of brain hemodynamics and electrophysiology across the lifespan leading to an unprecedented insight into the neurovascular unit in the context of behavior and aging.

ARML FUND RECIPIENTS:

Charles Jason Frazier, PhD

Our ARML funded work on the role of calcium activated calcium channels in producing NMDA receptor mediated hypofunction came to a close in August, 2014. During the current reporting period the project was reviewed and scored as an NIH R21 assigned to NIA, but was ultimately not funded. Before the completion date the project supported substantial and successful development of improved techniques for single cell electrophysiological studies in aged tissue, and was instrumental in helping us pioneer use of quantitative two-photon based epifluorescence microscopy in single spines from aged neurons. Both of these innovations have directly promoted increased collaboration between my lab and other ARML labs at the University of Florida, and both have further helped establish aging research as a new primary focus of our efforts. Indeed, we intend to continue to pursue extramural funding using technology, ideas, and data generated under our ARML award, and we are still enthusiastically committed to several collaborative projects that have been enabled by the success of this project in terms of technology development and application in aged tissue. In terms of the core academic hypothesis of our ARML funded work, results obtained through August 2014 have been consistent with the idea that increased SK channel activation could be a primary mechanism leading to NMDA receptor hypofunction in aged neurons. However, data obtained in Spring and Summer of 2014 point towards additional mechanistic complexities not included in our original model, largely revolving around the role of external magnesium in enabling an SK mediated shunt of NMDA mediated calcium current to occur. These data have potential to further increase value and relevance of the project, but would require additional work to fully evaluate.

Brandi Ormerod, PhD

Over the past year we have made significant progress on our MBRF ARML funded project testing "Causes and relationships between olfactory and hippocampal neurogenesis and age-related cognitive decline" consisting of 2 Aims. In the first aim, we proposed to extend collaborative work with Dr. Tom Foster's lab in which we had quantified hippocampal neurogenesis in behaviorally characterized rats that harvested blood serum and hippocampal protein and cortical protein from. The aim proposed to quantify olfactory bulb neurogenesis and cytokine levels in the collected samples from these rats to test whether neurogenesis declines concomitantly in both regions with age and whether age-related changes in neurogenesis and cognition may be mediated by age-related changes in cytokine signaling (i.e. inflammation). We presented the preliminary data in poster format at the 2014 Annual Society for Neuroscience Meeting proper and at the McKnight Satellite Event at that meeting and are currently completing the detailed and intensive data analyses for this aim. We expect to generate 2 manuscripts describing these data over the next few months.

In the second aim, we proposed a collaborative project with Dr. Jennifer Bizon that has expanded to also include collaboration with Dr. Sara Burke. In this aim, we are quantifying hippocampal neurogenesis and olfactory bulb neurogenesis in rats that have been characterized behaviorally in spatial and olfactory discrimination tasks as impaired or unimpaired to test whether age-compromised neurogenesis in either or both regions may produce impairments in their associated cognitive domains. We are also quantifying neuroinflammatory markers in the olfactory bulb and hippocampal regions of these rats. The behavioral data collected for this project were present in poster format at the 2014 Annual Society for Neuroscience meeting. We are currently processing most of the brain samples for this aim and anticipate submitting an abstract this spring to present the associated data at the upcoming 2015 Society for Neuroscience Meeting and the production of a manuscript shortly thereafter. James McGuiness, the PhD student supported by this funding to complete the work, has made excellent progress toward PhD candidacy through his diligent and careful collection of data for these projects.

In our other age-related memory loss research, we are developing an inflammatory model of cognitive aging, testing anti-inflammatory strategies to combat cognitive aging and testing the role of neuroinflammatory cytokines and aberrant neurogenesis

on seizure behavior. The Ormerod Laboratory is grateful for the ongoing support of the McKnight Brain Research Foundation, which has been instrumental for establishing the age-related memory loss branch of research in the lab.

PUBLICATIONS IN PEER REVIEWED JOURNALS: ARML PROGRAM FACULTY:

Jennifer Bizon, PhD

1. Orsini, CA, Trotta, R, **Bizon, JL** & Setlow, B. Dissociable roles for the basolateral amygdala and orbitofrontal cortex in decision-making under risk of punishment. *J. Neurosci. In press*.
2. Shimp, KM, Mitchell, MR, Beas, BS, **Bizon, JL** & Setlow, B. Affective and cognitive mechanisms of risky decision making. *Neurobiol Learn Mem*. 2014 Mar 15. pii: S1074-7427(14)00048-3. doi: 10.1016/j.nlm.2014.03.002. [Epub ahead of print]
3. Bañuelos, C, Beas, BS, McQuail, JA, Gilbert, RJ, Frazier, CJ, Setlow, B & **Bizon, JL**. Altered GABAergic signaling contributes to age-related impairments in working memory. *J Neurosci.* 2014 Mar 5;34(10):3457-66. doi: 10.1523/JNEUROSCI.5192-13.2014
4. Adolescent Risk Taking, Cocaine Self-Administration, and Striatal Dopamine Signaling. Mitchell MR, Weiss VG, Beas, BS, Morgan D, **Bizon, JL**, Setlow, B. *Neuropsychopharmacology*. 2014 Mar;39(4):955-62. doi: 10.1038/npp.2013.295.
5. Yoder, WM, Setlow, B, **Bizon, JL** & Smith, DW. Characterizing olfactory perceptual similarity using carbon chain discrimination in behaviorally-trained Fischer 344 rats. *Chemical Senses*. May;39(4):323-31. doi: 10.1093/chemse/bju001.
6. Centrally administered angiotensin-(1-7) increases the survival of stroke prone spontaneously hypertensive rats. Regenhardt, RW, Mecca, AP, Desland, F, Ritucci-Chinni, PF, Ludin, JA, Greenstein, D, Bañuelos, C, **Bizon, JL**, Reinhard, MK, Sumners, C. E*xp. Physiol.* 2014 Feb;99(2):442-53. doi: 10.1113/expphysiol.2013.075242.
7. Characterization of age-related changes in synaptic transmission onto F344 rat basal forebrain cholinergic neurons using a reduced synaptic preparation. Griffith, WH, Dubois, DW, Fincher, A, Peebles, KA, **Bizon, JL**, Murchison, DA. *J. Neurophysiol.* 2014 Jan;111(2):273-86. doi: 10.1152/jn.00129.2013.

Sara N. Burke, PhD

1. **Burke, SN**, Maurer, AP, Nematollahi, S, Uprety, A, Wallace, JL, Barnes, CA (2014). Advanced age has dissociative effects on dual functions of the perirhinal cortex. *Journal of Neuroscience*, 34(2): 467-480.
2. **Burke, SN**, Thome, A, Plange, K, Engle, JR, Trouard, TP, Gothard, KM, Barnes, CA (2014). Orbitofrontal cortex and basolateral amygdala volume show a dissociable relationship with reward devaluation in young and aged monkeys. *Journal of Neuroscience*, 34(30): 9905-16.
3. Maurer, AP, Lester, AW, **Burke, SN**, Ferng, J, Barnes, CA (2014). Back to the Future: Preserved hippocampal network activity during reverse ambulation. *Journal of Neuroscience*, 5;34(45):15022-31.
4. **Burke, SN**, Barnes, CA (2014). The Neural Representation of 3-Dimensional Objects in Rodent Memory Circuits. *Behavioural Brain Research*, Sep 6. pii: S0166-4328(14)00584-1. doi: 10.1016/j.bbr.2014.09.001. [Epub ahead of print].
5. Topper, NC, **Burke, SN**, Maurer, AP (2014). Multiple Frequency Audio Signal Communication as a Mechanism for Neurophysiology and Video Data Synchronization. *Journal of Neuroscience Methods*, Sep 26;238C:35-42. doi: 10.1016/j.jneumeth.2014.09.018. [Epub ahead of print].

Andrew Maurer, PhD

1. **Maurer, AP**, Lester, AW, Burke, SN, Ferng, JJ & Barnes, CA. Back to the Future: Preserved Hippocampal Network Activity during Reverse Ambulation. *J Neurosci* 34, 15022-15031.
2. Topper, NC, Burke, SN, **Maurer, AP** (2014). Multiple frequency audio signal communication as a mechanism for neurophysiology and video data synchronization. *J Neurosci Methods* 238C:35-42.

3. Burke, SN, **Maurer, AP**, Nematollahi, S, Uprety, A, Wallace, JL, Barnes, CA (2014). Advanced age dissociates dual functions of the perirhinal cortex. *J Neurosci* 34:467-480.

ARML FUND RECIPIENTS:

Charles Jason Frazier, PhD

1. 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. *J Neurosci* 34:3457-3466.
2. Graves, CL, Harden SW, LaPato M, Nelson M, Amador, B, Sorenson, H, **Frazier, CJ**, Wallet, SM (2014) A method for high purity intestinal epithelial cell culture from adult human and murine tissues for the investigation of innate immune function. In press, *Journal of immunological methods*.

Brandi Ormerod, PhD

1. Asokan, A, Ball, AG, Laird, C, Hermer, L and **Ormerod, BK** (2014). Desvenlafaxine may accelerate neuronal maturation in the dentate gyri of adult male rats. *PlosOne*, Jun 4; 9(6):e98530. doi: 10.1371/journal.pone.0098530.
2. Qia, X, Shana, Z, Jia, Y, Guerra, V, Alexander, JC, **Ormerod, BK**, Bruijnzeel, AW (2014). Sustained AAV-mediated overexpression of CRF in the central amygdala diminishes the depressive-like state associated with nicotine withdrawal in rats. *Translational Psychiatry*, 4:4385.
3. Hajihashemi, MZ, Zhang, T, **Ormerod, BK**, Jiang, H (2014). Non-invasive detection of seizure activity using time-series analysis of light scattering images in a rat model of generalized seizure. *J Neuroscience Methods*, 227:18-28.

PUBLICATIONS (OTHER): ARML PROGRAM FACULTY:

Jennifer L. Bizon, PhD

Invited Chapter

1. Beas, BS, Setlow, B, Samanez-Larkin, GR, **Bizon, JL**. Modeling cost-benefit decision making in aged rodents. In Hess, TM, Loeckenhoff, CE, Sttrough (Eds.) *Aging and Decision-Making: Empirical and Applied Perspectives*, Elsevier Press.

Sara N. Burke, PhD

1. **Burke SN**, Maurer AP, Cowen SL & Barnes CA (2013). Perirhinal cortical interneurons exhibit reduced firing rates with advanced age. *Society for Neuroscience Abstracts*, 43.
2. Plange K, Engle JR, **Burke SN**, Gray DT, Barnes CA (2013). Changes in sensory function are correlated with cognitive impairments in bonnet macaques. *Society for Neuroscience Abstracts*, 43.
3. Chance FS, Maurer AP, **Burke SN**, Barnes CA (2013). Dual input component models of CA1 activity in young and aged rats. *Society for Neuroscience Abstracts*, 43.
4. Lester AW, Maurer AP., **Burke SN**, Hoang LT, Barnes CA (2013). Preserved neural dynamics during reverse locomotion. *Society for Neuroscience Abstracts*, 43.

PRESENTATIONS AT SCIENTIFIC MEETINGS: ARML PROGRAM FACULTY:

Jennifer Bizon, PhD

Invited

- *"Good things come to those who wait: altered cost-benefit decision-making in aged rat models."* Meeting of the Scientific Research Network on Decision Neuroscience and Aging, St. Pete's Beach, FL
- *"Pharmacological approaches to enhancing synaptic plasticity and cognitive aging"* McKnight Brain Research Foundation Inter-institutional meeting, Gainesville, FL
- *"Targeting GABAergic signaling to improve memory function in aged individuals"* Center for Cognitive Aging and Memory-Clinical Translational Research Program External Advisory Board Meeting, Gainesville, FL

Poster Presentations

- McQuail, JA, Beas, BS, Simpson, K, Setlow, B & **Bizon, JL**. (2014) *"Subtypes of Prefrontal Cortical NMDA Receptors in Working Memory and Normal Aging."* American College of Neuropsychopharmacology Meeting, Phoenix, AZ
- Orsini, CA Trotta, R, **Bizon, JL** & Setlow, B (2014). *"Lesions of the orbitofrontal cortex decrease risk taking in rats."* American College of Neuropsychopharmacology Meeting, Phoenix, AZ
- McQuail, JA, Bañuelos, C, Beas, BS, Setlow, B & **Bizon, JL** (2014). "*Prefrontal cortical NMDA receptors in age-related working memory impairment."* Annual Meeting of the Society for Neuroscience, Washington D.C.
- Orsini, CA, Trotta, R, **Bizon, JL** & Setlow, B (2014). *"The basolateral amygdala and the orbitofrontal cortex have functionally dissociable roles in a rodent model of risky decision-making."* Annual Meeting of the Society for Neuroscience, Washington D.C.
- Setlow, B, Orsini, CA & **Bizon, JL** & Setlow, B (2014). *"Aging is associated with reduced choice of risky options in Fischer 344 rats."* Annual Meeting of the Society for Neuroscience, Washington D.C.
- Shimp, KG, Orsini, CA, Gilbert, RJ, Willis, M, **Bizon, JL** & Setlow, B (2014). *"Sex differences in a rat model of risky decision making."* Annual Meeting of the Society for Neuroscience, Washington D.C.
- Deng, JV, Orsini, CA, Shimp, KG, **Bizon, JL** & Setlow, B (2014). *"Risky decision-making behavior modulates the epigenetic factor MeCP2 in prefrontal cortex."* Annual Meeting of the Society for Neuroscience, Washington D.C.
- Bañuelos, C, **Bizon, JL** & Setlow, B (2014). *"Activation of basal forebrain GABAergic projection neurons alters mPFC-mediated working memory performance in young F344 rats."* Annual Meeting of the Society for Neuroscience, Washington D.C.
- Beas, BS, Simpson, K, Bañuelos, C, **Bizon, JL** & Setlow, B (2014). *"NMDA receptors hypofunction contribute to impaired working memory in aged F344 rats."* Annual Meeting of the Society for Neuroscience, Washington D.C.
- Yoder, WM, Gaynor, L, Windham, E, **Bizon, JL** & Setlow, B & Smith, DW. (2014). *"A psychophysical technique for characterizing age-associated alterations in olfactory function."* Annual Meeting of the Society for Neuroscience, Washington D.C.
- **Bizon, JL**, Yoder, WM, Lyman, M, Muizza, O, Burke, SN, Ormerod, BK, Setlow, B & Smith, DW. (2014). *"Interaction between age and perceptual difficulty in olfactory discrimination learning: relationship with spatial learning impairment."* Annual Meeting of the Society for Neuroscience, Washington D.C.
- Beas, BS, Bañuelos, C, Gilbert, RJ, **Bizon, JL** & Setlow, B (2014). *"GABA(B) receptor signaling and behavioral flexibility in aging."* Annual Meeting of the International Behavioral Neuroscience Society, Las Vegas, NV.
- Orsini, CA, Trotta, R, **Bizon, JL** & Setlow, B (2014). *"Lesions of the basolateral amygdala induce elevated risk-taking in rats."* Annual Meeting of the International Behavioral Neuroscience Society, Las Vegas, NV.
- Shimp, KG, Orsini, CA, Gilbert, RJ, Willis, M, **Bizon, JL** & Setlow, B (2014). *"Sex differences in a rat model of risky decision making."* Annual Meeting of the International Behavioral Neuroscience Society, Las Vegas, NV.
- Bañuelos, C, Setlow, B & **Bizon, JL** (2014). *"Activation of basal forebrain GABAergic projection neurons alters mPFC-mediated working memory performance in young F344 rats."* Annual Meeting of the International Behavioral Neuroscience Society, Las Vegas, NV.

Sara N. Burke, PhD

- April 25, 2014: McKnight Inter-Institutional Meeting, Rising Starts Symposium. *"Dissecting Cortical-Hippocampal Circuits across the Life Span"*
- Feb 11, 2014: Florida Atlantic University/Scripps/Max Planck Jupiter Campus Neuroscience Seminar. *"Senescence and Perirhinal Cortical Function: A Multi-level Approach to Understanding Cognitive Function"*
- Jan 16, 2014: Florida BRAIN Initiative Symposium, Gainesville, FL. *"Deriving Meaning from the Neural Code: Big Data is Neurophysiology"*
- Jan 6, 2014: Winter Conference on Learning and Memory, Park City, UT. *"Perirhinal Cortical Circuit Disruptions in a Rat Model of Normal Aging"*
- Jan 5, 2014: Winter Conference on Learning and Memory, Park City, UT. *"False Recognition in Normal Aging"*

ARML FUND RECIPIENTS:

Charles Jason Frazier, PhD

- Moroz, II, Meredith, G, Sun, Yu, Candelario, KM, Dhingra, D, Ianov, L, Rani, A, Harden, S, Kumar, A, **Frazier, CJ**, Steindler, DA, Foster, T, Khon, A. *"Single-neuron RNA-seq: Genomic dissection of memory circuits and cell census in the brain."* 2014 Society for Neuroscience Meeting, Washington DC, 464.24
- Kelly, KB, Carpenter, HE, McQuail, JA, Bizon, JL, **Frazier, CJ**. *"Effects of age on excitatory inputs to pyramidal cells and interneurons in rat medial prefrontal cortex."* 2014 Society for Neuroscience Meeting, Washington DC, 847.04

Brandi Ormerod, PhD

Invited

- **Ormerod, BK** (2014). Neuroimmune signaling, hippocampal neurogenesis and cognition across lifespan. 5th Annual PEI Bioalliance- and Neurodyn-sponsored Biotechnology and Human Health Symposium, *"Neuroprotection and Repair"*. Charlottetown, Prince Edward Island, Canada.

Poster Presentations

- McGuiness, J, Speisman, RB, Asokan, A, Kumar, A, Rani, A, Foster TC, **Ormerod, BK** (2014). "*Neurogenesis declines in the olfactory bulbs and hippocampi of middle-aged and aged rats.*" Annual Meeting of the Society for Neuroscience, Washington, DC. Soc Neurosci Abstr Vol 39. 495.11.
- Bizon, JL, Yoder, WM, Lyman, M, Munizza, O, Burke, SN, **Ormerod, BK**, Setlow, B, Smith, DW (2014). *"Interaction between age and perceptual difficulty in olfactory discrimination learning: relationship with spatial learning impairment."* Annual Meeting of the Society for Neuroscience, Washington, DC. Soc Neurosci Abstr Vol 39. 847.02.

PRESENTATIONS AT NON-SCIENTIFIC MEETINGS OR EVENTS: ARML PROGRAM FACULTY:

Jennifer Bizon, PhD

- *"Healthy brain aging and cognition across the lifespan"* Sia Yorker Brain Awareness Scholarship Luncheon, Deland, FL

Sara N. Burke, PhD

- Nov 20, 2014: Howard Hughes Medical Institute Science for Life Seminar, Gainesville, FL. *"Behavioral Insights into the Neurobiology of Aging"*

- Oct 13, 2014: NeuroEngineering Dinner Speaker Gainesville, FL. *"A Novel Tool for Examining Circuit Function in Aging and Disease"*
- Sep 11, 2014: Department of Neuroscience Data Blitz, Gainesville, FL. *"Examining Functional Connectivity Changes with Age"*
- April 15, 2014: University of Florida Neuroscience Club. *"The Neurobiology of Cognitive Aging"*

Andrew Maurer, PhD

- July 17th, 2014: Neuromedicine Summer Seminar Series; *"Multi-level approach for Cognitive Aging"*

ARML FUND RECIPIENT:

Brandi Ormerod, PhD

- Ormerod, BK (2014). *"Maternal Inflammation and adult Neurogenesis. Neuroscience Brain Journal Club."* UF Neuroscience Department (Gainesville, FL).

AWARDS (OTHER):

Joseph McQuail (Postdoctoral Fellow)

1. McKnight Brain Institute Fellowship ($50,000.00)
2. Travel award given by the North Central Florida Chapter of Society for Neuroscience

Caitlin Orsini (Postdoctoral Fellow, co-Mentored with Barry Setlow, PhD)

1. Society for Neuroscience Travel Award
2. International Behavioral Neuroscience Society Travel Award to attend annual meeting in Las Vegas
3. Runner-up McKnight Brain Institute Fellowship ($10,000.00)
4. Finalist in Maren Postdoctoral Award Competition

    b. Pre-doctoral

Sofia Beas (Graduate student)

1. International Behavioral Neuroscience Society Travel Award to attend annual meeting in Las Vegas
2. Bryan Robinson Endowment Honorable Mention

Cristina Bañuelos (Graduate student; received PhD in 2014 and is currently Postdoctoral Fellow at National Institute on Aging)

1. North Central Florida SfN Chapter Annual Conference Poster Competition – 1st place
2. International Behavioral Neuroscience Poster Competition (Las Vegas, NV) – 3rd place

3. Selected to attend Howard University SBE Research Day
4. Selected to attend SPINES course at MBL in Woods Hole (Full Scholarship)

c. Other

Sara N. Burke, PhD

1. 2014 UF Research Opportunity Seed Fund Recipient – Awarded 84K/2 years
2. 2014 Department of Neuroscience Data Blitz – voted best talk by the Neuroscience IDP students

FACULTY BIOGRAPHICAL SKETCHES: See page 91

TRAINEES:
ARML PROGRAM FACULTY:

Jennifer Bizon, PhD

a. **Post-doctoral**
Joe McQuail, PhD

b. **Pre-doctoral**
Cristina Bañuelos
Sofia Beas

Sara N. Burke, PhD

a. **Post-doctoral**
Sarah A. Johnson, PhD, joined the McKnight Brain Institute Age-related Memory Loss group in Sep, 2014. She has been running behavioral pharmacology experiments examining the relationship between perceptual difficulty and age-related memory impairments. Dr. Johnson has also been quantifying the expression of neural activity dependent immediate-early genes that is induced by difficult discrimination.

a. **Pre-doctoral**
Sarah E. Burke joined the Burke lab in May, 2014. Sarah is an IDP student and partially funded from Dr. Burke's ARML startup funds. She has been examining changes in functional connectivity that occur over the lifespan using behavioral analysis, pharmacology and gene expression assays.

ARML FUND RECIPIENTS:
Charles Jason Frazier, PhD

b. **Pre-doctoral**
Kyle Kelly
Haley Carpenter (graduated Summer 2013)
Scott Harden
Dipa Pati

Brandi Ormerod, PhD

b. **Pre-doctoral**
James McGuiness

Project: To understand the relationship between changes in cognition, inflammatory signaling, hippocampal neurogenesis and olfactory bulb neurogenesis across lifespan

Jeffrey Leibowitz
Project: To test the effect of somatostatin signaling on seizure behavior, inflammation and hippocampal neurogenesis in a rat model of epilepsy

Vivien Schwingel
Project: To test the effect of NSAID administration and age on microglial activation states

Garrett Donnelly
Project: Generation and characterization of axolotl neural progenitor cells

Kristina Zopf
Project: Testing the effects of age on hippocampal and olfactory bulb neurogenesis

Anna DeNadel
Project: A network analysis of cytokine signaling and hippocampal neurogenesis

CLINICAL/TRANSLATIONAL PROGRAMS: NA

TECHNOLOGY TRANSFER: ARML PROGRAM FACULTY:

Sara N. Burke, PhD

Patents applications
UF#15222 entitled *"FTIR Method of Rodent Gait Analysis"* Disclosure: Sara Burke, Rodney Ndum, Nicholas Topper and Andrew Maurer

Andrew Maurer, PhD

Patents applications
We have submitted two disclosures and are currently working with the Office of Technology Licensing:
Ref#15231: Low Cost Control for Operant Conditioning Box – Submitted: 05/28/2014

Ref#15222: FTIR Method of Rodent Gait Analysis – Submitted: 05/23/2014

ARML FUND RECIPIENTS:

Sofia Beas (Graduate Student)

Patents applications
In the last year, I have been involved in two invention disclosures. One is related to the use of GABA(B)R antagonists as a treatment for age-related memory loss and the second relates to a low-cost behavioral operant chamber that my collaborator Dr. Drew Maurer has designed.

BUDGET UPDATE: See page 70

EDUCATIONAL PROGRAMS FOCUSING ON AGE RELATED MEMORY LOSS: NA

COLLABORATIVE PROGRAMS WITH OTHER MCKNIGHT INSTITUTES, INSTITUTIONS AND RESEARCH PROGRAMS:

Cristina Bañuelos (Graduate student; received PhD in 2014 and is currently Postdoctoral Fellow at National Institute on Aging)

My laboratory designed and conducted the behavior assessments of prefrontal cortical function for the McKnight-funded epigenetics initiative.

COLLABORATIVE PROGRAM WITH NON-MCKNIGHT INSTITUTES, INSTITUTIONS AND RESEARCH PROGRAMS:

Cristina Bañuelos (Graduate student; received PhD in 2014 and is currently Postdoctoral Fellow at National Institute on Aging)

My laboratory has a collaboration with Dr. Greg Samanez-Larkin at Yale University to study the neural mechanisms of age-related alterations in decision-making. In the past year, we have begun a series of studies in which we are integrating decision-making behavioral paradigms with PET imaging of dopaminergic signaling. This collaboration has thus far resulted in 1 invited chapter (In Press In Aging and Decision-Making: Empirical and Applied Perspectives, Elsevier Press). In the next year, we hope this collaboration will result in at least one additional publication as well as a new grant submission.

A second, active collaboration of my laboratory is with Dr. David Smith (Psychology, UF). The focus of this collaboration is to investigate perceptual learning changes in aging and how degraded perceptual acuity can contribute to mnemonic dysfunction. This collaboration has resulted in data for several publications (to date, 1 manuscript is published in Chemical Senses, 1 manuscript in Under Review and 1 manuscript is In Preparation). In addition, the new findings resulting from these initial studies with Dr. Smith provide a critical foundation for a line of collaborative research being developed with Dr. Sara Burke. This latter collaboration will involve integration of our behavioral models and pharmacological approaches with Dr. Burke's in vivo electrophysiological recording techniques to investigate perceptual alterations in aging and how such alterations contribute to age-related cognitive decline.

Finally, we have an ongoing and productive collaboration with Dr. Jason Frazier (Pharmacodynamics, UF) that is related to our primary research program investigating the neural mechanisms of prefrontal cortical-mediated cognitive decline. This collaboration has thus far resulted in 1 published paper (J. Neuroscience), with another in preparation. The data acquisition for a third paper is largely complete (presented at the recent SfN meeting) and we expect that 2 papers will be submitted in the next year. Dr. Frazier and I are also actively working on a MPI R01 proposal, which we plan to submit in the next year.

BRIEFLY DESCRIBE PLANS FOR FUTURE RESEARCH AND/OR CLINICAL INITIATIVES:

Cristina Bañuelos (Graduate student; received PhD in 2014 and is currently Postdoctoral Fellow at National Institute on Aging)

Our research funding from the McKnight Brain Research Foundation ends this year. As such, in the upcoming year, we will prioritize targeting any funding opportunities that can help support our ongoing research related to age-related cognitive decline in our laboratory in an attempt to maintain our current level of productivity on this topic. We have several lines of ongoing research that are currently supported by the MBRF that we will use as the foundation for new grant proposals. These include projects related to: 1- molecular characterization of prefrontal cortical interneurons and their role in prefrontal cortical dependent cognition; 2- perceptual discrimination changes with age and their contributions to impaired mnemonic function; and 3- the role of HPA axis dysfunction in age-related changes in altered prefrontal cortical excitatory and inhibitory signaling dynamics and age-related cognitive decline.

In addition, through our existing contract with Sanford Burnham, we will continue our efforts to move the drug discovery program forward and to secure the required funds to test the novel compounds to be generated under this contract.

Sara N. Burke, PhD

I have recently established multiple collaborations within the Department of Neuroscience as well as other departments on campus. In collaboration for Drs. Jennifer Bizon (Neuroscience) and Brandi Ormerod (Biomedical Engineering), we are investigating deficits in cross-modal discrimination in aged animals and the role of neurogenesis in this cognitive process. We are currently preparing an R21 to be submitted at the beginning of 2015. Andrew Maurer and I are also collaborating with Brandi Ormerod to examine the role of neurogenesis on hippocampal activity patterns across the lifespan. This projects received 84K in funding from UF Research Seed Opportunity Fund. Finally, working with Jose Principe in the Department of Electrical and Computer Engineering, we are developing and testing novel signal processing algorithms to decompose local field potential data in order to enhance our ability to detect age differences and relate neurophysiology data to behavior. Each are these collaborations are directly aligned with ongoing research in my laboratory and are enriching already established research trajectories within the MBI Age-related Memory Loss group.

IF APPLICABLE, PLEASE PROVIDE ENDOWMENT INVESTMENT RESULTS FOR THE REPORT PERIOD: See page 78

WERE ANY FUNDS USED FOR A PROHIBITED PURPOSE DURING THE REPORT PERIOD? No

DO YOU RECOMMEND ANY MODIFICATION TO THE PURPOSE OR MANDATES IN THE GIFT AGREEMENT? No

DID ALL ACTIVITIES DURING THE REPORT PERIOD FURTHER THE PURPOSE? Yes

NEGATIVE EVENTS (LOSS OF PERSONNEL, SPACE, BUDGET ETC.):

Charles Jason Frazier, PhD

The senior post-doc originally hired to support this project left the lab at the end of 2012 and has been replaced by a new graduate student from the COP. As a result two graduate students (one senior, one junior) are currently focused 100% on projects consistent with the ARML mission.

ADDITIONAL COMMENTS: See letter on page 5

SIGNATURE, DATE AND TITLE OF PERSON SUBMITTING THE REPORT:

Tetsuo Ashizawa, MD
Executive Director, McKnight Brain Institute
Melvin Greer Professor
Chairman, Department of Neurology

McKnight Endowed Chair

2014 Progress Report

SUMMARY OF SCIENTIFIC ACHIEVEMENTS SINCE LAST REPORT:

The spatial water maze is routinely used to investigate hippocampal-dependent spatial memory and the biological mechanisms that underlie variability in cognitive decline during aging. The utility of the task for repeated testing in order to examine the trajectory of cognitive decline and to prescreen animals prior to therapeutic interventions maybe limited due to carryover effects of repeated training. We completed a study examining the reliability of individual differences using different spatial memory tasks *(Guidi et al., 2014)*. Results indicate that impaired acquisition of episodic spatial information emerges in middle-age and the propensity for impairment increases with advancing age. Learning was variable across animals; however, deficits in middle-age and aged animals were reliable across testing sessions. Together, the results point to a progressive impairment in episodic spatial memory with advancing age and suggest that tests of episodic spatial memory are reliable and more sensitive than reference memory for detecting cognitive decline. Thus, the episodic spatial memory task is good for examining the trajectory of cognitive decline and for examining the effects of treatments on this decline.

The oxidative stress theory of aging suggests that treatments, which enhance or reduce oxidative stress or damage will have predictable effects in promoting or delaying aging processes. Our work indicates that oxidation-reduction (redox) status of the intracellular environment impairs NMDAR function contributing to senescent neurophysiology which represents one of the earliest signs of cognitive aging. However, no study has explicitly tested the prediction that overexpressed antioxidant genes will modify NMDAR function in a manner consistent with this idea. In this study, viral vectors were used to express antioxidant enzymes in the hippocampus of middle-age rats *(Lee et al., 2014)*. The results provide strong support for the idea that a shift in the redox environment mediates the decrease in NMDAR function, which in turn results in impaired memory.

The shift in redox state alters Ca2+ regulation (including the decrease in NMDAR function) and the rise in senescent neurophysiology. One aspect of senescent neurophysiology is an increased susceptibility to induction of long-term depression (LTD) and weakening of synaptic transmission through the hippocampus. One study examined the signaling pathways involved in LTD in aged animals *(Kumar and Foster, 2014)*. The results indicate that several Ca2+ sources that are disrupted during aging contribute to the magnitude of LTD. Of particular importance are group I metabatropic receptors suggesting a novel mechanism for possible pharmacological intervention.

PUBLICATIONS IN PEER REVIEWED JOURNALS:

1. Lee, WH, Kumar, A, Rani, A, **Foster, TC**. Role of antioxidant enzymes in redox regulation of N-methyl-D-aspartate receptor function and memory in middle-aged rats. Neurobiol Aging 2014,35 1459-68. **PM: 3961498**
2. Bean, LA, Ianov, L, **Foster, TC**. Estrogen Receptors, the Hippocampus, and Memory. The Neuroscientist 2013, 2014 20, 534-545. **PM: 24510074**
3. Kumar, A and **Foster, TC**. Interaction of DHPG-LTD and synaptic-LTD at senescent CA3-CA1 hippocampal synapses. Hippocampus, 2014, 24 466-47. **PMID: 3959216**
4. Guidi, M, Kumar, A, Rani, A, **Foster, TC**. Assessing the emergence and reliability of cognitive decline over the life span in Fisher 344 rats using the spatial water maze. Front Aging Neurosci, 2014 6:2. **PMID: 3896816**

PUBLICATIONS (OTHER): NA

PRESENTATIONS AT SCIENTIFIC MEETINGS:

- *"Single-neuron RNA-seq: Genomic dissection of memory circuits and cell census in the brain."* (2014) Moroz, LL, Meredith, G, Sun, Y, Candelario, KM, Dhingra, D, Ianove, L, Rani, A, Harden, S, Kumar, A, Frazier, CJ, Steindler, DA, **Foster, TC**, Kohn, A. Soc for Neurosci. 464.24.
- *"Neurogenesis declines in the olfactory bulbs and hippocampi of middle-aged and aged rats."* (2014) McGuiness, Speisman, RB, Asokan, A, Rani, A, Kumar, A, **Foster, TC**, Ormerod, BK. Soc for Neurosci. 495.11
- *"Inflammation as a potential mediator of decreased NMDA receptor function and the onset of age-related cognitive decline: A test for the effectiveness of anti-inflammatory drugs."* (2014) Kumar, A, Rani, A, **Foster, TC**. Soc for Neurosci. 559.19.

- *"Epigenetic regulation of estrogen receptor a contributes to age-related differences in transcription across the hippocampal regions."* (2014) Ianov, L, Kumar, A, **Foster, TC**. Soc for Neurosci. 758.10.
- *"Estrogen and Neural Plasticity for the Winter Conference of Neural Plasticity."* Vieques, Puerto Rico (Feb 22-28).
- *"Effect of environmental enrichment on the aging hippocampus."* International Graduate School of Neuroscience, Ruhr University Bochum, Germany (Oct 6).
- The Florida Symposium on the BRAIN Initiative, Neurogenetics (1/16/2014).
- Update on the Inter-Institute Bioinformatics Core Project. MBRF Inter-Institute Meeting, 4/23-25/2014.
- *"Bridging the gap between senescent synapses and genomic programs for cell health."* Therapeutic Approaches for Extending Healthspan: The Next 10 years Scripps Research Institute Florida (5/6/2014).
- *"Age-related memory loss: Where synaptic plasticity meets oxidative stress."* The Florida Brain Project, Tallahassee, FL 7/28/2014.
- *"Animal models of age-related cognitive decline."* Animal Molecular & Cellular Biology Graduate Program, University of Florida IFAS, Gainesville, FL 10/24/2014.

PRESENTATIONS AT PUBLIC (NON-SCIENTIFIC) MEETINGS OR EVENTS:

- *"The Brain and Contemplation."* Fall Mind and Soul Lecture Series Kanapaha Presbyterian Church, Gainesville, FL (7/14/2014).

AWARDS (OTHER):

a. 2014-present: Member of the Steering committee for the Winter Conference on Neural Plasticity

b. 7/2014-6/2018: Member of the NIH Learning and Memory study section

FACULTY BIOGRAPHICAL SKETCHES: See page 91

TRAINEES:

a. Post-doctoral: NA

b. Pre-doctoral
Michael Guidi, Graduate Student, Department of Neuroscience, University of Florida (Graduated 2014)
Linda Bean, Graduate Student, Department of Neuroscience, University of Florida
Lara Ianov, Graduate Student, Department of Genetics, University of Florida

c. Other
Asha Rani (Technical)

CLINICAL/TRANSLATIONAL PROGRAMS:

a. New programs
Role of Systemic Inflammation in Age-Related Cognitive Decline: A group of researchers (Foster, Leeuwenburgh, Bizon, Setlow, Fraizer, Ormerod) met to develop plans and common interest for generating grant proposals. A common interest involved the role of inflammation in the onset and progression of age-related cognitive decline. $6,000 was obtained from the ARML program for a pilot study. The data was used for grants submitted to NIH. A proposal submitted by Dr. Foster, Systemic inflammation in regulating the onset and progression of brain aging, received a very good score and was ranked at the 12th percentile. The proposed studies will test a hypothesized mechanism that links inflammation induced

oxidative stress with synaptic mechanisms that regulate memory and the transcription of genes that maintain the health of neurons. This work builds off the recent paper from the Foster lab *(Guidi et al., 2014)*, showing that the behavioral tasks are reliable across testing session in order to test therapeutics, that the decline in NMDAR function is due to oxidative stress, possibly arising from inflammation *(Lee et al., 2014; Kumar and Foster, 2014)*, and preliminary data generated from the ARML pilot program.

University of Florida Bio-Informatics Core: Equipment: We have the new Ion Chef up and running. The Ion Chef is used to make the RNA libraries. In collaboration with the ICBR at the University of Florida, we are testing a Fluidigm C1 system for single cell analysis. It is hope that this system can be used to isolate RNA expression changes associated with age/cognitive to specific cell types. *Protocols:* We have tested two protocols for RNA enrichment. RiboMinus technology is designed to enrich the whole spectrum of RNA transcripts by selectively depleting ribosomal RNA molecules (rRNA), regardless of their polyadenylation status or the presence of of a 5'-cap structure. This technique has the advantage of preserving long noncoding RNA, but gives a low yield of total RNA. Traditionally, enrichment poly(A)+ RNAs has been used, which provides a more abundant yield of RNA, but does not preserve noncoding RNAs that are likely important for epigenetic regulation of transcription. Both techniques tend to correlate for relative expression of RNA. *Pipeline for Processing and Analysis:* For RNA we have a pipeline of analysis for sequencing on our system through quality checks, mapping/alignment, gene annotation, statistical tests, and functional annotation of pathways. Epigenetics (DNA methylation): It does not appear the Ion Proton can be used for examining DNA methylation. Therefore, we have secured the use of the Illumina NextSeq 500 equipment from a core facility at the University of Florida. Currently, we are testing the Model based Analysis of Bisulfite Sequencing (MOABS) for analysis of DNA methylation. This is our current top priority in establishing the DNA methylation as a component of the core. *Relationship between transcription and cognitive decline:* We have run 10 aged and 5 young through the behavioral battery, examining aging of multiple cognitive processes. The results indicate that, within a single subject, cognitive decline is variable across domains. Thus, individuals can decline in one domain (e.g. memory) and not another (e.g. attention). We have completed the RNA analysis for the medial prefrontal cortex and found that this correlates with a decline in attention. In addition, hippocampal tissue for a subset of these animals was submitted for RNA expression in hippocampal subregions (CA1, CA3, dentate gyrus) and bio-informatics analysis across institutions (see below).

b. Update on existing clinical studies

See the annual report from Dr Bizon for an update on GABAB receptor antagonists as a treatment for age-related cognitive decline.

TECHNOLOGY TRANSFER: NA

BUDGET UPDATE: See page 70

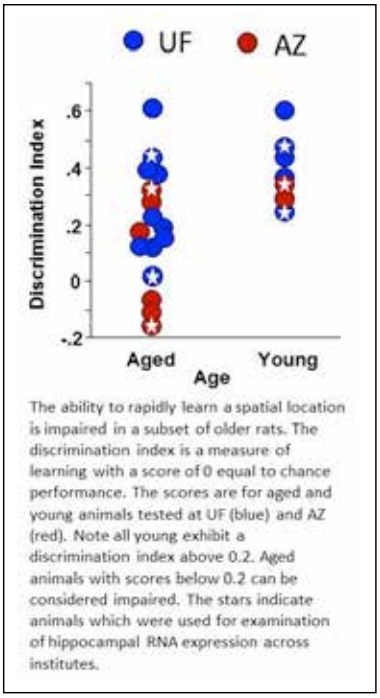
EDUCATIONAL PROGRAMS FOCUSING ON AGE RELATED MEMORY LOSS: NA

COLLABORATIVE PROGRAMS WITH OTHER MCKNIGHT INSTITUTES, INSTITUTIONS AND RESEARCH PROGRAMS:

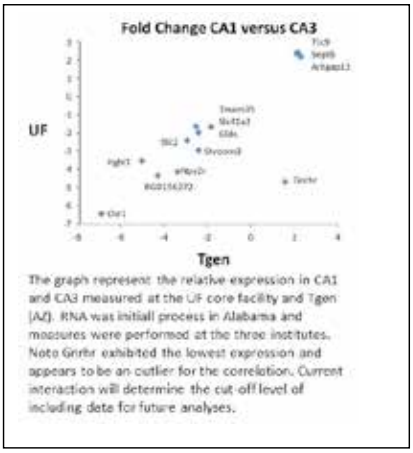
McKnight Inter-Institutional Bio-Informatics Core:

Recently we have examined the reliability of behavioral measures (episodic memory) and RNA expression measures across MBRF sponsored institutions. *Behavior:* Animals tested at UF and UofA exhibited similar distributions. Despite the use of separate techniques, the results are highly correlated.

RNA expression: The results were presented at the MBRF poster session at the recent Society for Neuroscience meeting in Washington D.C. Across institutes, differences in measures arise for transcripts with low level expression *(Gnrhr in the figure)*; however, this is to be expected. Currently we are discussing cut-offs and limits for accepting the data. Despite a limited number of cognitively tested animals (3 young and 4 aged), the results confirm our previous work in area CA1 of the hippocampus and point to biological markers and pathways for other hippocampal regions (CA3 and the dentate gyrus).



The ability to rapidly learn a spatial location is impaired in a subset of older rats. The discrimination index is a measure of learning with a score of 0 equal to chance performance. The scores are for aged and young animals tested at UF (blue) and AZ (red). Note all young exhibit a discrimination index above 0.2. Aged animals with scores below 0.2 can be considered impaired. The stars indicate animals which were used for examination of hippocampal RNA expression across institutes.



The graph represent the relative expression in CA1 and CA3 measured at the UF core facility and Tgen (AZ). RNA was initiall process in Alabama and measures were performed at the three institutes. Note Grin3r exhibited the lowest expression and appears to be an outlier for the correlation. Current interaction will determine the cut-off level of including date for future analyses.

COLLABORATIVE PROGRAM WITH NON-MCKNIGHT INSTITUTES, INSTITUTIONS AND RESEARCH PROGRAMS: NA

BRIEFLY DESCRIBE PLANS FOR FUTURE RESEARCH AND/OR CLINICAL INITIATIVES:

Currently we are meeting with the other institutes to insure progress for the bio-informatics core and developing the techniques for DNA methylation studies, single cell analysis, and the collection of blood from patients. In addition, to establishing the foundations of the core, we are conducting proof of principle studies examining the relation of RNA expression with cognition.

IF APPLICABLE, PLEASE PROVIDE ENDOWMENT INVESTMENT RESULTS FOR THE REPORT PERIOD. See page 78

WERE ANY FUNDS USED FOR A PROHIBITED PURPOSE DURING THE REPORT PERIOD? No

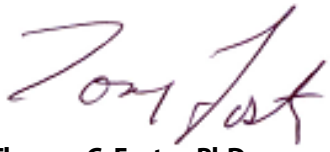
DO YOU RECOMMEND ANY MODIFICATION TO THE PURPOSE OR MANDATES IN THE GIFT AGREEMENT? No

DID ALL ACTIVITIES DURING THE REPORT PERIOD FURTHER THE PURPOSE? Yes

NEGATIVE EVENTS (LOSS OF PERSONNEL, SPACE, BUDGET, ETC.): NA

ADDITIONAL COMMENTS: NA

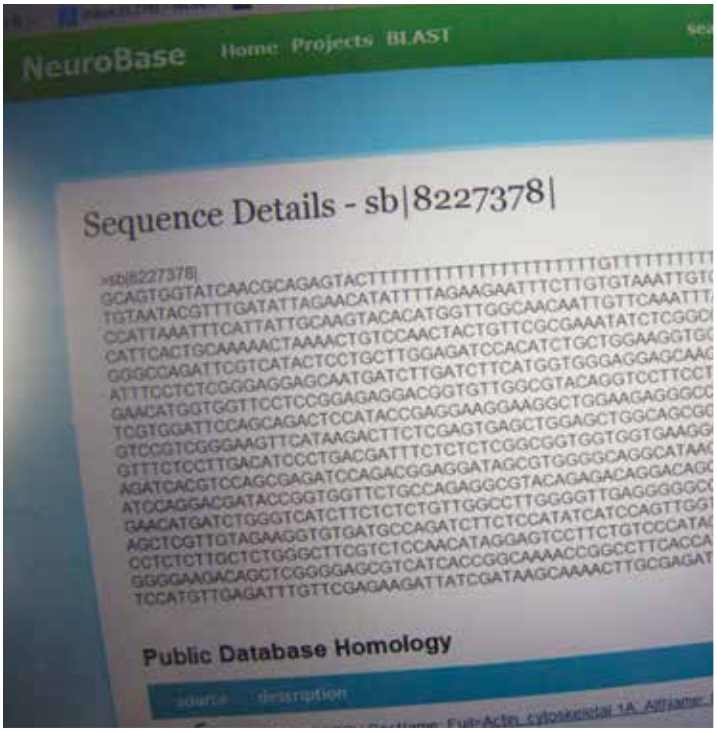
SIGNATURE, DATE AND TITLE OF PERSON SUBMITTING THE REPORT:



Thomas C. Foster, PhD
Professor and Evelyn F. McKnight Chair for Research in Cognitive Aging and Memory

Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP)

2014 Progress Report



Institute on Aging
Dept. of Aging and Geriatric Research
Cognitive Aging and Memory-
Clinical Translational Research Program
(CAM-CTRP)

PO Box 100107
Gainesville, FL
32610-0107
352-294-5841

November 20, 2014

Dear Trustees of the McKnight Brain Research Foundation:

We are providing you with a progress report of the Cognitive Aging and Memory-Clinical Translational Research Program (CAM-CTRP) for the year ending December 2014. The past year has been extremely busy and productive for the CAM-CTRP, even surpassing last year's activity. A majority of projects that were initiated last year are in progress and a number of new initiatives have been undertaken. The CAM-CTRP has enjoyed many successes that will keep the program on track for a future of exciting and groundbreaking clinical-translational research.

We hosted the second annual External Review Board Meeting at the CTRB, which offered valuable insight and recommendations as noted in the summary report by Dr. Marc Fisher, M.D. attached to this report. The advisory board was glowing in their review of our program. The board reported that they are "very impressed with the rapid development of the CAM-CTRP" and the number of initiatives that are currently ongoing. We had successfully addressed almost all issues raised in the first annual review and had gone well beyond our own benchmarks. The two areas of continued development that had been raised in the first review and continue to be a focus of our efforts are: 1) Recruitment of a physician scientist to service as the medical section director and to facilitate clinical trial development; and 2) Making further progress on the development of clinical translational research focusing on interventions for the elderly.

With respect to the physician recruitment, we currently have a preeminent neurologist from Germany, Dr. Michael Nitsche, who we will be bringing for a second visit in March 2015. We also have a cognitive aging researcher, Dr. Diego Iacono, from Mount Sinai University, NY, who will be coming for a first interview in January 2015. With respect to clinical translational efforts, we submitted a R01 application in response to the NIA-NCCAM-MBI RFA and received an excellent priority score of 16. However, we did not receive the primary award. We are currently working with the program officer at NIA, and the UF and University of Miami administrations to establish a cost-sharing arrangement

that may enable NIH to fund a smaller version of the grant. Other intervention research includes studies of on real-time FMRI designed as an intervention to enhance emotional function in the elderly (Ebner, Sitaram, Cohen), and transcranial direct current stimulation (tDCS), with studies being conducted by Woods and Cohen and grant applications being prepared for the winter NIH submission. Dr. Cohen has also been fostering research projects aimed at bringing novel pharmaceutical compounds to phase 1 clinical trial. Specifically, he has worked with Drs. Bizon, Ashizawa, and others in a workgroup focusing on a GABA inhibitor that has the potential to enhance learning and executive functioning in the elderly. A number of other initiatives are underway as outlined in this report.

Dr. Ron Cohen is currently co-mentoring 4 graduate students, and 2 Post-Doctoral Fellows. Dr. Adam J. Woods, Ph.D., who joined the faculty in 2013, has also been extremely productive. He was awarded KL2 career development award in March 2014, submitted a K01 to NIA in October 2014, and will be submitting two R01's in the next cycle. Dr. Woods is currently mentoring two graduate students, and co-mentoring 3 additional graduate students. We have also had two new faculty members join our group (Drs. Kim Sibille and Yenisel Cruz- Almeida). Both are funded by career development awards from NIH. Dr. Eric Porges, currently a post-doctoral fellow has written a K-99 proposal to NIAAA and will move into a tenure track faculty position when this is funded. In addition, Dr. Damon Lamb has also joined our group as an affiliate faculty member. Dr. Lamb is currently preparing a VA CDA2 career award.

The faculty of the CAM-CTRP has been extremely productive over the past year, publishing numerous manuscripts on topics related to cognitive and brain aging. We are particularly pleased to report that Dr. Cohen's RO1 proposal to the NIDDK on obesity and type II diabetes: bariatric surgery effects on brain function and aging was funded and participant recruitment has begun. The project has major implications for understanding the aging brain, particularly the influence of metabolic factors associated with obesity and diabetes on brain structure and function, and the brain effects resulting from reductions in these factors following bariatric surgery and significant weight loss. This clinical study provides an excellent experimental model for testing whether caloric reduction improves brain health, with major implications for healthy cognitive aging.

In addition, the CAM-CTRP faculty have over 20 pending grants in PI and Co-I roles. These include collaborations with UCLA, UF-College of Public Health & Health Professions, Malcolm Randal VAMC, University of Pittsburgh, University of Miami, University of Alabama at Birmingham, University of Arizona, University of Arkansas for Medical Sciences, City College of New York, University of Pennsylvania, and Brown University. The topics span a broad range of important areas for study of the aging brain, such as predicting brain changes, multi-modal brain training for broad cognitive transfer in elders, white matter integrity and ultra-high field neuroimaging of the aging brain, and non-invasive interventions for cognitive aging.

There continue to be number of pilot studies (13) that are either underway or will be initiated over the next 12 months. These are detailed in the body of this report, which indicate substantial growth in the program as a whole, and successful collaboration among many disciplines. The CAM-CTRP has enjoyed a wonderful year of successes, and we are poised to continue that trend with enthusiasm.

Sincerely,

Ronald Cohen, Ph.D., ABPP, ABCN
Professor, Aging, Neurology, and Psychiatry
Director, CAM-CTRP

Marco Pahor, M.D.
Professor and Chair
Department of Aging and Geriatric Research
Director, Institute on Aging

SUMMARY OF SCIENTIFIC ACHIEVEMENTS SINCE LAST REPORT:

The Cognitive Aging and Memory-Clinical Translational Research Program had a number of achievements since the last annual report. This included major developments within its administrative structure, faculty and affiliate faculty recruitment collaboration, an External Advisory Board full program review, startup of a large scale "normal aging" research study, multiple other pilot studies to support cognitive aging research, participation in the McKnight Inter-Institutional Initiative, startup of an NIH RO1 Grant on Type II Diabetes/Bariatric Surgery/ Aging and Cognition, and many important infrastructure development successes that will enable successful continuation of this important program. A number of specific scientific achievements have occurred which are outlined later in this report.

A. Since the last report, the Cognitive Aging and Memory-Clinical Translational Research Program (CAM-CTRP) hosted the second annual External Review Board Meeting. The distinguished board of external reviewers for the program were:

Marc Fisher, MD – University of Massachusetts Medical School

Peter Monti, PhD – Brown University

Jeff Williamson, MD, MHS – Wake Forest University

Mark Espeland, PhD – Wake Forest University

The reviewers were extremely impressed with the successes and progress achieved over the past year, since the first board meeting. An executive summary was generated by the board which has been included in the current report. In addition to continuing to be impressed by the vision, scientific expertise and resources available in the CAM-CTRP, they provided considerable praise for the rapid development of the program, the amount and quality of scientific productivity, and the growth of the faculty, including the involvement of faculty from across the University. The primary area that they felt required continued emphasis related to the recruitment of a physician researcher to augment the clinical translational elements of the program, particularly related to clinical trials of cognitive aging. A national search for a physician researcher with a strong NIH track record continues to be underway with several promising candidates in the pipeline.

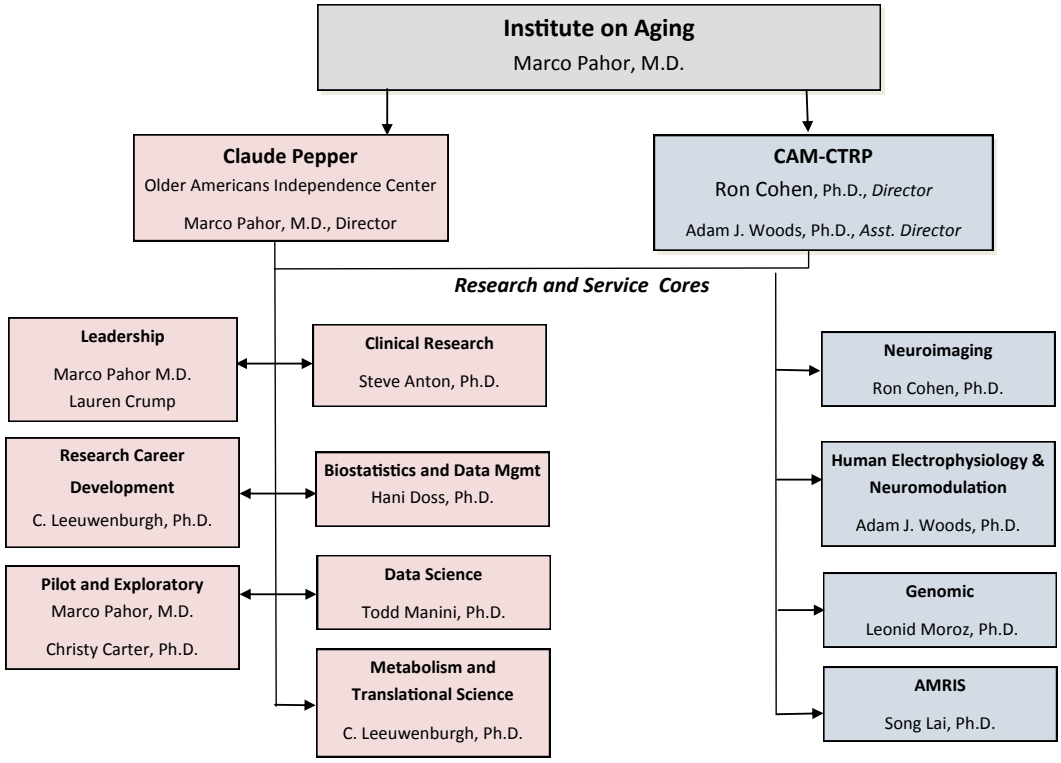
The board also emphasized the value of continued efforts to integrate basic neuroscience findings coming from Dr. Foster and others in the MBI-AMRL program into these clinical translation and clinical outcome efforts. We have directly addressed several of these points including initiating clinical trial/outcome development of novel agents to enhance cognitive and behavioral function in the elderly, including work with Dr. Bizon and her group on a GABA inhibitor. A number of other initiatives are underway as outlined in this report.

The Administrative Chart below gives a brief summary of specialized Core areas, and demonstrates the collaborations that have been established to assist with fulfilling the vision and mission of the CAM-CTRP, within the Institute on Aging. These include the highly productive Pepper Center Cores which are now partially funded by CAM-CTRP to support the CAM-CTRP mission, and the newly specialized CAM-CTRP Cores of Neuroimaging, AMRIS, Human Electrophysiology and Neuromodulation, and Genomic Science.

A key feature of the CAM-CTRP organizational structure is that it is highly integrated with the Pepper Center of the Institute on Aging. Accordingly, the CAM-CTRP contributes funds to support the Pepper Cores and benefits from expertise and resources available in these cores. Conversely, the Pepper Center and other entities of the University of Florida utilize Cores available within the CAM-CTRP.

McKnight Brain Research Foundation

CAM –CTRP Organizational Core Collaboration Chart



The personnel chart below provides a detailed list of all active members of the CAM-CTRP team.

McKnight Brain Research Foundation

CAM –CTRP Organizational Personnel Chart

CAM-CTRP Director
Ron Cohen, Ph.D.

Assistant Director
Adam J. Woods, Ph.D.

Core Faculty

Yenisel Cruz-Almeida, Ph.D.
Natalie Ebner, Ph.D.
Kimberly Sibille, Ph.D.
John Williamson, Ph.D.
Vonetta Dotson, Ph.D.
Adam Falchook, M.D.
Robert Cook, Ph.D.
Kenneth Cusi, M.D.
Mingzhou Ding, Ph.D.
Glenn Finney, M.D.
Tom Foster, Ph.D.
Ken Heilman, M.D.
Christina McCrae, Ph.D.
Steve Nadeau, M.D.
Michael Okun, M.D.
Cate Price, Ph.D.

Affiliate Faculty

T. Ashizawa, M.D.
Russ Bauer , Ph.D.
Kfir Ben-David, M.D.
Jennifer Bizon, Ph.D.
Dawn Bowers, Ph.D.
Sara Burke, Ph.D.
Huaihou Chen, Ph.D.

Post Doc Fellows

Tiffany Cummings, Psy.D. (Research and Clinical)
Damon Lamb, Ph.D.
Eric Porges, Ph.D. (Research)

Graduate Students

Talia Seider, M.S.
Amanda Garcia, M.S.
Vaughn Bryant, M.S.
Lindsey Richards, B.S.

Staff

Anne Banks, M.S.
Joy Johnson, A.S.
Taylor LeCorgne, B.S.
Andrew O'Shea, M.S.

Student Volunteers

Cassidy Langford
Narayan Kulkarni
Elizabeth Clark
Gi Lee
Quynh Pham
Daniela Vargas

For more information on the mission, vision, administrative structure and collaborating programs, please visit the website portfolio link below, for the complete External Advisory Board meeting and its presentations:
http://aging.ufl.edu/research/cognitive-aging-and-memory-clinical-translational-research-program/cam-ctrp-external-advisory-board-meeting

The CAM-CTRP webpage is in a continued development phase, and there are new informational pieces being posted and made available to the community, regarding faculty development, Clinical and Translational Research Studies and future areas of research interests: ***http://aging.ufl.edu/research/cognitive-aging-and-memory-clinical-translational-research-program***.

CAM-CTRP NIH FUNDED STUDIES:

Several NIH studies are currently in progress in the CAM-CTRP. These include R01 studies to Dr. Cohen, including a large multi-year study to examine how obesity and weight loss effect the brain in the context of aging (WISE), a study of the interactions of HIV, alcohol use and aging on brain function and structure (ARCH), and two other studies focusing on structural and functional brain connectivity in the context of HIV and aging. Dr. Cohen is the PI of the HIV component of the ENIGMA project which described below. He is also a co-I on a multicenter neuroimaging initiative studying brain changes over time as function of HIV and aging.

1. **WISE BRAIN Study:** This RO1 grant from the NIDDK (RO1DK099334-01A1) was funded in July of 2014 (5 years; direct cost approx. $385,194/yr). This project is currently underway. The focus of the project is the effects of chronic obesity on brain structure and function and subsequent improvements that occur following bariatric surgery. The study employs multimodal neuroimaging to address these aims. Participants include 120 individuals undergoing bariatric surgery, half of whom have type II diabetes. Sixty participants with severe obesity who are not undergoing bariatric surgery will serve as controls in this longitudinal study.

2. **ENIGMA-HIV:** (Cohen, Woods) – ENIGMA is a NIH-funded neuroimaging and genetics consortium involving over 70 institutions worldwide. The goal of ENIGMA is to facilitate a BIG-DATA approach to understanding the effect of select disorders on the human brain. The CAM-CTRP has been funded to lead the ENIGMA-HIV initiative. ENIGMA-HIV will bring together structural neuroimaging data from across the world to facilitate address high impact questions regarding HIV, the interaction between HIV and aging, and other topics.

3. **ARCH:** (Cohen, Woods, Cook) The Alcohol Research Center on HIV is a NIAAA-funded P01 located at Brown University. The CAM-CTRP will direct a the two-site project 1, with data collection at UF and Brown University. This project will evaluate the effectiveness and underlying mechanisms behind an alcohol reduction therapy (Motivational Interviewing) in people living with HIV that meet NIAAA standards for heavy alcohol consumption. The study will use multimodal neuroimaging, genetics, blood biomarkers and neurocognitive assessment. The project is a renewal of the original ARCH grant and is currently pending approval by NIAAA.

CAM-CTRP PILOT STUDIES (MBRF, PEPPER OR CTSI SUPPORTED):

A primary strategy is to use available funds designated for development of the CAM-CTRP research program to conduct pilot studies that will 1) establish a neuroimaging and neurocognitive normative database of healthy older adults with normal cognitive aging; 2) use data from these studies to develop possible neuroimaging and laboratory biomarkers for future clinical use in the assessment of cognitive aging; and 3) develop and implement novel therapeutic intervention to combat cognitive aging.

NEUROIMAGING OF COGNITIVE AGING

We first initiated the ACTIVE BRAIN study to achieve the first objective. The ACTIVE BRAIN study catalyzed a series of subsequent pilot studies designed to acquire functional and metabolic neuroimaging data and also proteomic and genomic data from the same cohort of elderly adults recruited for ACTIVE BRAIN. The goal of these studies is to extend knowledge of the brain systems and mechanisms affected by aging and how specific cognitive functions change with advanced age in people without neurodegenerative disease. The strategy for these pilot studies was sequential staging whereby participants completing one neuroimaging study would be asked to participate in the next. Each pilot study focuses on a particular neurocognitive domain; 1) Memory and Working Memory; 2) Semantics-Associative Representation; 3) Visual Perception and Spatial Representation; and 4) Attention.

This initiative has since expanded to an inter-institute neuroimaging study recently funded by the MBRF to collect neuroimaging and neurocognitive data on successful agers over the age of 85 years who are not physically frail.

1. **The ACTIVE BRAIN Study:** *(Cerebral metabolic, vascular and functional neuroimaging, NIH Toolbox Cognitive Measures, and physical activity as predictors of age associated cognitive dysfunction.)* All infrastructure and administrative groundwork has

been prepared, and data is being collected for the first IRB approved (IRB #2013000168) study for CAM-CTRP. This is a multi-cohort study with two separate research arms; including the Institute on Aging's LIFE Study participants from Gainesville and Jacksonville, and seniors from the greater North Florida community. The LIFE Study participants are part of a LIFE Ancillary Study, reviewed and approved by the LIFE Emerging Science Board. The study will collect three primary pieces of information from 200 total participants, including anatomical and functional neuroimaging, blood cytokines, inflammatory biomarkers and DNA analysis, and a broad cognitive performance test battery including piloting of the newly released NIH Toolbox Cognitive Measures. The study will cover a broad age range from 60-100 years, to establish a database of images and cognitive performance data for analysis, which will serve as the foundation for gathering independent peer review grant funding.

2. **Aging effects on semantic neural networks (Talking Brain Study):** *(Cohen, Heilman, Nadeau, Reilly, Woods, Garcia)* Study of 50 elderly participants, designed to analyze the semantic networks in the healthy aging brain. It will consist of newly designed tasks for performance during fMRI scans, with a variety of concrete vs. abstract words, across several different experimental paradigms including semantic generation tasks. This study will also serve as the basis for Amanda Garcia's doctoral dissertation. She has already collected association norms on 200 elderly people using Amazon survey. This is unique data in its own right.

3. **Aging effects on visual cortical systems (Seeing Brain Study):** *(Cohen, Porges, Woods, Seider)* Study of 50 elderly participants, aimed at characterizing age-associated changes in structural and functional brain systems involved in visual processing. This fMRI study will examine functional brain response across 7 visual paradigms that are sensitive to different processes underlying visual perception and higher order visual functions.

4. **Age-associated changes in attention and arousal (Attentive Brain Study):** *(Woods, Cohen)* 40 participants will undergo a comprehensive attentional battery while undergoing fMRI. This study is intended to identify unique elements of attention that decline with age, and the brain systems that govern these elements.

5. **McKnight Inter-Institute Neuroimaging Initiative:**
A neuroimaging workgroup was formed last year to foster collaboration among the four McKnight Brain Institutes. Dr. Cohen is the UF group leader for this initiative. Steps were taken towards development of a NIA-sponsored multicenter cognitive and brain aging study. The focus of this workgroup was to standardize neuroimaging methods across the four institutes, to plan for the collection of multimodal MR and MRS data that would provide a normative dataset of functional and structural neuroimaging data on healthy elderly adults at advanced age, and to collect preliminary data that would support future grant submissions. Considerable progress was made by the group, including the collection of MR data from a single adult who travelled to all MBI sites. We established initial reliability data for the scanners at the four sites. We are currently are developing a grant proposal to be submitted to the MBRF for a block grant to enable completion of standardization efforts and the collection of an initial sample of 200 elderly adults (50 per site). This sample will consist of individuals who are over the age of 80, and in good physical health, without significant medical disease or physical frailty, and who do not have evidence of AD, MCI, or other neurodegenerative disease. Contingent on receiving these funds, we will initiate a cross-sectional study, which we believe will set the stage for external funding aimed at achieving greater understanding of the structural and functional brain manifestations of normal cognitive aging. This initiative was recently funded by the McKnight Brain Research Foundation and will provide $200,000 per year for two years to each of the four sites. Each site is currently preparing IRB submissions for study initiation.

CAM-CTRP INTERVENTION PILOT STUDIES:

1. **Neuromodulation of cognition in older adults (Stimulated Brain Study):** *(Woods, Cohen)* 50 subjects in a pilot randomized clinical trial, investigating the benefit of Transcranial Direct Current Stimulation (tDCS) on working memory and attention training in older adults. The study will utilize a multi-disciplinary neuroscientific approach to determine the mechanisms and effectiveness of pairing tDCS with cognitive training. This study is IRB approved and is beginning to enroll participants.

2. **Induced arousal: an intervention in cognitive aging (Alert Brain Study):** *(Woods, Porges, Cohen, Ding)* IRB approved study of 50 participants to investigate the role of brain arousal mechanisms on cognitive decline and susceptibility to cognitive frailty. This study will use a combination of fMRI, ERP, and physiological recording to identify biomarkers of frailty.

3. **Effects of oxytocin on socio-emotional decisions in aging (FACES):** *(Ebner, Woods, Porges, Cohen)* Examines the effects of Oxytocin administration on various measures of socioemotional functioning and social decision making in aging adults. Young and older adults self-administer oxytocin or a placebo intranasally before working on a trust-related decision making task, a facial trust-worthiness rating task, and an emotion recognition task. The central hypothesis is that older compared to

younger adults particularly benefit from enhanced levels of oxytocin, as they experience increased difficulties with socioemotional tasks. This study is IRB approved and nearing completion.

4. **Oxytocin Clinical Trial (OXY):** *(Ebner, Woods, Porges, Cohen)* This clinical trial investigates the effects of 4 weeks of intranasal oxytocin administration on physical performance, cognitive functioning, and socioemotional functioning in older males. Older men will self-administer intranasal oxytocin or a placebo, twice daily over a period of 4 weeks. At baseline and post intervention, they will be examined on various measures of physical, cognitive, and socioemotional functioning, as well as various inflammatory markers will be analyzed. The central hypothesis is that older males in the oxytocin group will experience improvement in their physical health, their cognitive performance, and their social and emotional engagement over the trial period, mediated by oxytocin's anti-inflammatory effects. This study is IRB approved and is soon to be initiated.

5. **Think-2-Walk:** *(Clark, Williamson)* This study investigated whether peripheral sensory impairment increases cortical demand of walking. The primary hypotheses are that peripheral sensory impairments in older adults disrupt sub-cortical control of walking, leading to increased cortical demand of walking and concomitant deficits in mobility function. Co-funded by the NIH Pepper Center Grant. This study was completed and has led to a UF opportunity fund grant to investigate of the effects of tDCS brain stimulation on complex walking training.

BIOMARKERS OF COGNITIVE AGING

1. **U-TRACK:** *(Woods)* This six-month follow-up pilot study investigates mechanisms, predictive factors, and long-term consequences of acute cognitive impairment (e.g., delirium) with urinary tract infection (UTI) in older adults. UTI is one of the most common infectious diseases in older adults. Over 40% of older adults with UTI suffer from cognitive symptoms. This study will attempt to determine the role of neuroinflammation in cognitive impairment with UTI and the factors that increase the susceptibility of certain older adults to these episodes of cognitive frailty. This project is funded by the CAM-CTRP. The project is IRB-approved.

2. **Clinical Methods to Evaluate Neural Function in Aging MIND:** *(Buford, Manini, Clark, Cruz-Almeida, Woods)* The aim of the Mind study is to develop the ability of Clinical Research Core (RC1) to assess novel neural contributors to mobility and overall physical function in older adults. The development of these techniques will provide the RC1 with the tools to evaluate the potential involvement of the central and peripheral nervous systems in age-related cognitive decline. Co-funded by the NIH Pepper Center Grant and CAM-CTRP Pilot Research.

3. **The metabolic costs of daily activity in older adults:** A pilot study to evaluate the role of brain integrity on post-hospital sarcopenia and cognition in aging adults (The Strong Brain Study): *(Manini, Woods)*

   We will examine the integrity of the cortical-spinal tract and sarcopenia outcomes using the infrastructure of Dr. Catherine Price's funded R01 entitled, Neuroimaging biomarkers for post-operative cognitive decline in older adults (R01 NR014181; IRB # 487-2012). This R01 is a prospective longitudinal study with two groups: older adults (age > 60 years) having total knee replacement (n=80) and non-surgery age and education matched peers with osteoarthritis (n=80). Both groups will acquire baseline MRI using sophisticated diffusion and functional measures to define specific neuronal regions of interest that relate to cognition, and complete cognitive testing at a pre-surgery/baseline time point followed by repeat testing at 2 days, 3 weeks and three-months, and one-year post-operative/post-baseline. Funds from this pilot study will be used to support additional MRI scan time baseline and 3 weeks and 3 months post-surgery. Co-funded by the NIH Pepper Center Grant and CAM-CTRP Pilot Research. This study is IRB approved and data is being collected.

4. **Proteomics and genomics of cognitive aging:** *(Cohen, Leeuwenburgh, Moroz)* This pilot will study 50 elderly participants from the ACTIVE BRAIN Study, to analyze various circulating serum biomarkers, including inflammatory cytokines, metabolic factors and other proteins. Using the new UF Genomics System and in collaboration with the MBRF Genomics workgroup, DNA and RNA epigenetic biomarkers will also be examined in exploratory research on factors influencing normal brain aging. We are still collecting blood samples and have not yet initiated these analyses, but plan to in the coming year.

Infrastructure Development: *(Cohen, Woods)*

1. Developed and supplied technology for the CAM-CTRP Neuroimaging Processing and Data Analysis Lab on the second floor of the IoA-Clinical Translational Research Building. This continues to be a work in progress. We are rapidly expanding our multimodal neuroimaging capabilities.

2. Established IoA/CAM-CTRP connection to University HiPerGator computing system. We continue to work with the High Performance Computing Center on implementing neuroimaging processing through this system. Recent media attention

was received by our group for completing processing of 566 human brain scans in 17 hours, a task that would have taken 1.5 years on other systems.

3. A whole brain 31P-1H phosphorous MRS whole brain coil for cerebral metabolic spectroscopy was acquired from Dr. Woods' successful MBI instrumentation grant. This system has been installed and is currently being calibrated and readied for experimentation.

4. Methods for free-water analyses (a marker of neuroinflammation) from DTI data have been established by Dr. Woods through collaboration with Dr. Ofer Pasternack at Harvard University.

5. Brain Wellness Program has been implemented and is expanding to two days a week with the involvement of Drs. Bauer and Williamson.

6. Human Electrophysiology Laboratory in the Clinical Translational Research Unit, on the 1st floor of IoA-CTRB is operational and studies are running.

7. Transcranial Direct Current Stimulation studies are now underway.

8. International tDCS workshop initiated and run by Dr. Woods and colleagues. Four national meetings have occurred so far. This workshop will also be offered at the International Brian Stimulation Meeting in Singapore later this year. Others are planned.

9. University-wide Neuroimaging User Group comprised of over 75 UF investigators continues to grow and has been hugely successful *(Cohen, Woods)*.

10. University-wide monthly Human Neuroimaging Lecture Series is running and well attended with excellent speakers *(Woods)*. 50 attendees or more per session.

11. Clinical Trial Development with MBI's Age Related Memory Loss Program is proceeding with efforts to bring a GABA inhibitor for cognitive aging to clinical trial.

H. Past scientific achievements are best summarized in the list of publications for this year noted in the section below.

CAM-CTRP FACULTY ROLES:

The CAM-CTRP consists of core faculty supported in full or in part through the CAM-CTRP and IOA, and affiliated faculty who closely collaborate with the core faculty and has requested or been invited to be an affiliate with the CAM-CTRP.

Faculty in the CAM-CTRP were selected to provide expertise across a number of neuroscientific domains of importance to the study of aging. The faculty is multidisciplinary, including neuropsychologists, cognitive neuroscientists, neurologists, psychologists, geriatricians, geneticists, engineers, MR physicists, epidemiologists and biostatisticians. Several categories of clinical and cognitive neuroscience expertise exist among the faculty: 1) Cognition and Behavior; 2) Neuroimaging; 3) Neurophysiology; 4) Neuromodulation; 5) Pain; 6) Genetics; 7) Laboratory Biomarkers; 8) Clinical Neuropsychology/Behavioral Neurology; and 9) Clinical Trials. Prior to the list of publications for each faculty, a brief description of their expertise and research focus is provided.

PUBLICATIONS IN PEER REVIEWED JOURNALS:

Ron Cohen, PhD, Professor, CAM-CTRP Director

Expertise: Cognitive, Clinical neuropsychology, Neuroimaging, Clinical trials, Laboratory biomarkers
Research Focus: Cognitive aging, medical risk factors, neurodegenerative disease, attention
Role: Director of CAM-CTRP, Director of CAM-CTRP Neuroimaging Core, MBI Inter-institute Neuroimaging Workgroup, MBI Inter-Institute Cognitive Workgroup Leader

1. Alosco, M, Spitznagel, M, **Cohen, R**, Raz, N, Sweet, LH, Josephson, R, Hughes, J, Rosneck, J, Gunstad, J. (2014). Reduced cerebral perfusion predicts greater depressive symptoms and cognitive dysfuncion at a 1-year follow-up in patients with heart failure. *Int J Geriatric Psychiatry*. 29(4):428-436. **PMC: 3949179**

2. Alosco, M, Spitznagel, MB, **Cohen, R**, Raz, N, Sweet, LH, Josephson, R, Hughes, J, Rosneck, J, Gunstad, J. (2014). Decreased physical activity predicts cognitive dysfunction and reduced cerebral blood flow in heart failure. *J Neurol Sciences*. 339(1-2)169-175. **PMID: 24581672**

3. Hoshiko, S, Smith, D, Fan, C, Jones, CR, McNeel, SV, **Cohen, R**. (2014).Trends in CT scan rates in children and pregnant women: teaching, private, public and nonprofit facilities. *Pediatr Radiol*. May;44(5):522-528. **PMID: 24526278**

4. Seider, TR, Luo, X, Gongvatana, A, Devlin, KN, de la Monte, SM, Chasman, JD, Yan, P, Tashima, KT, Navia, B, **Cohen, R**. (2014). Verbal memory declines more rapidly with age in HIV infected versus uninfected adults. *J Clin Exper Neuropsychol*. **PMID: 24645772**

5. Xu, X, Jerskey, BA, Cote, DM, Walsh, EG, Hassenstab, JJ, Ladino, ME, Clark, US, Labbe, DR, Gunstad, JJ, Poppas, A, **Cohen, R**, Hoge, RD, Sweet, LH. (2014). Cerebrovascular perfusion among older adults is moderated by strength training and gender. *Neurosci lett*, 560:26-30. **PMC: 392072**

6. Alosco, ML, Garcia, S, Spitznagel, MB, van Dulmen, M, **Cohen, R**, Sweet, LH, Josephson, R, Hughes, J, Rosneck, J, Gunstad, J. (2014). Cognitive performance in older adults with stable heart failure: longitudinal evidence for stability and improvement. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 21(2), 239-256. **PMC: 3858403**

7. Alosco, ML, Spitznagel, MB, Strain, G, Devlin, M, **Cohen, R**, Paul, R, Crosby, RD, Mitchell, JE, Gunstad, J. (2014). Improved memory function two years after bariatric surgery. *Obesity*, 22(1), 32-38. **PMID: 23625587**

8. Fulcher, KK, Alosco, ML, Miller, L, Spitznagel, MB, **Cohen, R**, Raz, N, Sweet, L, Colbert, LH, Josephson, R, Hughes, J, Rosneck, J, Gunstad, J. (2014). *Greater physical activity is associated with better cognitive function in heart failure*. Jan 27. **PMID: 2467254**

9. Alosco, ML, Spitznagel, MB, Strain, G, et al. Pre-operative history of depression and cognitive changes in bariatric surgery patients. *Psychol Health Med* 2014:1-12.

10. Lavender, JM, Alosco, ML, Spitznagel, MB, et al. Association between binge eating disorder and changes in cognitive functioning following bariatric surgery. *J Psychiatr Res* 2014.

11. Alosco, ML, Spitznagel, MB, **Cohen, R**, et al. Cardiac rehabilitation is associated with lasting improvements in cognitive function in older adults with heart failure. *Acta Cardiol* 2014;69:407-414.

12. Alosco, ML, Gunstad, J, Xu, X, et al. The impact of hypertension on cerebral perfusion and cortical thickness in older adults. *J Am Soc Hypertens* 2014;8:561-570.

13. Alosco, ML, Spitznagel, MB, Strain, G, et al. The effects of cystatin C and alkaline phosphatase changes on cognitive function 12-months after bariatric surgery. *J Neurol Sci* 2014;345:176-180.

14. Alosco, ML, Gunstad, J, Beard, C, et al. The Synergistic Effects of Anxiety and Cerebral Hypoperfusion on Cognitive Dysfunction in Older Adults With Cardiovascular Disease. *J Geriatr Psychiatry Neurol* 2014.

15. Alosco, ML, Spitznagel, MB, **Cohen, R**, et al. Obesity and cognitive dysfunction in heart failure: The role of hypertension, type 2 diabetes, and physical fitness. *Eur J Cardiovasc Nurs* 2014.

16. Fulcher, KK, Alosco, ML, Miller, L, et al. Greater Physical Activity Is Associated With Better Cognitive Function in Heart Failure. *Health Psychol* 2014.

17. Alosco, ML, Galioto, R, Spitznagel, MB, et al. Cognitive function after bariatric surgery: evidence for improvement 3 years after surgery. *Am J Surg* 2014;207:870-876.

18. Alosco, ML, Spitznagel, MB, **Cohen, R**, et al. Reduced cerebral perfusion predicts greater depressive symptoms and cognitive dysfunction at a 1-year follow-up in patients with heart failure. *Int J Geriatr Psychiatry* 2014;29:428-436.

19. Alosco, ML, Garcia, S, Spitznagel, MB, et al. Cognitive performance in older adults with stable heart failure: longitudinal evidence for stability and improvement. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 2014;21:239-256.

20. Alosco, ML, Spitznagel, MB, Raz, N, et al. Executive dysfunction is independently associated with reduced functional independence in heart failure. *J Clin Nurs* 2014;23:829-836.

21. Sink, KM, Espeland, MA, Rushing, J, et al. The LIFE Cognition Study: design and baseline characteristics. *Clin Interv Aging* 2014;9:1425-1436.

22. Gongvatana, A, Correia, S, Dunsiger, S, et al. Plasma Cytokine Levels are Related to Brain Volumes in HIV-infected Individuals. *J Neuroimmune Pharmacol* 2014.

23. Daiello, LA, Gongvatana, A, Dunsiger, S, **Cohen, R**, Ott. BR. Association of fish oil supplement use with preservation of brain

volume and cognitive function. *Alzheimers Dement* 2014.

24. Caldwell, JZ, Gongvatana, A, Navia, BA, et al. Neural dysregulation during a working memory task in human immunodeficiency virus-seropositive and hepatitis C coinfected individuals. *J Neurovirol* 2014;20:398-411.

25. Harezlak, J, **Cohen, R**, Gongvatana A, et al. Predictors of CNS injury as measured by proton magnetic resonance spectroscopy in the setting of chronic HIV infection and CART. *J Neurovirol* 2014;20:294-303.

26. Bryant, V, Whitehead, N, Burrell, L,…**Cohen, R**.. *AIDS and Behavior*. In press.

27. **Cohen, R**, Seider, T, Navia, BF. HIV effects on age-associated neurocognitive dysfunction: Premature cognitive aging or neurodegenerative disease. *Alzheimers Disease Research and Therapy*. In press.

Adam J. Woods, PhD, Assistant Professor, CAM-CTRP Assistant Director

Expertise: Cognitive, Cognitive Neuroscience, Neuroimaging, Neurophysiology, Neuromodulation
Research Focus: Cognitive aging, cognitive frailty, neuroinflammation, non-invasive brain stimulation, attention
Role: Assistant Director of CAM-CTRP, Director of CAM-CTRP Neurophysiology and Neuromodulation Core, MBI Inter-institute Neuroimaging Workgroup Member, MBI Inter-Institute Cognitive Workgroup Member

1. **Woods, AJ**, Bryant, V, Sacchetti, D, Gervits, F, Hamilton, R. Effects of electrode drift on transcranial direct current stimulation. *Brain Stimulation*, (In press).

2. Aubertin-Leheudre, M, **Woods, AJ**, Anton, S, Cohen, R, Pahor, M. Clinical frailty phenotype: a physical and cognitive point of view. *Nestle Nutrition Institute Workshop Series*, (In press).

3. Yamamoto, N, Philbeck, JW, **Woods, AJ**, Gajewski, D, Chichka, D, Potollochio, S, Caputy, A. Medial temporal lobe role for trajectory prediction in human path integration. (2014). *PLoS ONE*, 9(5): e96583, doi: 10.1371/journal.pone.0096583, Impact Factor: 3.53

4. **Woods, AJ**, Hamilton, RH, Kranjec, A, Bikson, M, Minhaus, P, Yu, J, Chatterjee, A (2014). Space, time, and causal inference in the human brain. *Neuroimage*. 92: 285-97. doi: 10.1016/j.neuroimage.2014.02.015, Impact Factor: 6.13

5. **Woods, AJ**, Cohen, RA, Pahor, M (2013). Cognitive frailty: frontiers and challenges. *Journal of Nutrition, Health, and Aging*. 17, 741-743. doi: 10.1007/s12603-013-0398-8, Impact Factor: 2.65

Yenisel Cruz-Almeida, MSPH, PhD, Assistant Professor

Expertise: Pain, Neuroscience, Electrophysiology
Research Focus: Pain and cognitive aging, Intervention development, Neural systems of pain
Role: Member of the CAM-CTRP Pain working-group

1. Widerström-Noga, E, **Cruz-Almeida**, Y, Felix, ER, Pattany, PM. Somatosensory phenotype is associated with thalamic metabolites and pain intensity after spinal cord injury. *Pain*, 2014. In press.

2. Goodin, BR, Bulls, HW, Herbert, MS, Schmidt, J, King, CD, Glover, TL, Sotolongo, A, Sibille, KT, **Cruz-Almeida, Y**, Staud, R, Fessler, BJ, Redden, DT, Bradley, LA, Fillingim, RB. Temporal summation of pain as a prospective predictor of clinical pain severity in adults aged 45 years and older with knee osteoarthritis: ethnic differences. *Psychosom Med*. 2014 May;76(4):302-10. doi: 10.1097/PSY.0000000000000058.

3. **Cruz-Almeida, Y**, Black, ML, Christou, EA, Clark, DJ. Site-specific differences in the association between plantar tactile perception and mobility function in older adults. *Front Aging Neurosci*. 2014 Apr 11;6:68. doi: 10.3389/fnagi.2014.00068. eCollection 2014.

4. **Cruz-Almeida, Y**, Sibille, KT, Goodin, BR, Petrov, ME, Bartley, EJ, Riley, JL 3rd, King, CD, Glover TL, Sotolongo, A, Herbert, MS, Schmidt, JK, Fessler, BJ, Staud, R, Redden, D, Bradley, LA, Fillingim, RB. Racial and ethnic differences in older adults with knee osteoarthritis. *Arthritis Rheumatol*. 2014 Jul;66(7):1800-10. doi: 10.1002/art.38620.

5. Herbert, MS, Goodin, BR, Pero, ST 4th, Schmidt, JK, Sotolongo, A, Bulls, HW, Glover, TL, King, CD, Sibille, KT, **Cruz-Almeida, Y**, Staud, R, Fessler, BJ, Bradley, LA, Fillingim, RB. Pain hypervigilance is associated with greater clinical pain severity and enhanced experimental pain sensitivity among adults with symptomatic knee osteoarthritis. *Ann Behav Med*. 2014 Aug;48(1):50-60. doi: 10.1007/s12160-013-9563-x.

6. Riley, JL 3rd, **Cruz-Almeida, Y**, Glover, TL, King, CD, Goodin, BR, Sibille, KT, Bartley, EJ, Herbert, MS, Sotolongo, A, Fessler, BJ, Redden, DT, Staud, R, Bradley, LA, Fillingim, RB. Age and race effects on pain sensitivity and modulation among middle-aged and older adults. *J Pain*. 2014 Mar;15(3):272-82. doi: 10.1016/j.jpain.2013.10.015. Epub 2013 Nov 14.

7. Goodin, BR, Pham, QT, Glover, TL, Sotolongo, A, King, CD, Sibille, KT, Herbert, MS, **Cruz-Almeida, Y**, Sanden, SH, Staud, R, Redden, DT, Bradley, LA, Fillingim, RB. Perceived racial discrimination, but not mistrust of medical researchers, predicts the heat pain tolerance of African Americans with symptomatic knee osteoarthritis. *Health Psychol*. 2013 Nov;32(11):1117-26. doi: 10.1037/a0031592.

8. **Cruz-Almeida, Y**, Fillingim, RB. Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain Med*. 2014 Jan;15(1):61-72. doi: 10.1111/pme.12230. Epub 2013 Sep 6. Review.

Natalie Ebner, PhD, Assistant Professor

Expertise: Cognitive, Affective and Social Neuroscience, Neuroimaging, Hormones, Clinical trials
Research Focus: Cognitive aging, social and emotional changes with aging.
Role: Social-affective neuroscience expert in CAM-CTRP

1. Dark-Freudeman, AR, **Ebner, NC** & West, RL. (In press.) Psychosocial aspects of aging. In K. E. Light (Ed.), *Geriatric Rehabilitation*. F.A. Davis.

2. **Ebner, NC** & Fischer, H. (2014a). Studying the various facets of emotional aging: Introduction to the current Frontiers research topic. *Frontiers in Emotion Science*. doi: 10.3389/fpsyg.2014.01007

3. **Ebner, NC** & Fischer, H. (2014b). Emotion and aging: Evidence from brain and behavior. [Research topic] *Frontiers in Emotion Science*. doi: 10.3389/fpsyg.2014.00996

4. Voelkle, MC, **Ebner, NC**, Lindenberger, U & Riediger, M. (2014). A note on age differences in mood-congruent versus mood-incongruent information processing in faces. [Research topic] *Frontiers in Emotion Science*, 5, 635. doi: 10.3389/fpsyg.2014.00635

Kimberly Sibille, MA, PhD, Assistant Professor

Expertise: Pain, Clinical Psychology, Personality and Emotions, Electrophysiology, Interventions
Research Focus: Cognitive, affective, and personality influences on pain in aging
Role: Member of the CAM-CTRP Pain working-group.

1. Goodin, BR, Bulls, HW, Herbert, MS, Schmidt, J, King, CD, Glover, TL, Sotolongo, A, **Sibille, K**, Cruz-Almeida, Y, Staud, R, Fessler, BJ, Redden, DT, Bradley, LA, Fillingim, RB (2014). Temporal summation of pain as a prospective predictor of clinical pain severity in adults aged 45 years and older with knee osteoarthritis: ethnic differences. *Psychosom Med*. 76, 302-10. **PMID: 24804882**

2. Cruz-Almeida, Y, **Sibille, K**, Goodin, B, Ruiter, M, Bartley, E, Riley III, J, King, C, Glover, T, Sotolongo, A, Herbert, M, Schmidt, J, Fessler, B, Staud, R, Bradley, L, Fillingim, RB (2014).Racial and ethnic differences in older adults with knee osteoarthritis. *Arthritis & Rheumatology*. 66, 1800-10. **PMID: 24729357**

3. Herbert, MS, Goodin, BR, Pero, ST 4th, Schmidt, JK, Sotolongo, A, Bulls, HW, Glover, TL, King, CD, **Sibille, K**, Cruz-Almeida, Y, Staud, R, Fessler, BJ, Bradley, LA, Fillingim, RB (2014). Pain hypervigilance is associated with greater clinical pain severity and enhanced experimental pain sensitivity among adults with symptomatic knee osteoarthritis. *Behav Med*. 48, 50-60. **PMID: 24352850**

4. Riley III, JL, Cruz-Almeida, Y, Glover, TL, King, CD, Goodin, BR, **Sibille, K**, Bartley, EJ, Herbert, MS, Sotolongo, A, Fessler, BJ, Redden, DT, Staud, R, Bradley, LA, Fillingim, RB (2014). Age and race effects on pain sensitivity and modulation among middle-aged and older adults. *Journal of Pain*. 15, 272-82. **PMID: 24239561**

John B. Williamson, PhD, Assistant Professor

Expertise: Cognitive aging, Clinical neuropsychology, Neuroimaging, Microvascular disease, parasympathetic nervous system, PTSD, TBI
Research Focus: Cognitive aging, medical risk factors, neurodegenerative disease, attention
Role: Collaborator on aging-vascular cognitive impairment studies, Brain Wellness Clinic

1. **Williamson, JB**, Haque, S, Harciarek, M, Burtis, DB, Lamb, D, Zilli, E, Heilman, KM. The influence of stimulus proximity on judgments of spatial location in patients with chronic unilateral right and left hemisphere stroke. *Journal of Clinical and Experimental Neuropsychology* 2014 (epub ahead of print).

2. Falchook, AD, Salazar, L, Neal, D, Kesayan, T, **Williamson, JB**, Malaty, IA, McFarland, NR, Okun, MS, Rodriguez, RL, Wagle, SA, Heilman, KM. Global attentional neglect of segmented lines in Parkinson's disease. *Neurocase* 2014 (Epub ahead of print).

3. Acosta, LM, **Williamson, JB**, Heilman, KM. Which cheek did the resurrected jesus turn? *Journal of Religion and Health*, 2014 (epub ahead of print).

4. Burtis, DB, Heilman, KM, Mo, J, Wang, C, Lewis, GF, Davilla, MI, Ding, M, Porges, SW, **Williamson, JB**. The effects of constrained left and right monocular viewing on the autonomic nervous system. *Biological Psychology* 2014 (In press).

5. Clark, DJ, Chrisou, EA, Ring, SA, Williamson, JB, Doty L. Enhances somatosensory feedback reduces prefrontal cortical activity during walking in older adults. *Journal Gerontol A Biol Sci Med Sci* 2014, (epub ahead of print).

6. Milano, N, **Willamson, JB**, Heilman, KM. Improved verbal learning in the semantic variant of primary progressive aphasia when using semantic cues. *Neurocase* 2014, (epub ahead of print).

7. **Williamson, JB**, Heilman, KM, Porges, Eric C, Lamb, Damon, G, Porges, SW. A possible mechanism for PTSD symptoms in patients with traumatic brain injury: central autonomic network disruption. *Frontiers in Neuroengineering* 2013 doi: 10.3389/fneg.2013/00013.

CAM-Research Fellows

Eric S. Porges, PhD, Post-Doctoral Fellow

Expertise: Cognitive and social neuroscience of aging, Neuroimaging, Autonomic psychophysiology, hormones.
Research Focus: Cognitive aging, GABA, Neuroimaging methods
Role: Research Support

1. Clark, DJ, Rose, DK, Ring, SA, **Porges, ES** (2014). Utilization of central nervous system resources for preparation and performance of complex walking tasks in older adults. *Frontiers in Aging Neuroscience*, 6:217. DOI=10.3389/fnagi.2014.00217

2. *Smith, KE, ***Porges, ES**, Norman, GJ, Connelly, JJ & Decety, J (2014). Oxytocin receptor (OXTR) gene variation predicts empathic concern and autonomic arousal while perceiving harm to others. *Social Neuroscience*, 9: 1. PMCID: PMC3923324 (*contributed equally to this manuscript).

3. Williamson, JB, **Porges, ES**, Lamb, DG, Heilman, KM & Porges, SW (2013). A possible mechanism for PTSD symptoms in patients with traumatic brain injury: The role of central autonomic network disruption. *Frontiers of Neuroengineering*, 6:13. **PMCID: PMC3867662**

Affiliate Faculty

Stephen Anton, PhD, Associate Professor

Expertise: Behavioral medicine, Clinical Psychology, Clinical trials, Weight loss intervention
Research Focus: Obesity, Neutraceuticals, Drug trials for sarcopenia, Exercise RCTs
Role: Pepper Center Clinical Research Core Director

1. **Anton, SD**. Can non-nutritive sweeteners enhance outcomes of weight loss interventions? 2014. *Obesity*, 22(6):1413-4.

2. **Anton SD**, Embry, E, Marsiske, M, Lu, X, Doss, H, Leeuwenburgh, C and Manini, TM. (in press) Safety and metabolic outcomes of resveratrol supplementation in older adults: results of a twelve-week, placebo-controlled pilot study. *Experimental Gerontology*.

3. Manini, T, Lott, D, Vandenborne, K, Buford, TW, Knaggs, J, Leeuwenburgh, C, Pahor, M, Perri, MG and **Anton, SD**. Body composition changes with weight loss and exercise in older obese women with mild physical impairments. *Journal of Gerontology Medical Sciences*. In Press.

4. Buford, TW, **Anton, SD**, Clark, DJ, Higgins, TJ & Cooke, MB. Optimizing the Benefits of Exercise on Physical Function in Older Adults. *Journal of Aging and Physical Activity*.

5. Hausenblaus, HA, Hoyt, AL, Simkins, C, Dubyak, PJ and **Anton, SD**. Effects of Resveratrol and BioCell Collagen® Supplementation on Facial Aging and Skin Satisfaction: A Pilot Open-label Study. *Natural Medicine*.

6. Pahor, M, Guralnik, J, Ambrosius, W, Blair, S, Bonds, D, Church, TS, Espeland, MA, Fielding, RA, Gill, TA, Groessl, EJ, King, AC, Kritchevksy, SB, Manini, TM, McDermott, MM, Miller, ME, Newman, AB, Rejeski, WJ, Sink, KM, Williamson, JD, LIFE Study

Investigators. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE Study randomized clinical trial. *JAMA*. 2014; 311(23):2387-2396.

7. Rejeski, WJ, Axtell, R, Fielding, R, Katula, J, King, AC, Manini, TM, Marsh, AP, Pahor, M, Rego, A, Tudor-Locke, C, Newman, M, Walkup, MP, Miller, ME, LIFE Study Investigator Group. Promoting physical activity for elders with compromised function: the Lifestyle Interventions and Independence for Elders (LIFE) Study physical activity intervention. *Clin Interv Aging*. 8: 1119-31. 2013.

8. Fragoso, CA, Beavers, DP, Hankinson, JL, Flynn, G, Berra, K, Kritchevsky, SB, Liu, CK, McDermott, MM, Manini, TM, Rejeski, WJ, Gill, TM, LIFE Study Investigators. Respiratory impairment and dyspnea and their associations with physical inactivity and mobility in sedentary community-dwelling older persons. *J Amer Geriatrics Soc*. 62(4): 622-628.

9. Espeland, MA, Katula, JA, Rushing, J, Kramer, AF, Jennings, JM, Sink, KM, Nadkarni, NK, Reid, KF, Castro, CM, Church, T, Kerwin, DR, Williamson, JD, Marottoli, RA, Rushing, S, Marsiske, M, Rapp, SR; LIFE Study Group. Performance of a computer-based assessment of cognitive function in two cohorts of seniors. *Int J Geriatr Psychiatry*. 28 (12): 1239-1250. 2013.

10. ASPREE Investigator Group. Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized controlled trial. *2013 Contemp Clin Trials*, 36, 555-564.

11. Marsh, AP, Kennedy, K, Lovato, LC, Castro, C, Domanchuk, K, Glynn, NW, McDavitt, E, Rodate, R, Marsiske, M, McGloin, J, Groessel, EJ, Pahor, M, Guralnik, JM, LIFE Research Group. Lifestyle Interventions and Independence for Elders Study: Recruitment and Baseline Characteristics. *J Gerontol A Biol Sci Med Sci*. (update publication)

12. Aubertin-Leheudre, M, Woods, AJ, **Anton, SD**, Cohen, R & Pahor, M (in press). Frailty clinical phenotype: A physical and cognitive point of view. *Nestlé Nutrition Institute Workshops Series*. Volume 83

13. Buford, TW, **Anton, SD**. Resveratrol as a supplement to exercise training: Friend or Foe? *J Physiol*. 592(3):551-552. 2014.

Robert L. Cook, MD, MPH

Expertise: Internal Medicine, Epidemiology, HIV, Substance Abuse
Research Focus: Alcohol and Age Effects in HIV
Role: Director of the Southeastern HIV Alcohol Research Center (SHARC), collaborator on ARCH project

1. Sidani, JE, Shensa, A, Barnett, T, **Cook, RL**, Primack, BA. Knowledge, attitudes, and normative beliefs as predictors of hookah smoking initiation: a longitudinal study of university students. *Nicotine Tob Res*. 2014 Jun;16(6):647-54. doi: 10.1093/ntr/ntt201. Epub 2013 Dec 9. **PMID: 24323574**

2. Hu, X, Dodd, VJ, Oliverio, JC, **Cook, RL**. Utilization of information and communication technology (ICT) among sexually transmitted disease clinics attendees with coexisting drinking problems. BMC Research Notes 2014, Mar 26;7:178. doi: 10.1186/1756-0500-7-178. http://www.biomedcentral.com/content/pdf/1756-0500-7-178.pdf. **PMID: 24670037**

3. Miguez-Burbano, MJ, Espinoza, L, Whitehead, NE, Bryant, VE, Vargas, M, **Cook, RL**, Quiros, C, Lewis, JE, Deshratan, A. Brain derived neurotrophic factor and cognitive status: The delicate balance among people living with HIV, with and without alcohol abuse. *Curr HIV Res*. 2014;12(4):254-64. **PMID: 25053366**

4. Harle, CA, **Cook, RL**, Kinsell, HS, Harman, JS. Opioid Prescribing by physicians with and without electronic health records. (2014) *Journal of Medical Systems*. In press.

5. Bryant, VE, Whitehead, NE, Burrell, LE, Dotson, V, **Cook, RL**, Cohen, RA. Depression and apathy among people living with HIV: substance use and cognitive performance differences and the implications for treatment of HIV Associated Neurocognitive Disorders, Provisional acceptance at AIDS and Behavior.

Mingzhou Ding, PhD, Pruitt Family Professor

Expertise: Cognitive Neuroscience, Signal Processing, Neuroimaging, Computational Neuroscience
Research Focus: Functional and Structural Connectivity, Granger Causality, Interaction of Age and Fatigue, Attention, Working Memory
Role: CAM-CTRP Neuroimaging Core Member, Provides computational expertise for big data analyses of neuroimaging

1. Wang, C, **Ding, M** and Kluger, BM. "Change in Intraindividual Variability over Time as a Key Metric for Defining Performance-Based Cognitive Fatigability." *Brain and Cognition*. 85(2014)251-258

2. Burtis, DB, Heilman, KM, Mo, J, Wang, C, Lewis, GF, Davilla, MI, **Ding, M**, Porges, SW, Williamson, JB. "The Effects of Constrained

Left versus Right Monocular Viewing on the Autonomic Nervous System." *Biological Psychology*. 100(2014)79-85

3. Caldwell, JZ, Gongvatana, A, Navia, BA, Sweet, LH, Tashima, K, **Ding, M**, Cohen, R. "Neural dysregulation during a working memory task in human immunodeficiency virus-seropositive and hepatitis C coinfected individuals." *Journal of Neurovirology*. 20(2014)398-411

4. Liu, Y, Bengson, J Huang, H, Mangun, GR, **Ding, M**. "Top-down Modulation of Neural Activity in Anticipatory Visual Attention: Control Mechanisms Revealed by Simultaneous EEG-fMRI." *Cerebral Cortex*. In press.

5. **Ding, M**, Wang, C. "Analyzing MEG data with Granger causality: promises and pitfalls." in *Magnetoencephalography: From Signals to Dynamic Cortical Networks*, Edited by Selma Supek and Cheryl J. Aine, Springer Verlag, Heidelberg, 2013. In press.

Vonetta Dotson, PhD, Assistant Professor

Expertise: Cognitive aging, Late-Life Depression, Clinical neuropsychology
Research Focus: Depression, Exercise
Role: Collaborator on intervention development

1. **Dotson, VM**, Szymkowicz, SM, Kirton, JW, McLaren, ME, Green, M & Rohani, JY (2014). Unique and interactive effect of anxiety and depressive symptoms on cognitive and brain function in young and older adults. *Journal of Depression and Anxiety*. doi: 10.4172/2167-1044.S1-003

2. **Dotson, VM**, Green, ML, Kirton, JW, Szymkowicz, SM, Sozda, CN, Perlstein, WM, Anton, SD & Manini, TM. (In press.) Adult age differences in fMRI activity during memory encoding. *Psychology & Aging*.

3. Bryant, VE, Whitehead, NE, Burrell, LE, **Dotson, VM**, Cook, RL & Cohen, R. (In press.) Depression and apathy among people living with HIV: substance use and cognitive performance differences and the implications for treatment of HIV Associated Neurocognitive Disorders. *AIDS and Behavior*.

Adam D. Falchook, MD

Expertise: Behavioral Neurology, Attention, Stroke
Research Focus: Attention, Neglect syndrome, Behavioral Neurology of Aging
Role: Medical collaborator on intervention studies, Memory Disorder Clinic Liaison

1. **Falchook, AD**, Salazar, L, Neal, D, Kesayan, T, Williamson, JB, Malaty, IA, McFarland, NR, Okun, MS, Rodriguez, RL, Wagle Shukla, A, Heilman, KM. (2014). Global attentional neglect of segmented lines in Parkinson's disease. *Neurocase*, 30, 1-8.

2. Pundik, S, **Falchook, AD**, McCabe, J, Litinas, K, Daly, JJ. (2014). Functional Brain Correlates of Upper Limb Spasticity and Its Mitigation following Rehabilitation in Chronic Stroke Survivors. *Stroke Res Treat*, 2014, 306325. doi: 10.1155/2014/306325.

Glen R. Finney, MD, Assistant Professor

Expertise: Behavioral Neurology, Memory Disorders
Research Focus: Dementia, Behavioral Neurology of Aging, Pre-MCI interventions
Role: Medical collaborator, Memory Disorder Clinic Liaison

1. Rivera-Gutierrez, D, Kopper, R, Kleinsmith, A, Cendan, J, **Finney, GR**, Lok, B. "Exploring Gender Biases with Virtual Patients for High Stakes Interpersonal Skills Training." *14th Intelligent Virtual Agents Conference (IVA)*, 27-29 August 2014, Boston.

2. Falchook, AD, Heilman, KM, **Finney, GR**, Gonzalez-Rothi, LJ, Nadeau, SE. Neuroplasticity, Neurotransmitters, and New Directions for Treatment of Anomia in Alzheimer Disease, *Aphasiology*, 2014; 28: 219-235.

Kenneth M. Heilman, MD

Expertise: Behavioral Neurology, Neuropsychology, Attention, Cognitive Aging, Memory Disorders
Research Focus: Neglect Syndrome, Behavioral Neurology of Aging, Stroke, Attention, Creativity, Emotion, Case Study Methodology
Role: Director of Center for Neuropsychological Studies, Collaborator on studies of the behavioral neurology of aging

1. Milano, NJ, **Heilman, KM**. Cerebellar allocentric and action-intentional spatial neglect. *Cogn Behav Neurol*. 2014 Sep;27(3):166-72. doi: 0.1097/WNN.0000000000000033. **PMID: 25237748** [PubMed – in process]

2. Bowen, LN1, Subramony, SH, **Heilman, KM**. Apraxia in anti-GAD associated stiff person syndrome: Link to corticobasal degeneration? *Ann Neurol*. 2014 Aug 6. doi: 10.1002/ana.24245. [Epub ahead of print].

3. Falchook, AD, Salazar, L, Neal, D, Kesayan, T, Williamson, JB, Malaty, IA, McFarland, NR, Okun, MS, Rodriguez, RL, Wagle Shukla, A, **Heilman, KM**. Global attentional neglect of segmented lines in Parkinson's disease. *Neurocase*. 2014 Jul 30:1-8. [Epub ahead of print]

4. Skidmore, FM, Spetsieris, PG, Anthony, T, Cutter, GR, von Deneen, KM, Liu, Y, White, KD, **Heilman, KM**, Myers, J, Standaert, DG, Lahti, AC, Eidelberg, D, Ulug, AM. A Full-Brain, Bootstrapped Analysis of Diffusion Tensor Imaging Robustly Differentiates Parkinson Disease from Healthy Controls. *Neuroinformatics*. 2014 Jun 29. [Epub ahead of print]

5. **Heilman, KM**. Possible mechanisms of anosognosia of hemiplegia. *Cortex*. 2014 Jun 19. pii: S0010-9452(14)00193-2. doi: 10.1016/j.cortex.2014.06.007. [Epub ahead of print]

6. **Heilman, KM**. There is more than imitation. *Cortex*. 2014 August 2014, 57: 57:275-276

7. Pandey, AK, **Heilman, KM**. Conduction Aphasia with Intact Visual Object Naming. *Cogn Behav Neurol*. 2014 Jun;27(2):96-101.

8. Nadeau, SE, Bowers, D, Jones, TL, Wu, SS, Triggs, WJ, **Heilman, KM**. Cognitive Effects of Treatment of Depression with Repetitive Transcranial Magnetic Stimulation. *Cogn Behav Neurol*. 2014 Jun;27(2):77-87.

9. Burtis, DB, **Heilman, KM**, Mo, J, Wang, C, Lewis, GF, Davilla, MI, Ding, M, Porges, SW, Williamson, JB. The effects of constrained left versus right monocular viewing on the autonomic nervous system. *Biol Psychol*. 2014 May 27. pii: S0301-0511(14)00105-7. doi: 10.1016/j.biopsycho.2014.05.006. [Epub ahead of print]-(585).

10. Zilli, EM, **Heilman, KM**. Allocentric spatial neglect with posterior cortical atrophy. *Neurocase*. 2014 Feb 6. [Epub ahead of print].

11. Milano, NJ, Williamson, JB, **Heilman, KM**. Improved verbal learning in the semantic variant of primary progressive aphasia whe using semantic cues. *Neurocase*. 2014 Mar 11 [Epub ahead of print] PMID:24611440[PubMed – as supplied by publisher].

12. Price, CC1, Tanner, JJ, Schmalfuss, I, Garvan, CW, Gearen, P, Dickey, D, **Heilman, KM**, McDonagh, DL, Libon, DJ, Leonard, C, Bowers, D, Monk, TG. A pilot study evaluating presurgery neuroanatomical biomarkers for postoperative cognitive decline after total knee arthroplasty in older adults. *Anesthesiology*. 2014 Mar;120(3):601-13.

13. Susan A. Leon*, Lori, JP, Altmann, Lise, Abrams, Leslie J. Gonzalez Rothib & **Kenneth M. Heilman**. Divergent Task Performance in Older Adults: Declarative Memory or Creative Potential? *Creativity Research Journal*. 2014, 26: 21-29.

14. Gubernick, D, Ameli, P, Teng, Q, Velez, A, **Heilman, KM**, Hedna, VS. Visual-olfactory hallucinatory synesthesia: The Charles Bonnet Syndrome with olfactory hallucinations. *Cortex*. 2014 Jan;50:204-7.

15. Roth, HL, Bauer, RM, Crucian, GP, **Heilman, KM**. Frontal-executive constructional apraxia: When delayed recall is better than copying. *Neurocase*. 2014 Jun;20(3):283-95.

16. Falchook, AD, Burtis, DB, Acosta, LM, Salazar, L, Hedna, VS, Khanna, AY, **Heilman, KM**. Praxis and writing in a right-hander with crossed aphasia. *Neurocase*. 2014 Jun;20(3):317-272.

17. Sitek, EJ, Narozanska, E, Barczak, A, Jasinska-Myga, B, Harciarek, M, Chodakowska-Zebrowska, M, Kubiak, M, Wieczorek, D, Konieczna, S, Rademakers, R, Baker, M, Berdynski, M, Brockhuis, B, Barcikowska, M, Zekanowski, C, **Heilman, KM**, Wszolek, ZK, Slawek, J. Agraphia in patients with frontotemporal dementia and parkinsonism linked to chromosome 17 with P301L MAPT mutation: dysexecutive, aphasic, apraxic or spatial phenomenon? *Neurocase*. 2014; 20(1):69-86.

18. **Heilman, KM**, Leon, SA, Burtis, DB, Ashizawa, T, Subramony, SH. Affective communication deficits associated with cerebellar degeneration. *Neurocase*. 2014;20(1):18-26.

Catherine E. Price, PhD, Associate Professor

Expertise: Clinical Neuropsychology, Cognitive Aging, Neuroimaging
Research Focus: Post-surgical cognitive consequences, white matter tractography methods
Role: Clinical collaborator on cognitive aging and post-surgical intervention effects in older adults

1. **Price, CE**, Pereira, DB, Andre, R, Garvan, CW, Nguyen, P, Herman, M, Seubert, C. (in press, October 2014). Prospective pilot investigation: Pre-surgical depressive symptom severity and anesthesia response in women undergoing surgery for gynecologic mass removal. *International Journal of Behavioral Medicine*.

2. *Schwab, NA, Tanner, JJ, Nguyen, P, Schmalfuss, IM, Okun, M, Bowers, D, **Price, CE** (In press, October 2014). Proof of principle: Transformation approach alters caudate nucleus volume and structure-function associations. *Brain Imaging and Behavior*.

3. Benzdicek, O, Libon, DJ, Stepankova, H, Panenkova, E, Lukavsky, J, Garrett, KD, Lamar, M, **Price, CE**, Kopecek, M (2014, In press). Development, validity, and normative data study for the 12-word Philadelphia Verbal Learning Test (czP®VLT-12) among older and very old Czech adults. *The Clinical Neuropsychologist*.

4. Libon, DJ, Penney, DL, Davis, R, Tabby, D, Eppig, J, Nieves, C, Block, A, Donohue, JB, Rife, K, Lamar, M, **Price, CE**, Au, R, Swenson, R, Garrett, K (2014, In press). Deficits in processing speed and decision making in relapsing-remitting multiple sclerosis: The Digit Clock Drawing Test (dCDT). *Journal of Multiple Sclerosis*.

5. Libon, DJ, Drabick, DAG, Giovannetti, T, **Price, CE**, Bondi, MW, Epiig, J, Devlin, K, Nieves, C, Wicas, G, Lamar, M, Delano-Wood, L, Nation, DA, Brennan, L, Au R, Swenson, R (2014, In press). Neuropsychological syndromes associated with Alzheimer's/ Vascular Dementia: A latent class analysis. *Journal of Alzheimer's Disease*.

6. **Price, CE**, Tanner, JJ, Schmalfuss, IM, Garvan, C, Gearen, P, Dickey, D, Heilman, K, McDonagh, D, Libon, DJ, Leonard, T, Bowers, D, Monk, T (2014). A pilot study evaluating pre-surgery neuroanatomical biomarkers for postoperative cognitive decline after total knee arthroplasty in older adults. *Anesthesiology*, 120(3), 601-13. **PMID: 24534857**

7. Jones, JD, Jacobson, C, Murphy, M, **Price, CE**, Okun, MS, Bowers, D (2014). Influence of hypertension on neurocognitive domains in nondemented Parkinson's disease patients. *Parkinsons Dis*. 2014, epub PubMed **PMID: 24587937**

Ranganatha Sitaram, PhD, ME

Expertise: Biomedical Engineering, Real-time Neuroimaging, Neurofeedback
Research Focus: Real-time Neuroimaging Intervention Development, Neurofeedback
Role: CAM-CTRP Neuroimaging Core Member, CAM-CTRP Neurophysiology and Neuromodulation Core Member

1. Sitaram, R, Caria, A, Veit, R, Gaber, T, Ruiz, S, Birbaumer, N. Volitional control of the anterior insula in criminal psychopaths using real-time fMRI neurofeedback: A pilot study. *Frontiers in Behavioral Neuroscience*. 8, 344, October 2014.

2. van der Heiden, L, Liberati, G, **Sitaram, R**, Kim, S, Jaśkowski, P, Raffone, A, Olivetti Belardinelli, M, Birbaumer, N, Veit, R. Insula and inferior frontal triangularis activations distinguish between conditioned brain responses using emotional sounds for basic BCI communication. *Front Behav Neurosci*. 2014 Jul 21;8:247. doi: 10.3389/fnbeh.2014.00247. eCollection 2014. PubMed **PMID: 25100958**; PubMed Central **PMCID: PMC4104703**

3. Kotchoubey, B, Bütof, S, **Sitaram, R**. Flagrant Misconduct of Reviewers and Editor: A Case Study. *Sci Eng Ethics*. 2014 Aug 26. [Epub ahead of print] PubMed **PMID: 25156788**

4. Ruiz, S, Buyukturkoglu, K, Rana, M, Birbaumer, N, **Sitaram, R**. Real-time fMRI brain computer interfaces: self-regulation of single brain regions to networks. *Biol Psychol*. 2014 Jan;95:4-20. doi: 10.1016/j.biopsycho.2013.04.010. Epub 2013 May 1. Review. PubMed **PMID: 23643926**

5. Rea, M, Rana, M, Lugato, N, Terekhin, P, Gizzi, L, Broetz, D, Fallgatter, A, Birbaumer, N & **Sitaram, R**, Caria, A. Lower Limb Movement Preparation in Chronic Stroke: A Pilot Study Toward an fNIRS-BCI for Gait Rehabilitation. *Neurorehabil Neural Repair*. 2014 Jan 30. PubMed **PMID: 24482298** (Impact Factor, IF: 4.88)

Samuel S. Wu, PhD, Professor

Expertise: Biostatistics, Data Security, Adaptive Clinical Trial Design
Research Focus: Trial Design Implementation Strategies, Cloud Data Security Methodology
Role: CAM-CTRP Biostatistician, Pepper Biostatistics Core Leader

1. **Wu, SS**, Tu, Y, He, Y. (2014). Testing for efficacy in adaptive clinical trials with enrichment. *Statistics in Medicine*. 33(16):2736-45. **PMID: 24577792**

2. Valencia, C, Fillingim, RB, Bishop, M, **Wu, SS**, Wright, TW, Moser, M, Farmer, K, George, SZ. (2014). Investigation of central pain processing in post-operative shoulder pain and disability. *Clin J Pain*. 30(9):775-86. **PMID: 24042347**

3. George, SZ, Parr, JJ, Wallace, MR, **Wu, SS**, Borsa, PA, Dai, Y, Fillingim, RB. (2014). Inflammatory Genes and Psychological Factors Predict Induced Shoulder Pain Phenotype. *Med Sci Sports Exerc*. 46(10):1871-81. **PMID: 24598699**

4. Bega, D, **Wu, SS**, Pei, Q, Schmidt, PN, Simuni, T (2014). Recognition and treatment of depressive symptoms in Parkinson's disease: the NPF dataset. *J Parkinsons Dis*. 165:1-8. **PMID: 25038641**

5. Nadeau, SE, Bowers, D, Jones, TL, Wu, SS, Triggs, WJ, Heilman, KM. (2014). Cognitive effects of treatment of depression with

repetitive transcranial magnetic stimulation. *Cogn Behav Neurol*. 27(2):77-87. **PMID: 24968008**

6. George, SZ, Parr, J, Wallace, MR, **Wu, SS**, Borsa, PA, Dai, Y, Fillingim, RB (2014). Biopsychosocial influence on exercise-induced injury: genetic and psychological combinations are predictive of shoulder pain phenotypes. *J Pain*. 15(1):68-80. **PMID:24373571**

7. Nutt, JG, Siderowf, AD, Guttman, M, Schmidt, PN, Zamudio, JI, **Wu, SS,** Okun, MS, Simuni, T, Parashos, SA, Dahodwala, NA, Davis, TL, Giladi, N, Gurevich, T, Hauser, RA, Jankovic, J, Lyons, KE, Marsh, L, Miyasaki, JM, Morgan, JC, Santiago, AJ, Tarsy, D, Mari, Z, Malaty, IA, Nelson, EC; National Parkinson Foundation Quality Improvement Initiative Investigators (2014). Mobility, mood and site of care impact health related quality of life in Parkinson's disease. *Parkinsonism Relat Disord*. 20(3):274-9. **PMID: 24182524**

8. Childs, JD, **Wu, SS**, Teyhen, DS, Robinson, ME, George, SZ (2014). Prevention of low back pain in the military cluster randomized trial: effects of brief psychosocial education on total and low back pain-related health care costs. *Spine J*. 14(4):571-83. **PMID: 23608562**

Other Publications: N/A

Note: This list only includes core faculty and CAM-CTRP Scholars. For a complete listing of the publications of all CAM-CTRP affiliated faculty, please see our website.

PRESENTATIONS AT SCIENTIFIC MEETINGS:

Core Faculty

Ron Cohen, PhD, Professor, CAM-CTRP Director

Annual McKnight Inter-Institute Meeting: Neuroimaging Panel and Symposium Leader

McKnight Annual Executive Board Meeting: Neuroimaging and MRS

Cognitive Clinical Translation Interventions and Approaches

MR Spectroscopy Session

Augmenting Cognitive Training in Elders: A proposal for research, Florida Neuropsychological Society/International Neuropsychological Society Pre-meeting, Vancouver

Adam J. Woods, PhD, Assistant Professor, CAM-CTRP Assistant Director

Woods, AJ. Combating Cognitive Aging with Non-Invasive Brain Stimulation. *University of Florida Institute on Aging Annual Spotlight on Aging Research Special Lecture*, Gainesville, FL, USA, June 4, 2014.

Woods, AJ. Transcranial Direct Current Stimulation. *Cognitive Aging and Memory Clinical Translational Research Program 2nd Annual Extrernal Advisory Board Meeting*, Gainesville, FL, USA, June 2, 2014.

Woods, AJ. Neuroimaging, Electrophysiology, and Neurmodulation. *Cognitive Aging and Memory Clinical Translational Research Program 2nd Annual Extrernal Advisory Board Meeting*, Gainesville, FL, USA, June 2, 2014.

Woods, AJ. Enhancing Cognitive Function using Transcranial Direct Current Stimlation. *The Mcknight Brain Institute Multi-Institution Meeting*, Gainesville, FL, USA, March 27, 2014.

Woods, AJ. The alert brain: the role of brain alerting mechanisms in cognitive function. *Oak Hammock Institute on Higher Education Lecture Series*, Gainesville, FL, USA, March 5, 2014.

Woods, AJ. Space, Time, and Causality in the Human Brain. *GATOR Pre-INS Conference*, British Columbia, Canada, February 11, 2014.

Woods, AJ, Porges, E, O'Shea, A, Bryant, V, Harris, A, Edden, R, Cohen, R. Frontal NAA concentrations predict global cognitive function in older adults. *Cognitive Neuroscience Society*.

Porges, E, **Woods, AJ**, O'Shea, A, Bryant, V, Harris, A, Edden, R, Cohen, R. GABA concentrations predict global cognitive function in older adults. *Cognitive Neuroscience Society*.

Woods, AJ, Bryant, V, Sacchetti, D, Gervits, F, Hamilton, R. Effects of electrode drift on transcranial direct current stimulation. *International Brain Stimulation*.

Floyd, T, Lairamore, C, Garrison, K, **Woods, AJ**, Smitherman, S, Young JA & Mennemeier, M. Using tDCS to Jump Start Gait Training in Chronic Stroke Patients. Poster presented at the *Arkansas Biosciences Institute, Fall Research Symposium*, 10/7/2014, Arkansas State University, Jonesboro Arkansas.

Mennemeier, M, Harrison, M, Settle, M & **Woods, AJ**. Advantages and shortcomings of using lesion subtraction to associate behavioral deficits with localized brain injury. Poster presented at the *Arkansas Biosciences Institute, Fall Research Symposium*, 10/7/2014, Arkansas State University, Jonesboro Arkansas.

McLaren, M, Szymkowicz, S, O'Shea, A, **Woods, AJ**, Manini, T, Anton, S, Dotson, VM. Symptom dimensions of depression and frontal brain volume in older adults. *International Neuropsychological Society*.

Szymkowicz, S, McLaren, M, O'Shea, A, **Woods, AJ**, Manini, T, Anton, S, Dotson, VM. Subthreshold depressive symptoms are associated with age-related structural brain changes. *International Neuropsychological Society*.

Muhlhaus, J, Habel, U, **Woods, AJ**, Cardillo, E, Yu, J, Chatterjee, A. Are nouns and verbs neurally separable based on semantic relations? *Human Brain Mapping*.

Woods, AJ, Chatterjee, A, Kranjec, A, Bikson, M, Minhaus, P, Yu, J, Hamilton, R. Exploring Structure-Function Relationships using tDCS and fMRI in Parallel. Presented at *NYC Neuromodulation 2013; Brain Stimulation*, 7 (2), e9.

Kessler, S, **Woods, AJ**, Minhas, P, Rosen, A, Bikson, M. Safety parameters for transcranial direct current stimulation in children. Presented at *NYC Neuromodulation 2013; Brain Stimulation*.

John Williamson, PhD, Assistant Professor

Williamson, JB, Harciarek, M, Acosta, L, Cibula, J, Heilman, KM. Closure in temporal lobe epilepsy: Laterality and open endings. Poster presented at the *2014 annual meeting of the International Neuropsychological Society*, Seattle.

Williamson, JB, Drago, V, Harciarek, M, Falchook, A, Lamb, D, Wargovitch, B, Heilman, KM. The influence of emotional valence on the chronology of autobiographical memory salience. Poster presented at the *2014 annual meeting of the International Neuropsychological Society*, Seattle.

Harciarek, M, **Williamson, JB**, Biedunkiewicz, B, Debska-Slizien, A, Rurkowski, B. Defective performance on Trail Making Test in adequately hemodialyzed patients: A general slowing or an executive phenomenon? Poster present at the *2014 annual midyear meeting of the International Neuropsychological Society*, Jerusalem.

Falchook, AD, Salazar, L, Neal, D, Kesayan, T, **Williamson, JB**, Malaty, I, McFarland, N, Okun, MS, Rodriguez, R, Wafle-Skukla, A, Heilman, KM. Spatial neglect and Parkinson disease. Poster presented at the *2014 annual meeting of the American Academy of Neurology*, Philadelphia.

Kesayan, T, Falchook, AD, **Williamson, JB**, Heilman, KM. The mind's eye: Effects of aging, hemispace and movement direction on estimates of distance. Poster presented at the *2014 annual meeting of the American Academy of Neurology*, Philadelphia.

Yenisel Cruz-Almeida, MSPH, PhD, Assistant Professor

American Pain Society Shared Interest Group Meeting Invited Presentation

American Pain Society Invited Symposium Presentation

Gerontological Society of America Presentation

Kimberly Sibille, MA, PhD, Assistant Professor

KT Sibille, Y Cruz-Almeida, C King, MC Ribeiro-Dasilva, T Glover, E Bartley, B Goodin, A Sotolongo, M Heberi, J Schmidt, B Fessler, D Redden, R Staud, J Riley III, L Bradley, and RB Fillingim (2014). Exploring immune system profiles in individuals with chronic knee OA pain compared to no chronic knee OA pain. Poster presentation at the *33rd Annual Scientific Meeting of the American Pain Society*, April 30-May 3, 2014 in Tampa, FL.

Hassett, A, **Sibille, KT**, Tracey, I (2014). Pain and affect: Where experience and neurobiology merge. Topical workshop presentation at the *15th World Congress on Pain, International Association for the Study of Pain*, October 6-11, 2014 in Buenos Aires, Argentina.

Neilsen, C, **Sibille, KT**, Bruehl, S (2014). Big pain data: Applying experimental and biological approaches in high-throughput

epidemiological studies. Topical workshop presentation at the *15th World Congress on Pain, International Association for the Study of Pain*, October 6-11, 2014 in Buenos Aires, Argentina.

Affiliate Faculty

Robert L. Cook, MD, MPH

Isakov, K, **Cook, RL**, Friary, JA. Phosphatidylethanol (PEth): An alcohol biomarker for alcohol consumption in hazardous drinkers. Poster presentation: *Florida Undergraduate Research Conference*, University of Florida, February 2013.

Abbott, S, Trainor, A, Hu, X, **Cook, RL**. Youth Perception: Correlation of Sexual Risk Behaviors and Alcohol or Marijuana Use. Poster Presentation: 2014 SHARC Conference. Florida International University. Miami, FL. January 29, 2014. Poster Presentation: *2014 PHHP Research Day*. University of Florida. Gainesville, FL. May 9, 2014.

Bryant, V, Whitehead, NE, Burrell, LE, Hearn, LE, **Cook, RL**, Cohen, RA. Depression, apathy and history of alcohol dependence: Possible prognostic indicators for HAND? Poster Presentation: *2014 SHARC Conference*. Florida International University. Miami, FL. January 29, 2014.

Hook, A, Cook, CL, **Cook, RL**. Identifying Barriers to Mental Health Care among HIV Patients in a Developing Cohort. Poster Presentation: *2014 SHARC Conference*. Florida International University. Miami, FL. January 29, 2014.

Mills, JC, Escobar-Viera, CG, Harman, J, **Cook, RL**. Association between Population Characteristics and Unmet Mental Health, Alcohol or Substance Abuse Treatment Needs. Poster Presentation: 2014 SHARC Conference. Florida International University. Miami, FL. January 29, 2014. Poster Presentation: *2014 CHAART Conference*, Washington D.C. May 14, 2014.

Okafor, C, Loy, C, **Cook, RL**, Cohen, R. Is Body Mass Index (BMI) associated with neurocognitive impairment (NCI) in persons living with HIV (PLWH)? Poster Presentation: *2014 SHARC Conference*. Florida International University. Miami, FL. January 29, 2014.

Peters, L, Cook, CL, Mills, J, **Cook, RL**. Differences in Depression between Older and Younger People Living with HIV. Poster Presentation: *2014 SHARC Conference*. Florida International University. Miami, FL. January 29, 2014.

Hu, X, Cook, CL, Harman, J, **Cook, RL**. Drinking patterns and health care utilization among persons living with HIV. Poster Presentation: *2014 SHARC Conference*. Florida International University. Miami, FL. January 29, 2014. Poster Presentation: *2014 CHAART Conference*, Washington D.C. May 14, 2014.

Subero, EJ, Trainor, A, **Cook, RL**. Diversity among People Living with HIV: Achieving a Representative Sample. Poster Presentation: *College of Public Health and Health Professions Diversity Day*. Gainesville, FL. March 19, 2014.

Wallace, JA, Hu, X, **Cook, RL**. Prevalence of depression and its association with emergency room visits among patients with HIV in a developing Florida cohort. Poster presentation: *College of Medicine Research Day*, University of Florida. Gainesville, FL. May 7, 2014. *1st Place Lawrence M. Goodman Research Award*.

Cook, RL, Hu, X, Wizzard, T, Quiros, C, Trainor, A, Miguez, MJ. Correlation between PEth Biomarker and Self-Reported Drinking: Preliminary Findings from the WHAT-IF? Clinical Trial. Poster Presentation: *2014 CHAART Conference*, Washington D.C. May 14, 2014.

Mingzhou Ding, PhD, Pruitt Family Professor

"Network Interactions from Time Series Data," International Symposium on Nonlinear Sciences and Applications, Shanghai, June, 2014

"Beyond Averaging: Granger Causality and Single Trial Analysis of ERPs," Department of Psychology, Peking University, July, 2014

"Topics in Human Brain Imaging," College of Medicine, Xi'an Jiaotong University, Xi'an, July 2014

"Analyzing Functional Brain Networks with Granger Causality," Department of Biomedical Engineering, Purdue University, October, 2014

Vonetta Dotson, PhD, Assistant Professor

McLaren, ME, Rohani, JY, Kirton, JW, Manini TM, Anton, SD & **Dotson, VM**. BDI-II factors' relationship to neural activity during the n-back task in older adults. Poster presented at the *27th Annual PHHP Research Day*, University of Florida, Gainesville, FL.

Kirton, JW, Szymkowicz, SM, Sozda, CN, **Dotson, VM** (2014). Cognitive Sequelae of Increased Body Mass Index. Poster presented at the *27th Annual PHHP Research Day*, University of Florida, Gainesville, FL.

Szymkowicz, SM & **Dotson, VM** (2014). Impact of subthreshold depression and anxiety on cognitive function. Poster presented at

the *16th biennial Cognitive Aging Conference (CAC)*, Atlanta, GA.

Rohani, JY, McLaren, ME, Kirton, JW, Szymkowicz, SM, Anton, SD, Manini TM & **Dotson, VM** (2014). fMRI Activity during Working Memory Related to Subclinical Depression and Anxiety in Older Adults. Poster presented at the *2014 Cognitive Aging conference* in Atlanta, GA.

McLaren, ME, Rohani, JY, Kirton, JW, Manini TM, Anton, SD & **Dotson, VM** (2014). BDI-II factors' relationship to neural activity during the n-back task in older adults. Poster presented at the *2014 Cognitive Aging conference* in Atlanta, GA.

Kirton, JW, Szymkowicz, SM, Sozda, CN & **Dotson, VM** (2014). Cognitive sequelae of increased body mass index. Poster

Natalie Ebner, PhD, Assistant Professor

Ebner, NC, Fischer, H & Cohen, RA (April, 2014). Oxytocin and aging: Effects on social decision-making and emotion processing. Poster at the *Cognitive Neuroscience Society*, Boston, MA, USA.

Fischer, H, **Ebner, NC** & Westberg, L (April, 2014). Relation between an oxytocin receptor gene variant, face recognition and amygdala activation. Poster at the *Cognitive Neuroscience Society*, Boston, MA, USA.

Ebner, NC (June, 2014). Processing social-emotional information in aging: A neuro-behavioral analysis. *Colloquium*, Max Planck Institute for Human Development, Berlin, Germany.

Ebner, NC (June, 2014). Oxytocin and socioemotional aging: Effects on social decision-making and emotion processing. *Colloquium*, University of Zurich, Zurich, Switzerland.

Ebner, NC (May, 2014). Oxytocin and aging: Effects on social decision-making and emotion processing. Invited workshop, *Scientific Research Center on Decision Neuroscience and Aging*, Tampa, FL, USA.

Ebner, NC (February, 2014). Oxytocin and aging: Effects on social decision-making and emotion processing. *External Advisory Board Meeting of Claude D. Pepper Older Americans Independence Center*, Institute on Aging, University of Florida, Gainesville, FL, USA.

Strickland-Hughes, CM, **Ebner, NC** & West, RL (August, 2014). Visual attention and aging: Effects of Feedback on Face-Name Memory. Poster at the *American Psychological Association Convention*, Washington, DC, USA.

Strickland-Hughes, CM, West, RL & **Ebner, NC** (June, 2014). Aging and self-stereotyping effects on face-name memory. Poster at the *5th Annual Spotlight on Aging Research*, Gainesville, FL, USA.

Ebner, NC, Fischer, H & Cohen, RA (April, 2014). Oxytocin and socioemotional aging. Talk at the *Cognitive Aging Conference*, Atlanta, GA, USA.

Lendry, RE, Lin, T & **Ebner, NC** (April, 2014). Effects of face likability on memory in younger and older adults. Poster at the *Cognitive Aging Conference*, Atlanta, GA, USA.

Lin, T, Ankudowich, E, Johnson, MK & **Ebner, NC** (April, 2014). Distancing from the own-age group: An age-group comparison. Poster at the *Cognitive Aging Conference*, Atlanta, GA, USA.

Strickland-Hughes, CM, West, RL & **Ebner, NC** (April, 2014). Aging and self-stereotyping effects on face-name memory. Poster at the *Cognitive Aging Conference*, Atlanta, GA, USA.

Adam D. Falchook, MD

Successful implementation of the CDA1 study Motor Impairments in Traumatic Brain Injury: Effects of Callosal Disconnection. *Center for Neuropsychological Studies lecture series* (lecture): January 2014

Falchook, AD, Salazar, L, Neal, D, Kesayan, T, Williamson, JB, Malaty, IA, McFarland, NR, Okun, MS, Rodriguez, RL, Shukla, AW and Heilman, KM. Spatial Neglect and Parkinson Disease. *American Academy of Neurology 2014 annual meeting* (poster).

Glen R. Finney, MD, Assistant Professor

Finney, GR. Rapidly Progressive Dementia Clinical Pathological Case Discussion. *University of Miami Department of Neurology Grand Rounds*. May 16, 2014.

Finney, GR. Neurology Advocacy Update. Consortium of Neurology Program Directors. *American Academy of Neurology 66th Annual Meeting*. April 27, 2014.

Finney, GR, Kleinsmith, A, Rivera-Gutierrez, D, Borish, M, Cendan, J, Velazquez, M, Stalvey, C, Lok, B. Virtual Patient Cranial Neuropathy Simulator – Preliminary Results of the UF Nerve Study. *Clerkship and Program Directors Conference, American Academy of Neurology 66th Annual Meeting* April 26, 2014.

Falchook, AD, Heilman, KM, **Finney, GR**, Gonzalez-Rothi, LJ, Nadeau, SE. Neuroplasticity, Neurotransmitters, and New Directions for Treatment of Anomia in Alzheimer Disease, *Aphasiology*, 2014; 28: 219-235.

Finney, GR. The Dementias. *University of South Florida Department of Neurology Grand Rounds*. January 17, 2014.

Finney, GR. Organized Neurology. *University of South Florida Department of Neurology Grand Rounds*. January 17, 2014.

Kenneth M. Heilman, MD

Amin Demerdash, **Kenneth M. Heilman**, Joanna Myers, Chase Mitchell, David Standaert, Frank Skidmore. Neurobehavioral Disorders In Parkinsonian Patients Without Dopamine Deficits (SWEDD). Presented at the *66th Annual Meeting of the American Academy of Neurology*, Philadelphia, PA. April 29, 2014. [P2.170]

Tigran Kesayan, Adam Falchook, John Williamson, **Kenneth M. Heilman**. The Mind's Eye: Effects of Aging, Hemispace and Movement Direction on Estimates of Distance. Presented at the *66th Annual Meeting of the American Academy of Neurology*, Philadelphia, PA. Thursday, May 1, 2014. [P7.287]

Nicholas Milano, Anouchka Douyon, Adam Falchook, **Kenneth M. Heilman**. Changes of Vertical and Horizontal Pseudoneglect with Aging. Presented at the *66th Annual Meeting of the American Academy of Neurology*, Philadelphia, PA. Thursday, May 1, 2014. [P7.290]

Anouchka Douyon, Adam Falchook, **Kenneth M. Heilman**, Nicholas Milano. Things Look Up With Aging. Presented at the *66th Annual Meeting of the American Academy of Neurology*, Philadelphia, PA. Thursday, May 1, 2014. [P7.292]

Adam Falchook, Liliana Salazar, Dan Neal, Tigran Kesayan, John Williamson, Irene Malaty, Nikolaus McFarland, Michael Okun, Ramon Rodriguez, Aparna Wagle-Shukla, **Kenneth M. Heilman**. Spatial Neglect And Parkinson Disease. Presented at the *66th Annual Meeting of the American Academy of Neurology*, Philadelphia, PA. Thursday, May 1, 2014. [P7.294]

Stamps, JJ, **Heilman, KM**, Moscovich, M, Okun, MS, Bartoshuk, LM. Taste and oral somatosensory function and the effects on retronasal olfaction during healthy aging, Alzheimer's disease, and Parkinson's disease. *Association for Chemoreceptive Sciences*. April 11, 2014. Bonita Springs, FL

D. Szeles, H. Behforhuzi, J. Stamps, J. Chin, D. Na & **K.M. Heilman**. Consistency Promotes Fluency. *Forty Second Annual Meeting, International Neuropsychological Society*, February 12-15, 2014, Seattle, Washington, USA

N. Milano & **K.M. Heilman**. Impairment of Propositional and Automatic Speech with Bilateral Mesial Frontal Atrophy: A New Primary Progressive Aphasia Variant? *Fourty Second Annual Meeting, International Neuropsychological Society*, February 12-15, 2014, Seattle, Washington, USA.

J.A. Byars & **K.M. Heilman**. Higher Levels of Body Image Concern Are Associated With Allocentric Visuospatial Attention Bias. *Fourty Second Annual Meeting, International Neuropsychological Society*, February 12-15, 2014, Seattle, Washington, USA.

J.B. Williamson, M. Harciarek, L. Acosta & **K.M. Heilman**. Closure in temporal lobe epilepsy: Laterality and open endings. *Fourty Second Annual Meeting, International Neuropsychological Society*, February 12-15, 2014, Seattle, Washington, USA.

M.L. Cohen, C. Price, N. Schwab & **K.M. Heilman**. Endogenously and Exogenously Evoked Movement Preparation, Initiation and Reprogramming in Parkinson's Disease. *Fourty Second Annual Meeting, International Neuropsychological Society*, February 12-15, 2014, Seattle, Washington, USA.

J.B. Williamson, V. Drago, M. Harciarek, A. Falchook, D. Lamb, B. Wargovitch & **K.M. Heilman**. The Influence of Emotional Valence on the Chronology of Autobiographical Memory Salience. *Fourty Second Annual Meeting, International Neuropsychological Society*, February 12-15, 2014, Seattle, Washington, USA.

D. Szeles, H. Behforuzi & **K.M. Heilman**. Diminished Vowel Letter Fluency Not Enhanced with Normal Aging. *Fourty Second Annual Meeting, International Neuropsychological Society*, February 12-15, 2014, Seattle, Washington, USA.

E. Marques Zilli & **K.M. Heilman**. Allocentric Neglect with Posterior Cortical Atrophy. *Fourty Second Annual Meeting, International Neuropsychological Society*, February 12-15, 2014, Seattle, Washington, USA.

Catherine E. Price, PhD, Associate Professor

Beaver, TM, Shushrutha, HV, Khanna, A, Miles, W, **Price, CE**, Schmalfuss, IM, Aalaei-Andabili, SH, Robertson, D, Karimi, A, Waters, M. *Thorascopic Pulmonary Vein Isolation and Atrial Appendage Ligation (TPVIAL) is superior to Medical management for Prevention of Stroke and Improvement of Energy in Atrial Fibrillation Patients with Prior Stroke.* American Academy of Neurology.

Cohen, ML, **Price, CE**, Schwab, N, Heilman, M (2014). Endogenously and Exogenously Evoked Movement Preparation, Initiation, and Reprogramming in Parkinson's Disease. *Journal of the International Neuropsychological Society*, 20(Supplement s1), p.222.

Evans, S, Tanner, J, Ahn, A, **Price, CE** (2014). Pain Intensity and Interference in Parkinson's Disease. *Florida Society of Neurology*.

Haiqing, H, Nguyen, P, **Price, CE**, Ding, M (2014). Functional connectivity analysis of dorsal and ventral caudate in humans. *Society for Neuroscience*.

Hizel, LP, Tanner, JJ, Nguyen, PT, Schwab, N Lininger, S, **Price, CE** (2014). Visuoconstruction in healthy older adults. *American Academy of Clinical Neuropsychology Annual Meeting*.

Hizel, LP, Schwab, N, Tanner, J, **Price, CE** (2014). Organizational and Neuroanatomical Contributions to Rey-Osterrieth Complex Figure in Non-Demented Older Adults with Parkinson's Disease. *Florida Society of Neurology*.

Lafo, JA, Jones, JD, Mangal, P, Okun, MS, **Price, CE**, Bauer, R, Bowers, D (2014, published abstract). Visuoperceptual task impairments in Parkinson's Disease: A pathway-specific association of executive function and memory? *Journal for the International Neuropsychological Society*, 20(supplement, s1), p. 67.

LeMonda, BC, Giles, K, **Price, CE**, Marsiske, M, Okun, MS, Bauer, RM & Bowers, D (2014, published abstract). A data-drive approach to the classification of neurocognitive subtypes of Parkinson's disease: Clinical correlations and relationship to MDS criteria. *Journal of the International Neuropsychological Society*, 20(supplement, s1), p.167.

*Peck, CP, **Price, CE** (2014, published abstract). Further support for Geshwind's theory of a disconnection syndrome: An atypical case of Germann's syndrome. *Journal of the International Neuropsychological Society*, 20 (supplement, s1), p. 174.

Penney, DL, Libon, DJ, Au, R, **Price, CE**, Lamar, M, Swenson, R, Macaulay, C, Garrett, KD, Devine, S, Delano-Wood, L, Scala, S, Flanagan, A, Davis, R (2014, published abstract). Detecting mild cognitive impairment using the MoCA clock drawing subtest. *Journal of the International Neuropsychological Society*, 20(supplement, s1), 164.

Penney, DL, Libon, DJ, Au, R, **Price, CE**, Lamar, M, Swenson, R, Macaulay, C, Garrett, KD, Devine, S, Delano-Wood, L, Scala, S, Flanagan, A, Davis, R (2014, published abstract). What the Digital Clock Drawing Test (dCDT) tells us about the MoCA clock scoring criteria. *Journal of the International Neuropsychological Society*, 20(supplement, s1), p. 164.

Penney, DL, Libon, DJ, Au, R, **Price, CE**, Lamar, M, Swenson, R, Macaulay, C, Garrett, KD, Devine, S, Delano-Wood, L, Scala, S, Flanagan, A, Davis, R (2014, published abstract). Working harder but producing less: The Digital Clock Drawing Test (dCDT) differentiates amnestic mild cognitive impairment and Alzheimer's disease. *Journal of the International Neuropsychological Society*, 20, (Supplement, s1), p. 164.

Schwab, NA, Tanner, JJ, Nguyen, PN, Schmalfuss, IM, Bowers, D, **Price, CE** (2014). Warning to Individuals Studying Structure-Function: Registration Matters. *Florida Society of Neurology*.

Slonena, E, Schwab, N, Coronado, N, Tanner, J, Nguyen, P, **Price, CE** (2014). Asymmetry of motor onset and associations with pulse pressure in Parkinson's disease. *Journal of the International Neuropsychological Society*, 20(supplement, s1), p.168.

Tanner, J, Waters, M, Audette, A, Parvataneni, H, Rice, M, **Price, CE** (2014). Patent Foramen Ovale and Cerebrovascular Emboli in a Controlled Surgery Sample. *Florida Society of Neurology*.

Ranganatha Sitaram, PhD, ME

Invited Talk: *"Real-time fMRI Brain-Computer Interface: Principles and Applications"* Pontificia Universidad Catolica de Chile, Santiago. Jan 2014. Kick-off of our Chile-US Collaborative Research Grant on RtfMRI Brain-Computer Interface.

Invited Talk/Discussion: *"Portable Near Infrared Spectroscopy as an Imaging Modality to Detect Biomarkers of Stress and Attention in Aircraft Cockpits"* Jacksonville University, Feb 2014. Project Ideation Meeting.

Samuel S. Wu, PhD, Professor

Wu, SS. "New data collection methods with privacy protection." The *15th National Statistical Science Symposium for Young Researchers*, Tianjin, PR China, September 27, 2014. (Invited)

Wu, SS. "New data collection methods with privacy protection." The *4th International Biostatistics workshop of Jilin University*, Jilin, PR China, June 5, 2014. (Invited)

Wu, SS. "New data collection methods with privacy protection." *The Joint Statistical Meeting*, Boston, MA, August 5, 2014.

Wu, SS. "Some new data collection techniques for preserving privacy." The *6th Symposium of Science, Engineering, and Biomedicine*, Daytona Beach Shores, FL, August 30, 2014. (Invited)

Wu, SS. "New data collection methods with full privacy protection." The *2014 Florida Chapter of the American Statistical Association Annual Meeting*, Gainesville, FL, February 8, 2014.

Wu, SS. "New data collection methods with privacy protection." *Department of Mathematics, Zhejiang University*, Hangzhou, PR China, September 29, 2014. (Invited)

Post-Doctoral Fellows

Tiffany L. Cummings, PhD

The Shepherd Verbal Learning Test: Validation of a Simple 10-Item Supraspan test for Use in the Memory Clinic Population, *Florida Society of Neurology*, September 12-14, 2014

Eric S. Porges, PhD, Post-Doctoral Fellow

AD, Falchook, **ES, Porges**, SE, Nadeau, SA, Leon, JB, Williamson, DB, FitzGerald, and KM Heilman. A Right Hemispheric Disconnection Syndrome after Severe Traumatic Brain Injury. Presented at the *Veterans Administration Research Day* in Gainesville, FL.

ES, Porges, Woods, AJ, O'Shea, A, Bryant, V, Harris, A, Edden, R, Cohen, R. GABA concentrations predict global cognitive function in older adults. *Cognitive Neuroscience Society*.

Natalie Ebner, **Eric S. Porges**, Tian Lin, Hakan Fisher, Ronald Cohen. Oxytocin and Aging: Effects on Reading Facial Cues of Trust and Emotion. Presented at the *annual meeting of the Cognitive Neuroscience Society* in Boston, MA.

PRESENTATIONS TO THE COMMUNITY (NON-SCIENTIFIC MEETINGS):

Stephen Anton, PhD, Associate Professor

What is Healthy Aging, *The Village*, March 3, 2014

Judge for *Oak Hammock Research Poster Day*, February 18, 2014

Treatment of Obesity in Older Adults, Invited Presentation – *Rehabilitation Research Seminar Series*, February 12, 2014

Ron Cohen, PhD, Professor, CAM-CTRP Director

The Aging Brain, *Gainesville Senior Recreational Center*

Yenisel Cruz-Almeida, MSPH, PhD, Assistant Professor

IOA Translational Science Meeting

Oak Hammock Lecture Series

Tiffany L. Cummings, PhD

Guest Lecturer for *Functional Human Neuroanatomy*

Guest Lecturer for *Neuropsychological Assessment*

Careers in Neuropsychology Lecture given at *Florida Institute of Technology Symposium*

Natalie Ebner, PhD, Assistant Professor

Maura, G & **Ebner, NC**. Social memory and aging. Institute for Learning in Retirement at Oak Hammock & at the PrimeTime Institute at the Senior Recreation Center, *Institute of Aging Senior Health Series*, University of Florida, Gainesville, FL, December, 2013.

Catherine E. Price, PhD, Associate Professor

Considerations for Post Operative Cognitive Decline. *Pepper Center Recruitment Core Speaker Series*. October 15, 2014.

Cognitive Function and Parkinson's Disease. *St. Augustine Parkinson's Disease Support Group*. January 30, 2014.

The Frontal Lobes. *Neuroanatomy Course*. July 10, 2014.

White and Gray Matter for Cognitive Profile of Parkinson's Disease. *Movement Disorder Grand Rounds*. August 12, 2014.

Post Operative Cognitive Decline in At Risk Groups. *CHP Case Conference*. January 3, 2014.

Neuropsychology and Anesthesia. *ACEM Lecture Series*, October 15, 2014.

John Williamson, PhD, Assistant Professor

Neurological mechanisms of PTSD in patients with TBI. *North Florida VAMC: CE credit course*.

Adam Woods, PhD

Combating Cognitive Aging with Non-Invasive Brain Stimulation. *University of Florida Institute on Aging Annual Spotlight on Aging Research Special Lecture*, Gainesville, FL, USA, June 4, 2014.

Enhancing Cognitive Function using Transcranial Direct Current Stimlation. The *Mcknight Brain Institute Multi-Institution Meeting*, Gainesville, FL, USA, March 27, 2014.

The alert brain: the role of brain alerting mechanisms in cognitive function. *Oak Hammock Institute on Higher Education Lecture Series*, Gainesville, FL, USA, March 5, 2014.

Space, Time, and Causality in the Human Brain. *GATOR Pre-INS Conference*, British Columbia, Canada, February 11, 2014.

AWARDS:

Stephen Anton, PhD, Associate Professor; Core Leader, Pepper Clinical Research Core

Active

R01 AT007564-01 Anton (PI) 06/01/13-05/30/17 NCCAM/NIA

Resveratrol to Enhance Vitality and Vigor in Elders (REVIVE)

This study will examine whether resveratrol supplementation can affect changes in mitochondria, and whether these changes are associated with improvements in physical function in older adults who are 70 years and older.

Role: PI

Pending

R21 04/01/15-03/31/17

Resveratrol and exercise to treat functional impairments in late life

This application proposes to conduct a pilot study to investigate the potential of resveratrol, a commercially-available nutritional product, to enhance the efficacy of physical exercise in improving physical function among older adults with functional impairments.

Role: Co-I

R34 04/01/15-03/31/18

Resveratrol and Exercise to Reduce Cardiovascular Risk in Late-Life Hypertension

The overarching objective of this project is to conduct a pilot, double-masked randomized controlled trial to evaluate the safety and efficacy of combining resveratrol supplementation with physical exercise among sedentary persons aged > 65 years with hypertension.

Kfir Ben-David, MD, FACS

Academic Awards & Honors

2014 UF Health Shands Physician Service Key Award

2013 University of Florida College of Medicine Exemplary Teacher Award

2013 UF Health Shands Physician Service Key Award

2013 Dragstedt Outstanding Department of Surgery Teaching Faculty Award

Ron Cohen, PhD, Professor, CAM-CTRP Director

Active

1R01DK09933401A1 Cohen (PI) 09/30/14 - 08/30/19

"Obesity and Type-2 Diabetes: Bariatric Surgery Effects on Brain Function"

The study will delineate mechanism underlying the effects of chronic obesity on brain functioning and determine if cognitive benefits of bariatric surgery and weight loss contribute to enhanced cerebral metabolic or hemodynamic function assessed using multimodal neuroimaging methods. 35% effort

1U54EB020403-01 Thompson (PI)

ENIGMA: Center for Worldwide Medicine, Imaging and Genomics

The Enigma Center for Worldwide Medicine, Imaging and Genomics is an unprecedented global effort bringing together 287 scientists and all their vast biomedical datasets, to work on 9 major human brain diseases: schizophrenia, bipolar disorder, major depression, ADHD, OCD, autism, 22q deletion syndrome, HIV/AIDS and addictions. Enigma integrates images, genomes, connectomes and biomarkers on an unprecedented scale, with new kinds of computation for integration, clustering, and learning from complex biodata types. Enigma, founded in 2009, performed the largest brain imaging studies in history (N>26,000 subjects; Stein +207 authors, Nature Genetics, 2012) screening genomes and images at 125 institutions in 20 countries. Responding to the BD2K RFA, ENIGMA'S Working Groups target key programmatic goals of BD2K funders across the NIH, including NIMH, NIBIB, NICHD, NIA, NINDS, NIDA, NIAAA, NHGRI and FIC. Enigma creates novel computational algorithms and a new model for Consortium Science to revolutionize the way Big Data is handled, shared and optimized. We unleash the power of sparse machine learning, and high dimensional combinatorics, to cluster and inter-relate genomes, connectomes, and multimodal brain images to discover diagnostic and prognostic markers. The sheer computational power and unprecedented collaboration advances distributed computation on Big Data leveraging US and non-US infrastructure, talents and data. Our projects will better identify factors that resist and promote brain disease, that help diagnosis and prognosis, and identify new mechanisms and drug targets. Our Data Science Research Cores create new algorithms to handle Big Data from (1) Imaging Genomics, (2) Connectomics, and (3) Machine Learning & Clinical Prediction. Led by world leaders in the field who developed major software packages (e.g., Jieping Ye/SLEP), we prioritize trillions of computations for gene-image clustering, distributed multi-task machine learning, and new approaches to screen brain connections based on the Partition Problem in mathematics. Our Enigma Training Program offers a world class Summer School coordinated with other BD2K Centers, worldwide scientific exchanges. Challenge-based Workshops and hackathons stimulate innovation and Web Portals disseminate tools and engage scientists in Big Data science. Dr. Cohen is a co-I (10% effort) and director of HIV data initiative.

Role: Co-Investigator

Robert L. Cook, MD, MPH

Active

1 U01 AA020797-01 Cook (PI) 9/01/11- 08/30/16 NIH/NIAAA

Pharmacotherapy to reduce hazardous drinking in HIV-infected women: randomized trial

The major goal of this grant is to complete a phase III randomized controlled trial on the effectiveness of naltrexone to reduce hazardous drinking and clinical outcomes among women with HIV infection.

3 U01 AA020797-04S1 Cook (PI) 09/01/14-08/31/2016 NIH/NIAAA

Pharmacotherapy for alcohol consumption in HIV-infected women: randomized trial (Diversity Supplement)

This award provides support under the Research Supplements to Promote Diversity in Health-Related Research Program for Shantrel Canidate. This research will facilitate translation of the findings from an ongoing RCT into practice by understanding the

salient factors that led to drinking behavior change in HIV-infected women with hazardous drinking.

NIH U24 AA022002 Cook (PI) 09/01/12 -08/31/17 NIH/NIAAA

Southern HIV Alcohol Research Center (SHARC) admin and research support core

The objective of this proposal is to establish the administrative structure and to provide research support for the SHARC, a collaboration that links several universities and investigators with a common goal of supporting new research related to HIV and alcohol consumption.

1U01AA020800-01 Desai (PI) 09/10/11-08/31/16 NIH/NIAAA

Immune Dys-regulation in HIV-infected Women with Heavy Alcohol Consumption

The major goal of this project is to examine whether chronic cumulative alcohol exposure is associated with more rapid CD4 T cell decline and immune dys-functionality (microbial translocation, immune activation, inflammation and immune senescence) leading to early advent of AIDS and non AIDS co-morbidities

1UO1AI103397-01 Fischl (PI) 01/01/13-12/31/17 NIH/NIAID

Miami Women's Interagency HIV Study

The goal of the Miami WIHS study is to join with other sites involved in the WIHS by recruiting new women with and without HIV infection, and to conduct research related to health outcomes for women with HIV.

Pending

NIH/NIAAA R13 AA023167 2014 SHARC Conference

The Southern HIV & Alcohol Research Consortium (SHARC) Conference project will showcase current research activities and also help to develop new ideas and collaborations related to SHARC encouraging interaction and collaboration among senior investigators, trainees, research staff, NIH scientists and community stakeholders.

NIAAA/NIA 1R01AG048657-01 Cohen (PI) 2014

HIV and the Aging Brain

The proposed study will examine the effects of HIV in the aging brain. Preliminary studies suggest that this is occurring at a much younger age than occurs in the healthy aging.

1R01HS023306-01A1 Harle (PI) 04/01/15 – 03/31/19 AHRQ

Designing User-Centered Decision Support Tools for Chronic Pain in Primary Care

The goal of this research is to examine how clinical work happens and could be improved to develop clinical decision support tools that to increase quality of care for chronic pain.

R01AA024085 Cottler (PI) 07/01/15 – 06/30/20 NIH

Reducing Heavy Drinking and Prescription Drug Misuse Among Older Women

Role: Co- Investigator

Academic Awards & Honors

2013-2016 UF Research Foundation (UFRF) Professor

Yenisel Cruz-Almeida, MSPH, PhD, Assistant Professor

Active

UF CTSI Junior Faculty Pilot Award Cruz-Almeida (PI) 06/01/14-12/30/16

Cortico-striatal connectivity in predicting widespread pain in older adults

The overall aim of the research project is to obtain pilot data to characterize cortico- striatal connectivity in older adults with and without widespread pain and its relation to physical performance.

Pending Award expected in April 2015

NIH/NIA 1K01AG048259-01A1 Cruz-Almeida (PI) 04/01/15-03/31/20

Neuroimaging age-related changes in pain modulation

The primary goal of this award is to provide the necessary training and mentoring for Dr. Cruz-Almeida to establish an independent neuroscience research program aimed at studying the neurobiological mechanisms underlying abnormal pain modulation in older adults that may account for increased clinical pain in this population.

Tiffany L. Cummings, PhD

Academic Awards & Honors
Florida Society of Neurology Travel Scholarship Award

Mingzhou Ding, PhD, Pruitt Family Professor

Active

NIMH R01 MH100820	Kocsis/Ding (PI)	04/01/14-03/31/19

Spatiotemporal Network Dynamics in a Rat Model of Schizophrenia

Objective: To study the spectral structure, anatomy, physiology and pharmacology in normal rats and pharmacological rat models of schizophrenia.

NIA R21 AG044862	Ding/Kluger (PI)	09/15/14-04/30/16

Measuring Cognitive Fatigability in Older Adults

Objective: To examine the relationship between an objective measure of cognitive performance fatigability and activity levels in older adults.

NSF BCS-1439188	Ding (PI)	09/01/14–08/31/17

Mechanisms of anticipatory attention

Objective: To study the neural basis of anticipatory attention in both humans and monkeys using electrophysiology and advanced computational methods.

Academic Awards & Honors
Senior Member of IEEE, 2014

Vonetta Dotson, PhD, Assistant Professor

Pending

NIMH R01	Dotson (PI)	07/01/15-06/31/18	NIH

Genotype and the Impact of Physical Activity on Depressive Symptoms and Cognition

The goal of this study will be to determine the effect of genetic variation on changes in subthreshold depressive symptoms and cognitive functioning in older adults after an exercise intervention.

Role: PI

NIA R03	Dotson (PI)	07/01/15-06/30/17	NIH

Dissociating Components of Anhedonia in Older Adults: A Pilot fMRI Study

The goal of this study will be to gather preliminary behavioral and functional magnetic resonance imaging (fMRI) data in healthy young and older adults on a novel measure of consummatory and motivational aspects of anhedonia.

Role: PI

Natalie Ebner, PhD, Assistant Professor

Active

NSF SaTC EAGERs NSF 13-037	Ebner (PI)	9/01/14-08/31/2016

Age-Targeted Automated Security Cueing Against Web-Based Social Engineering Attacks

The goal of this project is to develop and validate an open-source browser extension that provides visual security cues in an age-targeted fashion to protect older adults from web-based social engineering attacks during their everyday internet use.

Scientific Research Network on Decision Neuroscience and Aging (SRNDNA; sponsored by NIH/NIA;

Ebner(PI) 09/01/14-03/31/2015

The Role of Oxytocin in Prosocial Decision Making in Aging Across Humans and Monkeys

The goal of this project is to compare the effects of the neuropeptide oxytocin on social preferences and altruism in young and older primates and humans.

University of Florida Center for Cognitive Aging and Memory & Claude D. Pepper Older Americans Independence Center (sponsor: NIH/NIA); Ebner (PI) 08/01/14-07/31/15

Neurofeedback and Aging

The goal of this project is to examine trainability of volitional control over brain regions associated with emotion processing via use of neurofeedback and subsequent benefits for emotion perception in aging.

Pending

NSF Ebner (co-PI; PI Oliveira)

TWC: Medium: Collaborative: Developer Crowdsourcing: Capturing, Understanding, and Addressing Security-related Blind Spots in APIs

The goal of this project is to identify and prevent security blind spots software developers are face with.

Role: PI

Academic Awards & Honors

2014 International Max Planck Research School on the Life Course (LIFE) Outstanding Alumni Award

Eric S. Porges, PhD, Post-Doctoral Fellow

Active

Department of Veterans Affairs Williamson (PI) 06/01/14 – 12/01/14

Brain Rehabilitation Research Center Pilot Innovation (VA RR&D grant) External autonomic nervous system modulation for the treatment of PTSD.

Role: Co-I

Academic Awards & Honors

2014 Present, Editorial Board Review Editor, Frontiers in Psychology, Emotion Science

2014 Postdoctoral Fellow, Cognitive Aging and Memory Program, Clinical Translational

Research Program (CAM-CTRP), Institute on Aging, University of Florida

Catherine E. Price, PhD, Associate Professor

Active

NSF 12-543 Price (PI, UF site) 09/01/14 to 08/30/17

Title: Collaborative Research: Think-Inferring Cognitive State from Subtle Behaviors. This study will use smart technology to examine patterns of cognitive function relative to neuroanatomical connections.

R01 N5082386-02 Price (PI) 09/01/14 to 08/30/19 NIH NINDS

Title: White Matter Connectivity and PD Cognitive Phenotypes

The goal of this research project is to determine if cognitive phenotypes and cognitive trajectory can be partially explained by frontal and temporal circuit integrity.

Supplement to R01NS082385-01A1 Price (Mentor) 07/01/14-06/30/16

Title: Research Supplement to Promote Diversity in Health-Related Research (Admi Supplement) to White Matter Connectivity and PD Cognitive Phenotypes; Post-doctoral Fellow: Shellie-Anne Levy, PhD.

Academic Awards & Honors

UF Research Foundation Professorship

Paul Satz Term Professorship

Kimberly Sibille, MA, PhD, Assistant Professor

Active

NIAMS K23AR062099 Sibille (PI) 04/01/10-03/31/14

Biological markers of system burden in symptomatic knee OA: A prospective study

The overall aim of this study is to train the PI in biomarkers and biological systems important for OA pain.

American Pain Society and the Sharon S. Keller Chronic Pain Research Grant

Sibille (PI) 06/14-05/16

Optimizing Chronic Pain Treatment with Enhanced Neuroplastic Responsiveness

The overall aims of the study are to identify strategies to optimize the neurobiological environment to respond to clinical treatment interventions and override the maladaptive neuroplastic changes associated with chronic pain in individuals with osteoarthritis.

John Williamson, PhD, Assistant Professor

Active

VAMC BRRC Pilot Award Williamson (PI) 2014

Brain Rehabilitation and Research Pilot Award

External, non-invasive vagal nerve stimulation for the treatment of post-traumatic stress disorder.

The goal of this funding is to provide pilot data for the effect of VNS on autonomic response to emotional stimuli in patients with TBI and PTSD

Role: PI

Adam J. Woods, PhD, Assistant Professor, CAM-CTRP Assistant Director

Active

CTSI KL2 Woods (PI) 03/15/14-03/15/16

Clinical Translational Science Institute KL2 Career Award

Neuromodulation of working memory function in older adults.

The goal of this funding is to provide investigators with further training in clinical translational science. The funded project will involve a randomized clinical trial pairing transcranial direct current stimulation with cognitive training to enhance working memory function in older adults.

Role: PI

1U54 EB020403 Thompson (PI) 09/29/14-09/30/18 NIH

ENIGMA Center for Worldwide Medicine, Imaging, and Genomics

The goal of this study is to utilize a worldwide research consortium to facilitate big data computing of medical, neuroimaging, and genome data to further our understanding of disease states in the human brain.

Role: Co-I

2 P30 AG028740-06 Pahor (PI) 04/15/12-03/31/17 NIH

Claude D. Pepper Older Americans Independence Center (OAIC) Pilot Project:

A pilot study to evaluate the role of brain integrity on post-hospital sarcopenia (Pilot PI: Manini)

The goal of this funding is to provide pilot data on the role of brain white matter integrity in post-hospital physical decline.

Role: Co-PI

2 P30 AG028740-06 Pahor (PI) 04/15/12-03/31/17 NIH

Claude D. Pepper Older Americans Independence Center (OAIC) RC1 Development Project:

Development of Clinical Methods to Evaluate Neural Function in Aging (Project PI: Buford)

The goal of this development project is to provide support for the enhancement of the methodological skills of Pepper Center investigators to include modern methods of diffusion tensor imaging analysis.

Role: Co-I

McKnight Brain Research Foundation Cohen (PI) 10/15/13-10/15/16

McKnight Brain Research Foundation

CAM-CTRP Pilot Study Pilot Study: The ACTIVE Brain Study

The goal of this funding is to provide neuroimaging biomarkers of successful aging.

Role: Co-I

McKnight Brain Research Foundation Woods (PI) 11/1/13-11/1/15

McKnight Brain Research Foundation

CAM-CTRP Pilot Study: Brain Arousal Mechanisms in Aging

The goal of this funding is to investigate the role of brain arousal mechanisms in cognitive and physical decline associated with advanced age.

Role: PI

McKnight Brain Research Foundation Woods (PI) 12/1/13-12/1/15

McKnight Brain Research Foundation

CAM-CTRP Pilot Study: Electrophysiological markers of aging

The goal of this funding is to identify biomarkers of aging using event-related electrophysiology in the human brain.

Role: PI

McKnight Brain Research Foundation Cohen (PI) 01/01/14-01/01/16

McKnight Brain Research Foundation

CAM-CTRP Pilot Study: Visual assessment of aging processes in the human brain.

The goal of this funding is to investigate aging related changes in visual processing and assessment in the human brain.

Role: Co-I

McKnight Brain Research Foundation Porges (PI) 01/01/14-01/01/16

McKnight Brain Research Foundation

CAM-CTRP Pilot Study: Differential declination in attentional processes in advanced age

The goal of this funding is to identify differential change in the four major components of attentional processing using functional magnetic resonance imaging.

Role: Co-PI

McKnight Brain Research Foundation Woods (PI) 01/01/14-01/01/16

McKnight Brain Research Foundation

CAM-CTRP Pilot Study: Neuromodulation using transcranial direct current stimulation to improve working memory function in healthy aging

The goal of this funding is to use transcranial direct current stimulation to improve functional neuroimaging biomarkers of cognitive and metabolic decline in healthy aging.

Role: PI

Cure Stroke Fund Mennemeier (PI) 05/15/14-05/15/16 Cure Stroke

Jump-starting motor function after stroke using tDCS

The goal of this study will be to determine the efficacy of tDCS at facilitating motor recovery after stroke using transcranial direct current stimulation paired with GaitRite motor training.

Role: Consultant

NIA K99AG048762 Fazeli (PI) NIH

A novel neurorehabilitation approach for cognitive aging with HIV

The goal of this study will be to train Dr. Fazeli in aging and tDCS research methods.

Role: Co-mentor

Pending

NIA K01 Woods (PD/PI) NIH

Neuromodulation of Cognition in Older Adults

The goal of this study will be to investigate the ability of transcranial direct current stimulation to enhance the effectiveness of cognitive training targeting attention, speed of processing, and working memory function in older adults.

Role: PD/PI

NIAAA P01 Monti (PI); Renewal NIH

Alcohol and HIV: Biobehavioral Interactions and Intervention

The goal of this study focuses on the interactive effects of HIV and alcohol use on metabolic-vascular disturbances underlying brain dysfunction.

Role: Co-I

NIA R01 Cohen/Marsiske (PIs) NIH

Augmenting Cognitive Training in Older Adults (ACT)

The goal of this study will be to perform the definitive multi-site RCT establishing methods for optimized CT effectiveness in older adults through mindfulness meditation stress reduction and transcranial direct current stimulation (tDCS).

Role: Site PI (UF)

NHLBI R01 Williamson (PI) NIH

The effects of heart failure and cardiac resynchronization on the brain and cognition

The goal of this study is to determine the influence of increased blood flow through cardiac resynchronization on the brain and cognition.

Role: Co-I

NIA R01 Dotson (PI) NIH

Exercise as a moderator of late-life depression

The goal of this study will be to investigate the effects of exercise on late-life depression.

Role: Co-I

Academic Awards & Honors

2014 Clinical Translational Science Institute KL2 Research Fellow, University of Florida

2014 Elected as Junior Fellow to the World Academy of Art and Science

Samuel S. Wu, PhD, Professor; Core Leader, Pepper Center Biostatistics Core

Active

1R01DK099334 06/25/14 to 05/31/19

Obesity and type-2 diabetes: Bariatric surgery effects on brain function

This project is to determine the effect of bariatric surgery on brain function in adults with obesity and type-2 diabetes.

Role: Co-I

FACULTY BIOGRAPHICAL SKETCHES: See page 91

TRAINEES AND RECRUITMENT:

Recruitment efforts have been successful, and are ongoing for development of the CAM-CTRP team of Faculty, Post Docs, Pre Docs and others being mentored.

Huaihou Chen, PhD, received his Ph.D. in Biostatistics in 2012 from Columbia University, followed by postdoctoral training in the Department of Child and Adolescent Psychiatry at the New York University School of Medicine. He is currently an Assistant Professor in the Department of Biostatistics, College of Medicine and College of Public Health and Health Professions. His primary research interests lie in longitudinal and functional data analysis, predictive modeling, and neuroimaging. He is currently developing advanced statistical methods for using multimodal brain imaging biomarkers to predict motor and cognitive decline in the older adults.

Yenisel Cruz-Almeida, MSPH, PhD is an Assistant Professor in Aging and Geriatric Research. She is a member of the UF Pain Research & Intervention Center of Excellence (PRICE). As a clinical neuroscientist, her research interests are related to understanding the mechanisms involved in age-related pain perception and modulation in humans. Using multiple interdisciplinary and translational approaches (neuroimaging, quantitative sensory testing, non-invasive brain stimulation), her research examines nervous system factors contributing to the observed inter-individual differences in pain phenotypes in older adults. Specifically, her ongoing projects are examining the shared neural circuitry between pain and cognition that lead to mobility impairments in this population.

Tiffany Cummings, PsyD, has come to UF as a Post-Doctoral Fellow, with a three-fold educational opportunity. She is equally supported by CAM-CTRP, PHHP-Clinical and Health Psychology and Dept. of Psychiatry. She has been tasked with assisting in the development of the Brain Wellness Clinic initiative at multi sites, including the IOA-Senior Care Clinic and the Movement Disorders Center for Neurorestoration.

Vonetta Dotson, PhD, is an Assistant Professor in the Department of Clinical and Health Psychology (CHP) at the University of Florida, with a joint appointment in the Department of Neuroscience at the University of Florida. She is also a Claude C. Pepper scholar. She received her Ph.D. from CHP in 2006 with a specialization in neuropsychology and a certificate in gerontology. She completed her postdoctoral training in the Laboratory of Personality and Cognition in the National Institute on Aging Intramural Research Program under the mentorship of Drs. Susan Resnick and Alan Zonderman. Her research focuses on studying the interaction of psychological disorders such as depression with cognitive and brain aging using both neuroimaging and behavioral techniques. Her more recent work focuses on the impact of aerobic exercise on depression-related cognitive and brain changes in older adults.

Natalie Ebner, PhD has been an Assistant Professor in the Department of Psychology at University of Florida since 2011. She is Adjunct Faculty at Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP) since 2013. She received her Ph.D. in 2005 in Psychology with a particular focus on lifespan development and aging from the Free University of Berlin in Germany. She completed post-doctoral fellowships at the Max Planck Institute for Human Development in Berlin, Germany, and at Yale University, where she also worked as Associate Research Scientist before joining the faculty at University of Florida. Dr. Ebner's faculty mentors are Dr. Ron Cohen, Dr. Julia Graber, Dr. Tom Foster, and Dr. Michael Marsiske.

Dr. Ebner's research is at the intersection of cognitive, social, and developmental psychology, with a particular focus on age-related changes in cognitive processing of social and emotional information and on development and interplay of motivation, emotion, and cognition in adulthood. In particular, Dr. Ebner examines how emotional (e.g., faces displaying different emotion expressions, positive and negative personality traits) and self-relevant information (e.g., related to one's own age, personal goals and agendas, age stereotypes, etc.) affect attention, decision-making, and memory, how and why this may change across the lifespan. She uses a multi-methods approach that combines convergent measures, including self-report, behavior observation, eye tracking, genetics, hormonal markers, and functional neuroimaging techniques, with the aim to integrate introspective, behavioral, and neuropsychological data.

The two most current project that Dr. Ebner is engaged in in collaboration with researchers from the CAM-CTRB are (a) a set of studies on the short-term and long-term effects of intranasal oxytocin on cognition, physical health, and socioemotional functioning in aging, and (b) a study on neural dysregulation related to emotion processing in aging using real-time fMRI.

Damon Lamb, PhD, joined the CAM team in August 2014, but has been informally collaborating and contributing since moving to the University of Florida and the Malcom Randal VAMC in August 2013. He is predominantly funded through the

VA where he is applying his computational neuroscience background in collaborations with Drs. Heilman and Williamson investigating the alterations to the allocation of attention after stroke and the relationship between TBI and PTSD. With the CAM, he is developing neuroimaging workflows, teaching graduate students computational techniques, contributing to grants, and developing his own ideas for his own K level grant submissions.

Eric Porges, PhD, is now a second year Post- Doctoral Fellow. He recently submitted a K99 to the NIAAA investigating the role of GABA in alcohol consumption effects in persons living with HIV. He has worked to facilitate acquisition of a GABA MRS sequence for the AMRIS 3T scanner through establishing a collaboration with Richard Edden, PhD at the Johns Hopkins University. He is also currently involved in a number of projects at the CAM-CTRP, including but not limited to the ACTIVE BRAIN Study, where he is implementing the functional neuroimaging tasks, setting up a Semi-automated neuroimaging pipeline to expedite analysis of data collected in this study.

Kimberly T. Sibille, MA, PhD is an Assistant Professor in the Department of Aging & Geriatric Research in the UF College of Medicine. She is a faculty member in the Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP) and the Pain Research and Intervention Center of Excellence (PRICE) with an Affiliate appointment in the School of Advanced Dental Sciences (SADS), College of Dentistry. Dr. Sibille earned a doctoral degree in Psychology/Clinical Psychology with concentrations in Neuropsychology and Health Psychology from Fielding Graduate University and completed post-doctoral training in Clinical and Translational Pain Research through the UF Comprehensive Center for Pain Research. Dr. Sibille's research interests and investigative pursuits are associated with the interactive influences of biological, psychological, cognitive, behavioral, and social factors specific to osteoarthritis and other musculoskeletal chronic pain conditions with a focus on aging, resilience factors, and optimizing treatment response. Dr. Sibille is currently funded by a K23 Career Development Award through the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). She is a recipient of the 2014 American Pain Society Sharon S. Keller Chronic Pain Research Grant and the 2014 UF Clinical and Translational Science Institute (CTSI) Patient-Oriented Pilot Award. In 2011-2013, she was selected and received funding as a University of Florida Institute on Aging Pepper Junior Scholar and a CTSI KL2 Scholar. In 2010 she received the American Pain Society Future Leaders in Pain Research Award.

John Williamson, PhD is funded through the Alzheimer's Foundation collaborating with Kenneth Heilman, MD in the education of behavioral neurology and neuropsychology/neuroscience fellows and students in research methods and content related to diseases of aging. He is the director of a stroke neuropsychology clinic through the University of Florida Department of Clinical and Health Psychology. Our service has expanded to include neurodegenerative diseases (early and moderate stage) in collaboration with behavioral neurology. John recently (July 2013) joined the CAM team. "We have quickly developed an exciting program of collaborative projects involving multiple UF departments and the VAMC. The support of the McKnight Brain Research Foundation has enabled us to be bold in our vision and I am expecting great things moving forward." Dr. Williamson recently submitted an R01 investigating the effects of cardiac resynchronization on the brain in collaboration with the CAM-CTRP team. This grant received favorable reviews and scores and will be resubmitted in the next cycle.

Vaughn Bryant, MS, Vaughn is currently a 2nd year doctoral student in the program in Clinical and Health Psychology. His current mentors are Dr. Ronald Cohen and Dr. Adam Woods. Vaughn recently received a fundable score on his F31 submitted to the NIAA. He will be working with Drs. Cohen, Woods, Cook, and Ding to investigate the role of working memory in response to alcohol intervention treatments in persons living with HIV. He is also working with Drs. Cohen, Cook (Epidemiology) and Woods, on projects for the SHARC (Southern HIV and Alcohol Research Consortium) and Neurocognitive working group, which involve addressing neurocognitive issues in people living with HIV. Vaughn is particularly interested in the neuropsychiatric symptoms of apathy and depression, specifically, how these neuropsychiatric symptoms affect cognitive performance and neuroimaging results.

Amanda Garcia, MS, Amanda is a fourth year graduate student in the neuropsychology track in the department of Clinical and Health Psychology. Dr. Cohen is serving as her primary mentor for her dissertation. She has interest and background in the cognitive neuroscience of semantic processes and language, and also in functional neuroimaging, including FMRI. She will be conducting research in the CAM-CTRP on normal age-associated changes in semantic brain networks as measured by FMRI.

Joshua Kirton, MS is a fifth year doctoral student in Clinical Neuropsychology working with Vonetta Dotson and Ronald Cohen. His research interest includes neuroimaging in aging and depression. He is currently working on research to quantify regional white matter hyperintensities in older adult and examine their relationship to depressive symptom dimensions. He is also engaged in fMRI research on a variety of cognitive aging and depression projects.

Nicole Nissam is a first year PhD student in the College of Medicine IDP PhD program current performing a first-year rotation

in Dr. Woods' lab. She is currently working to learn structural brain imaging analyses. She will be applying these skills to a dataset investigating the interaction of heavy alcohol consumption on the aging brain.

Lindsey Richardson is a first year masters student in Educational Counseling working with Dr. Woods. Her research is focused on understanding the relationship between acute cognitive impairment and urinary tract infection. She is currently working with members of the Emergency Department to recruit for the UTrack Study.

Talia Seider, BA, Talia is a third year graduate student in the neuropsychology track in the department of Clinical and Health Psychology. Her interests are cerebrovascular disease effects on cognition, neuroimaging, HIV, and aging. She is working on quantification of white matter hyperintensities in a cohort with HIV and studying their effect on cognitive functioning in the context of aging.

Undergraduate Volunteers: CAM-CTRP has 6 of the very brightest and best qualified undergraduate students serving as research assistants. Dr. Cohen mentors 2 of these, and Dr. Woods mentors 4.

Faculty Recruitment: Efforts were made to recruit a physician researcher. We brought four senior faculty members from around the world for interviews: Drs. Pasinetti, Rizzo, Mark and Nitsche. Drs. Rizzo and Nitsche remain as candidates. They plan to return for a second visit. We are particularly keen on Dr. Nitsche, and hope he will be able to make a move from his home country of Germany.

Two more junior physician researchers are being interviewed in the coming months. This represents a shift in strategy to find promising young investigators who are more likely to make a move to UF.

In addition, two prospective candidates were interviewed on multiple occasions. We were close to completing their recruitment this spring Dr. James Morris, Ph.D., and Dr. Jessica Connelly, Ph.D.). However, their home institute (University of Virginia) offered them a great deal to remain there, so they will not be coming. Unfortunately, this led to a delay in the initiation of our Epigenetics initiative. Efforts are now underway to move the initiative forward in collaboration with Dr. Leonid Moroz (CAM-CTRP Genetics Core Leader) through the Proteomics and genomics of cognitive aging Pilot Study.

Two new faculty members were recruited (Drs. Yenisel Cruz-Almeida and Kim Sibille). They are both pain researchers who focus on aging and the neuroscience of pain. Both successfully competed for NIH career development awards (K01, K23), and will be funded for five years.

Dr. Eric Porges submitted a K99 award focusing on GABA MRS and neural plasticity in HIV and ETOH use. He will join the faculty upon being funded.

Dr. Damon Lamb, a systems neuroscientist has joined as an adjunct faculty member at 20% effort. He is currently preparing a VA Hospital CDA2 proposal. He is also involved in efforts to complete our neuroimaging pipeline.

CLINICAL /TRANSLATIONAL PROGRAMS:

Augmenting Cognitive Training in Older Adults (ACT) grant submission *(Cohen, Marsiske, Woods)***:** This proposal involved collaboration between UF, University of Miami, University of Arizona, and Florida State University to respond to a NIA and NCCAM RFA requesting techniques for combating cognitive decline in older adults. This proposal involved investigation of the adjunctive effects of transcranial direct current stimulation and mindful-based stress reduction meditation on cognitive training in older adults. The original proposal was not funded through the RFA. However, the NIA is currently negotiating with UF and University of Miami to potentially co-fund a two-site version of the proposed project.

The LIFE–ARISE Grant Submission (1RO1AG046134-01): This study will significantly advance the field of Alzheimer's disease prevention in an understudied high risk frail population not currently targeted in any other large randomized clinical trial. LIFE –ARISE will provide conclusive evidence whether physical activity effectively improves a comprehensive array of neuroimaging, cognitive and biological markers of AD. This trial will have a major public health and policy impact regarding the benefits of physical activity for AD prevention in frail older adults.

The PCORI (Patient-Centered Outcomes Research Institute) Grant Submission: A $17Million Dollar collaboration proposal from CTSI was initiated for funding related to areas of Patient Centered Outcomes Research. The CAM-CTRP (Cohen, Woods) was invited to collaborate with the Pepper Center (Manini, Anton) to develop Physical and Cognitive Frailty Assessments that would be used as

an initial screening within all health care provider centers in North Florida. This submission was not funded.

ADRC (Alzheimer's Disease Research Center) Grant submission *(Todd Golde, PhD, and Ron Cohen, PhD)***:** This proposal involved collaboration between UF and Mt. Sinai in Miami, to develop an Alzheimer's Disease Research Center. Cohen was invited to be Co-I for several aspects of the project including a neuroimaging core. Unfortunately, this was not funded, but will likely be resubmitted.

Cognitive Aging Drug Development CAM-CTRP *(Cohen et al.,)* **and ARML** *(Foster, Bizon)* have initiated efforts to identify promising compounds worthy of clinical trials, to examine possible effects on improving cognitive function, performance and brain health. Four classes of compounds have been identified, and initial organizational efforts have been taken to plan out trials needed for compounds within each class.

Neuroimaging Users Group Consortium *(Woods, Cohen, et al.,)***:** Adam Woods has taken the lead on collaborating with the Administration of AMRIS (Long, Mareci, Lai) to self-start and develop a Neuroimaging User Group to facilitate human clinical translational research involving AMRIS 3T MR system. A total of 64 multidisciplinary MR users have opted into the group list-serve, and 40+ attended the first Users Group meeting in mid-November, 2013. It was determined that subgroups would be formed as a result of the identified areas of development, to focus efforts on specific needs of neuroimaging investigators across the campus. Areas of special interest so far include:

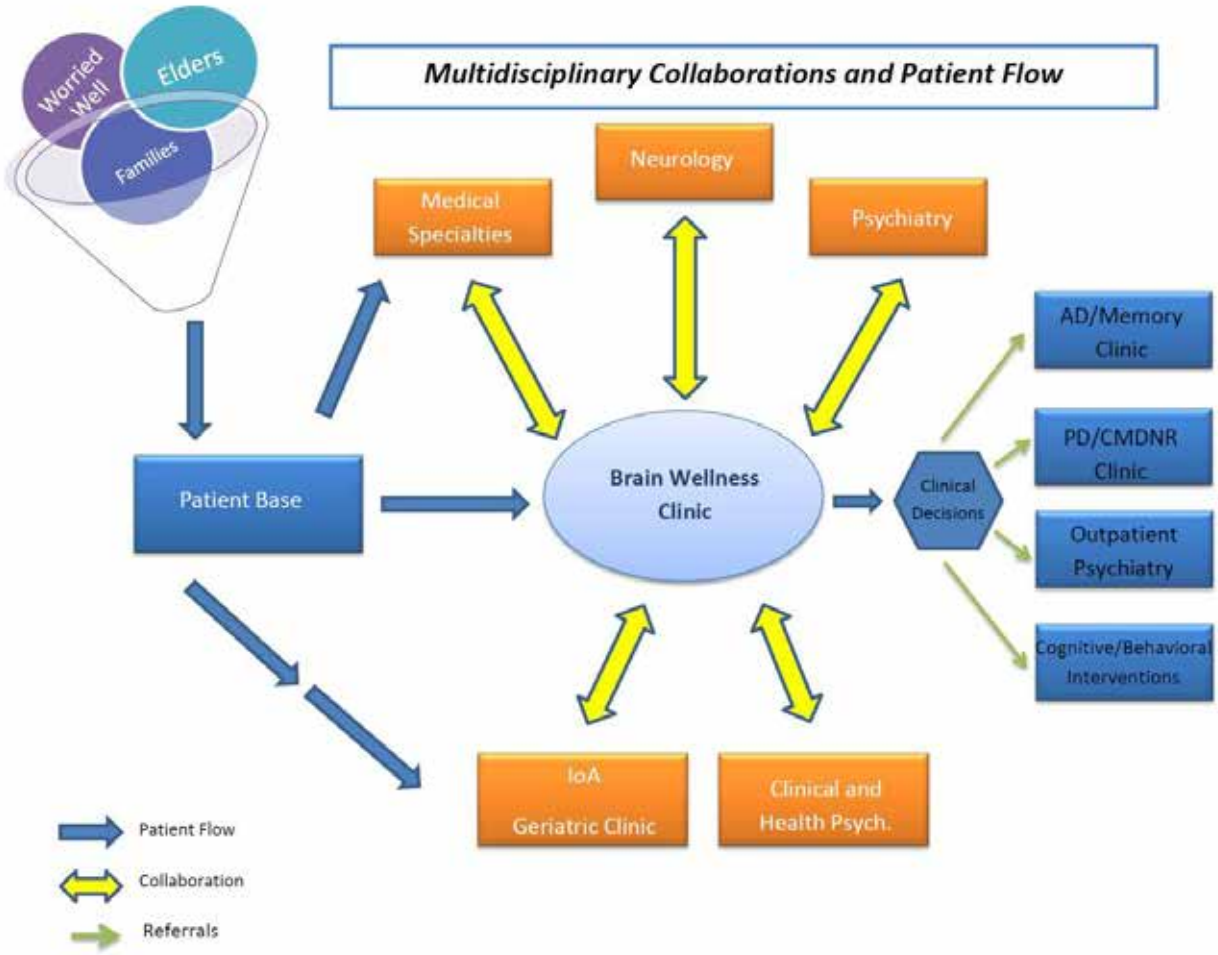
1. **Sequence Bank:** A compilation of common MR sequences (eg: DTI, MPRAGE, BOLD etc.) available to all UF 3T MRI users to facilitate cross lab and project collaborations. These data are intended to foster acquisition of large data sets that will allow the CAM-CTRP and other UF investigators to address a variety of aging and brain related studies.
2. **Standard Operating Procedures and organization of MR Suite:** To establish a working order for use of the 3T AMRIS facilities to assist investigators in making maximal use of all available resources.
3. **Acquisition of Arterial Spin Labeling:** Group organized to facilitate the acquisition of Phillips ASL sequences for multiple MR users. The acquisition of ASL will foster the inclusion of advanced MR methodology and numerous ongoing and planned grant submissions and opportunities.

TECHNOLOGY TRANSFER: NA

BUDGET UPDATE: See page 70

EDUCATIONAL PROGRAMS FOCUSING ON AGE RELATED MEMORY LOSS:

CAM-CTRP has initiated a Brain Wellness Program, housed in the 1st floor of the new CTRB-IOA Senior Care clinic. It will serve as an interface between clinical geriatric and clinical research programs of IOA, provide appropriate screenings, information on potential interventions for brain wellness and referrals. This program will be integrated with parallel Brain Wellness clinics under the direction of Dawn Bowers, PhD, at the Movement Disorders Center for Neurorestoration.



T-32 Training Grant in Development *(Cohen)*: Submission scheduled for May 2014. Program will support 6 Post-Doctoral Fellows at a time, with 2 new fellows recruited annually for a 2 year rotation. The program will focus on neuroscience of cognitive and physical aging. We will train Post Doc Fellows in research methods and provide a valuable and unique educational experience, directed at the aging brain, including opportunities to learn neuroimaging, electrophysiology approaches, other neuroscientific methods, epidemiology, biostatistics, and to obtain exposure to clinical trials, and clinical translational research.

Monthly CAM-CTRP Neuroimaging Seminar Series *(Woods)*: This seminar series is intended to provide a University wide forum for presentation of state of the art neuroimaging research and methodology. This series will fill an educational gap at the University of Florida where currently there is no educational structure in place to disseminate this widely used neuroscientific modality. This talk series will feature a monthly speaker, and lunch for attendees.

Non-Invasive Brain Stimulation Practical Course *(Woods)*: Dr. Woods is the course director of an annual non-invasive brain stimulation practical course, taught at the NYC Neuromodulation Conference. This course provides over 100 clinicians and researchers per year with practical knowledge of transcranial direct current stimulation techniques. This technique is a novel tool for interventions aimed at slowing aging related cognitive decline. This topic serves as a central point in the educational structure of the practical course.

COLLABORATIONS WITH MCKNIGHT INSTITUTES, INSTITUTIONS, RESEARCH PROGRAMS, AND OTHERS:

A. Inter-Institute neuroimaging initiative has funded and is underway.

B. ARML/ CAM-CTRP clinical translational initiatives; this collaborative effort between the McKnight ARML and CAM-CTRP is focusing on bringing promising compounds that may benefit cognitive aging to clinical trials. Specifically we have initiated a GABA inhibitor developmental project as described earlier.

C. CAM-CTRP/ AMRIS neuroimaging initiatives; efforts are underway to develop a NIPYP (neuroimaging analysis pipeline) that will facilitate the processing and preliminary analysis of multimodal neuroimaging data obtained by the CAM-CTRP, and other AMRIS investigators. Also, the initiation of a neuroimaging user group reflects this collaboration (see above).

D. Integration of Memory Disorders Clinic data, including IRB approved coherent records review, and analysis of MR data via the HiPerGator Computing System – Glenn Finney, MD, Dept. of Neurology, Adam J. Woods, PhD, Ron Cohen, PhD

E. Study of Semantic Networks – Kenneth Heilman, MD, Steve Nadeau, MD, Robert Cook, MD, Amanda Garcia, MS

F. Obesity and Type 2 Diabetes, Bariatric Surgery effects on brain function – NIH RO1 Grant Submission July, 2013, Study initiated

G. Effect on Exercise on memory in Geriatric Depression; fMRI pilot study – Vonetta Dotson, PhD

COLLABORATIVE PROGRAMS WITH NON-MCKNIGHT INSTITUTES, INSTITUTIONS AND RESEARCH PROGRAMS:

These grant proposals involve collaboration with core and affiliated CAM-CTRP faculty, as well as investigators from other departments in the university and the VA Medical Center, as well as other university collaborations.

A. Heart Failure and the aging brain – John Williamson, PhD, Ron Cohen, PhD, Kenneth Heilman, MD – Extension of ongoing line of research that Dr. Cohen has been involved in over past 2 decades.

B. Resynchronization of Heart Failure and Cognition in aging (submitted) – John Williamson, PhD, Ron Cohen, PhD, Kenneth Heilman, MD, Michael Jansen, MD, James Hill, MD (cardiologists at University of Florida).

C. HIV and the Aging Brain – Robert Cook, MD, Ron Cohen, PhD – NIH RO1 Grant Submission Dec. 5, 2013.

   a. Ongoing collaborations among UF and Brown University, including Gundstadt and group from Kent State, Brickman and group from Columbia University.

D. Alcohol and HIV: Biobehavioral interactions and intervention – Ron Cohen, PhD, Collaborations with investigators from Brown University and Tufts.

E. Cognitive Effects of Cardiac Rehabilitation in Heart Failure – Ron Cohen, PhD, and collaborations with Gundstadt and group from Kent State.

F. Predicting Brain Changes in HIV/AIDS – to be submitted: Continued work with Brad Navia and group from Tufts, Suzanne DeLaMonte from Brown University and Paul Thompson from UCLA.

G. ENIGMA – Center for Worldwide Medicine, Imaging and Genomics – Ron Cohen PhD, with Paul Thompson from UCLA and Brad Navia from Tufts (Funded).

H. Mindfulness Training to improve adherence behaviors in Heart Failure outpatients – Continued collaboration with Beth Brock at Brown University and University of Massachusetts Medical Center.

I. Southern HIV Alcohol Research Consortium (SHARC) (Cohen) – Robert Cook, MD, and other collaborators at the UF CTSI.

J. Obesity and Type II Diabetes – Collaborations among Kfir Ben-David MD, UF Surgery, Kenneth Cusi, MD, Diabetes Center of Excellence, Christina McCrae PhD, UF Sleep Research Lab, Ron Cohen, PhD, CAM-CTRP.

K. VITAL2: Engagement plus training for broad cognitive transfer in elders – (Marsiske,Bowers).

BRIEFLY DESCRIBE PLANS FOR FUTURE RESEARCH AND OR CLINICAL INITIATIVES:

CAM RFA mechanism. In an effort to foster research on cognitive aging and memory, the CAM-CTRP is in the process of developing a RFA funding mechanism for junior investigators and also for pilot projects that would provide preliminary data for R01 submissions. Every six months, a request for applications will be posted by the CAM-CTRP. Each RFA will be targeted on a specific topic area. Since these topics will vary from cycle to cycle, the specific requirements of the RFA will also vary, though a general set of guidelines, application processes, review procedures, and annual budget allocation will be formulated and decided on over the next three months.

The proposed pilot studies will create enough pilot data for future RO1 projects over the next several years. Development of the novel compounds for clinical trial interventions will also be a major area of effort in near the future (see below).

Epigenetics initiative. The Epigenetics initiative is moving forward through the Proteomics and genomics of cognitive aging Pilot Study in collaboration with Dr. Leonid Moroz (Genetics Core Leader). This project will investigate genetic markers of GABA expression in conjunction with magnetic resonance spectroscopy markers of GABA concentrations, in an effort to identify

epigenetic markers of cognitive aging. These markers will prove important in our Clinical Outcome initiative as a marker of change from GABA-oriented pharmacological interventions.

Clinical Outcome initiative. The Clinical Outcome intitiative is currently working to intitate initial clinical trials testing using a GABA inhibitor compound demonstrating positive effects in cognitive aging animal models pioneered in the MBI AMRL program (Bizon, Foster). The efforts of the Epigenetic initiative dovetail with the Clinical Outcome initiative, in identification of biomarkers of change in GABA expression.

Dr. Cohen and other faculty of the CAM are the PIs for multiple pending grants. These include collaborations with UCLA, UF-College of Public Health & Health Professions, Gainesville VA, University of Pittsburgh, Brown University, University of Miami, University of Arizona, and UAB, as described in this report.

IF APPLICABLE, PLEASE PROVIDE ENDOWMENT INVESTMENT RESULTS FOR THE REPORT PERIOD:

See page 78

WHERE ANY FUNDS USED FOR A PROHIBITED PURPOSE DURING THE REPORT PERIOD?

No

DO YOU RECOMMEND ANY MODIFICATIONS TO THE PURPOSE OR MANDATES IN THE GIFT AGREEMENT?

No

DID ALL ACTIVITIES DURING THE REPORT PERIOD FURTHER THE PURPOSE?

Yes

NEGATIVE EVENTS (LOSS OF PERSONNEL, SPACE, BUDGET):

No

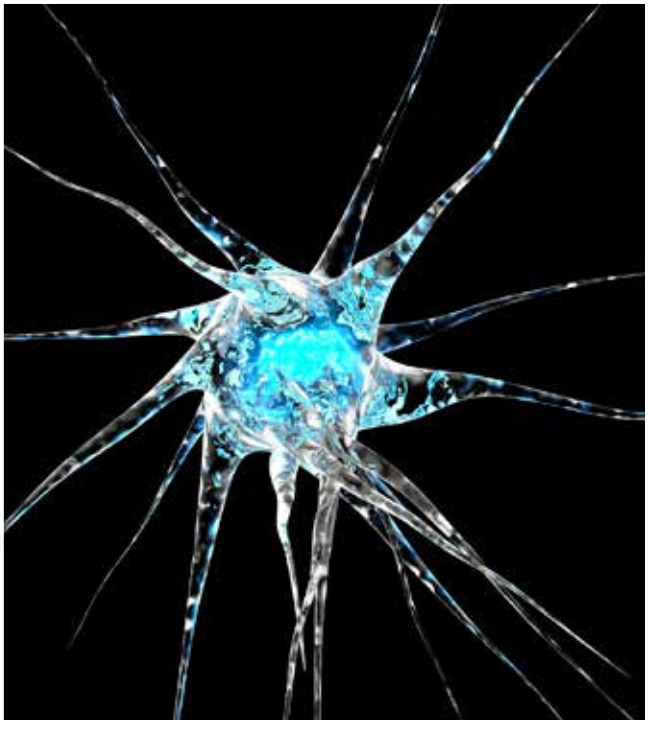
ADDITIONAL COMMENTS:

See letter on page 29

SIGNATURE, DATE AND TITLE OF PERSON SUBMITTING THE REPORT:

Ronald Cohen, PhD, ABPP, ABCN
Professor, Aging, Neurology, and Psychiatry
Director, CAM-CTRP

William G. Luttge Lectureship in Neuroscience



The MBI and Department of Neuroscience are extremely grateful for the generous gift from the McKnight Brain Research Foundation which established the Luttge Lectureship in memory of Dr. William G. "Bill" Luttge. This lectureship provides an excellent opportunity to bring leading neuroscientists to UF's campus to inspire the future generation of basic and clinical researchers. To this aim, the lectureship benevolently honors the late Dr. Luttge, the founding Director of the Evelyn F. and William L. McKnight Brain Institute and former Chairman of the Department of Neuroscience in UF's College of Medicine.

On March 10, 2014, for the second annual Luttge Lectureship, the MBI hosted Steven DeKosky, MD, whose talk titled "The Brain Fights Back: Neuroplasticity in Aging and Disease" focused on Alzheimer's Disease research and packed the MBI's DeWeese Auditorium. Dr. DeKosky is a medical researcher and academic known for his work in the field of Alzheimer's Disease. DeKosky has served as professor and chairman of the Department of Neurology and director of the Alzheimer's Disease Research Center at the University of Pittsburgh as well as dean of the University of Virginia's School of Medicine for five years.

Dr. DeKosky received his bachelor's degree from Bucknell University and completed graduate work in neuroscience and psychology at UF, graduating from the UF's College of Medicine in 1974. He completed a residency in internal medicine at Johns Hopkins Hospital and a three-year residency in neurology at UF, concluding in 1978, then completed a postdoctoral fellowship in neurochemistry at the Clinical Neuroscience Research Center in the University of Virginia's Department of Neurology. His first academic appointment was in the Department of Neurology in 1979.

The Luttge Lectureship Committee at the University of Florida has the following members:

- **Tetsuo Ashizawa, MD, Executive Director of the Evelyn F. and William L. McKnight Brain Institute at UF and Melvin Greer Professor and Chairman of the Department of Neurology**
- **Lucia Notterpek, PhD, William T. and Janice M. Neely Professor and Chair of the Department of Neuroscience**
- **Tom C. Foster, PhD, Professor and Evelyn F. McKnight Chair for Research on Age-related Memory Loss in the Department of Neuroscience**
- **David R. Borchelt, PhD, Professor of Neuroscience and Director of the Santa Fe Health Alzheimer's Disease Research Center**
- **Sara Jo Nixon, PhD, Professor, Addiction Research Division Chief, and Director of the Neurocognitive Laboratory in the Department of Psychiatry**

The Committee has begun organizing the third Luttge Lectureship scheduled for May 4, 2015. Special guest and Gator alumni, Fred H. "Rusty" Gage, PhD has agreed to speak. Dr. Gage is a professor and the Vi and John Adler Chair for Research on Age-related Neurodegenerative Disease at the Salk Institute for Biological Studies in La Jolla, California.

Dr. Gage received his BS degree from the University of Florida and his PhD from Johns Hopkins University. Among his many honors and awards, Dr. Gage was elected to the National Academy of Sciences in 2003, and named to the National Academy of Inventors in 2013. He serves as a member of the Science Advisory Board of the Genetics Policy Institute. Dr. Gage has published in excess of 600 articles in high impact journals such as Nature, Cell, Science, Nature Medicine, and Neuron.

A financial summary of the Luttge Lectureship endowment and spendable funds as of December 31, 2014 are included in the Financials section of this report.

Tetsuo Ashizawa, MD
Executive Director, McKnight Brain Institute
Melvin Greer Professor and Chair, Department of Neurology

Lucia Notterpek, PhD
William T. and Janice M. Neely Professor and Chair, Department of Neuroscience

Program Financials

McKnight Brain Research Grant
Age-related Memory Loss Program

Financial Summary
January 1 to December 31, 2014

Foundation Spendable Account		Amount	
Endowment income transferred in:			
Mar 31, 2014	$ 271,087		
Jun 30,2014	273,255		
Sept 30, 2014	278,810		
Dec 31, 2014	279,070		
Total endowment income transferred in		1,102,222	
Additional funds from MBRF:			
Reimbursement for 7th Annual Inter-inst. Meeting	52,620		
Reimbursement for Epigenomics Core expenditures	38,240		
Total additional funds from MBRF		90,861	
Total funds available		1,193,083	
Transferred out:			
To Institute on Aging / CAM-CTRP	652,756		
Transferred to UF Peoplesoft spendable accounts	1,017,055		(a)
Total transferred out		1,669,811	
Net change in foundation spendable account		(476,728)	
Beginning balance, January 1, 2014		776,890	
Ending balance, December 31, 2014		**$ 300,162**	

UF PeopleSoft Accounts		Amount	
Received from foundation spendable account		$ 1,017,055	(a)
Residual funds from closed seed grants		34	
Total funds available		1,017,089	
Transferred out:			
Dr. Bizon startup final year	144,600		
Drs. Bizon and Foster NIA supplement	51,879		
Dr. Burke startup and salary support (year 2 partial)	97,320		
Total transferred out		293,799	
Expenditures:			
ARML faculty salaries	403,798		
McKnight Inter-institutional Meeting	52,620		
Ion Chef equipment acquisition	48,625		
Epigenomics Core	62,457		
Total expenditures		567,500	
Total transfers out and expenditures		861,299	
Net change in UF Peoplesoft accounts		155,790	
Beginning balance, January 1, 2014		490,851	
Ending balance, December 31, 2014		**$ 646,641**	
Due to the Institute on Aging / CAM-CTRP		$ 415,567	(b)
Total funds available to ARML, December 31, 2014		**$ 531,236**	(c)

(a) Transfers from foundation spendable account to Peoplesoft account in 2014.

(b) Accumulation of the Institute on Aging's portion of the endowment interest income (50%), per the 2009 Gift Agreement Amendment. Scheduled to be transferred in Jan 2015.

(c) All spendable accounts less funds due to CAM-CTRP.

McKnight Brain Research Grant
Age-related Memory Loss Program

Seed Grant Balances
January 1 to December 31, 2014

Dr. Frazier - Seed Grant (UF PeopleSoft Accounts)		Amount
Received from ARML Program in 2014		$ -
Expenditures:		
Salary expenses	9,389	
Equipment	26,616	
Operating expenses (lab supplies, services, and other)	30,637	
Total expenditures		66,642
Net change in UF Peoplesoft accounts		(66,642)
Beginning balance, January 1, 2014		79,893
Ending balance, December 31, 2014		**$ 13,251**

Dr. Ormerod - Seed Grant (UF PeopleSoft Accounts)		Amount
Received from ARML Program in 2014		$ -
Expenditures:		
Salary expenses	36,157	
Operating expenses (lab supplies, services, and other)	19,382	
Total expenditures		55,540
Net change in UF Peoplesoft accounts		(55,540)
Beginning balance, January 1, 2014		67,003
Ending balance, December 31, 2014		**$ 11,463**

McKnight Endowed Chair
Tom Foster, PhD

Financial Summary
January 1 to December 31, 2014

Foundation Spendable Account		Amount	
Endowment income transferred in:			
March 31, 2014	$ 41,334		
June 30,2014	41,665		
Sept 30, 2014	42,511		
Dec 31, 2014	42,551		
Total endowment income transferred in		168,061	
Transferred to UF Peoplesoft spendable accounts		197,411	(a)
Net change in foundation spendable account		(29,350)	
Beginning balance, January 1, 2014		71,901	
Ending balance, December 31, 2014		**$ 42,551**	

UF PeopleSoft Accounts		Amount	
Received from foundation spendable account		$ 197,411	(a)
Expenditures:			
Faculty and research staff salaries	32,297		
Research equipment, supplies, and services	9,895		
Travel and other	5,356		
Total expenditures		47,548	
Net change in UF Peoplesoft accounts		149,863	
Beginning balance, January 1, 2014		216,999	
Ending balance, Dec 31, 2014		**$ 366,862**	

(a) Transfers to UF Peoplesoft accounts in 2014

Cognitive Aging & Memory
Clinical Translational Research Program

Financial Summary
January 1 to December 31, 2014

Foundation Spendable Account		Amount	
Transferred in from McKnight master account		$ 652,756	
Transferred out to UF Peoplesoft spendable accounts		2,913,466	(a)
Net change in foundation spendable account		(2,260,710)	
Beginning balance, January 1, 2014		2,260,710	
Ending balance, December 31, 2014		**$ 0**	

UF PeopleSoft Accounts		Amount	
Received from foundation spendable account		$ 2,913,466	(a)
Expenditures:			
Faculty and research staff salaries	679,125		
Research equipment, supplies, and services	172,882		
Travel and other	86,293		
Total expenditures		938,300	
Net change in UF Peoplesoft accounts		1,975,166	
Beginning balance, January 1, 2014		203,966	
Ending balance, Dec 31, 2014		**$ 2,179,132**	
Due from McKnight master account		415,567	
Total funds available to CAM-CTRP, December 31, 2014		**2,594,699**	

(a) Transfers to UF Peoplesoft accounts in 2014

William G. Luttge
Lectureship in Neuroscience

Financial Summary
Balances through December 31, 2014

Endowment account balance, Dec. 31, 2014	**$**	**273,402**

Spendable account activity[(a)]	**Amount**
Endowment income transfers, 4 quarters ending Dec. 31, 2014	9,256
Less UF Foundation gift overhead fees	1
Total funds available	9,255
Expenses for March 2014 lectureship	4,767
Net change in spendable funds	4,487
Beginning balance, January 1, 2014	51,765
Ending balance, December 31, 2014	**$ 56,252**

[(a)]Spendable account activity includes all Luttge Lectureship spendable funds in the UF Foundation and the Department of Neuroscience.

McKnight Brain Research Grant
Fund Report

with related accounts
Balances through December 31, 2014

Evelyn F. McKnight Brain Research Grant	Market Value Balance of Endowment	Fiscal Year Ending	Annual Endowment Transfers from Principal	Total Expenses / Net Transfers	Additional Investment Revenue[3]	Ending Spendable Fund Balance
	F008057		F008058			
F008057 / 58	$ 12,967,682	2000	$ -	$ -		$ -
	$ 12,967,682	2001	$ 648,384	$ -	$ 7,264	$ 655,648
	$ 13,157,047	2002	$ 657,852	$ (37,840)	$ 315,280	$ 1,590,940
	$ 20,249,996	2003	$ 651,801	$ (1,139,621)	$ 89,549	$ 1,192,669
	$ 25,363,355	2004	$ 729,335	$ (944,138)	$ 266,063	$ 1,243,930
	$ 26,681,575	2005	$ 843,131	$ (502,502)	$ 174,351	$ 1,758,910
	$ 29,091,810	2006	$ 881,347	$ (250,000)	$ 52,383	$ 2,442,639
	$ 33,148,130	2007	$ 1,056,031	$ (500,000)	$ 73,172	$ 3,071,843
	$ 32,666,165	2008	$ 1,172,824	$ (350,003)	$ 66,972	$ 3,961,636
	$ 25,549,465	2009	$ 1,086,475	$ (1,300,000)	$ (479,678)	$ 3,268,433
	$ 26,893,099	2010	$ 941,689	$ (1,864,217)	$ 67	$ 2,345,972
	$ 30,185,328	2011	$ 971,846	$ (2,413,940)	$ -	$ 903,877
	$ 28,834,098	2012	$ 1,026,301	$ (1,017,551)	$ -	$ 912,627
	$ 29,845,891	2013	$ 1,028,384	$ (1,415,244)	$ -	$ 525,767
	$ 32,801,128	2014	$ 1,063,533	$ (920,824)	$ -	$ 668,477
	$ 32,831,771	2015	$ 557,880	$ (1,017,055)	$ 90,861	$ 300,162 [1,2]
Life-to-date Totals			**$ 13,316,813**	**$ (13,672,934)**	**$ 656,284**	

CAM-CTRP		Fiscal Year Ending	Transferred from F008058 (1/2 of MBRF Grant Income)	Total Expenses / Net Transfers	Additional Investment Revenue[3]	Ending Spendable Fund Balance
			F016327			
F016327		2010	$ 1,634,217	$ (200,000)	$ -	$ 1,434,217
		2011	$ 941,689	$ -	$ -	$ 2,375,906
		2012	$ -	$ -	$ -	$ 2,375,906
		2013	$ 784,804	$ (400,000)	$ -	$ 2,760,710
		2014	$ 652,756	$ (1,000,000)	$ -	$ 2,413,466
		2015	$ -	$ (2,413,466)	$ -	$ -
Life-to-date Totals			**$ 4,013,466**	**$ (4,013,466)**	**$ -**	

AMENDED GIFT AGREEMENT - reconciliation		Fiscal Year Ending	Endowment Transfers from Principal	1/2 allocated to CAM-CTRP	Actual transfers to CAM-CTRP	Still due to CAM-CTRP
Initial Transfer	9/17/2009	2010		$ (1,634,217)	$ 1,634,217	$ -
		2010	$ 941,689	$ (470,845)	$ -	$ 470,845
		2011	$ 971,846	$ (485,923)	$ 941,689	$ 15,078
		2012	$ 1,026,301	$ (513,151)	$ -	$ 528,229
		2013	$ 1,028,384	$ (514,192)	$ 784,804	$ 257,617
		2014	$ 1,063,533	$ (531,767)	$ 652,756	$ 136,628
		2015	$ 557,880	$ (278,940)	$ -	$ 415,567
	Life-to-date Totals		**$ 5,589,633**	**$ (4,429,033)**	**$ 4,013,466**	

[1]Endowment market value balance as of Sept. 30, 2014. All other balances as of Dec. 31, 2014.

[2]The McKnight Brain Research Grant had a spendable account balance of $300,162 as of Dec. 31, 2014. As of July 1, 2014, the UF Foundation changed its practice for transfering spendable funds to UF Peoplesoft accounts. Now all interest earned from the endowment transfers to the MBI Peoplesoft account and MBI then transfers half to the CAM-CTRP.

[3]Distributions from investment income were limited and variable from 2003-2009, resulting in additional revenues (/losses) from the reinvested endowment income.

Evelyn F. McKnight Chair Account

for Brain Research in Memory Loss
Balances through December 31, 2014

Evelyn F. McKnight Chair for Brain Research in Memory Loss	Market Value Balance of Endowment	Fiscal Year Ending	Annual Endowment Transfers from Principal	Total Expenses / Net Transfers	Additional Investment Revenue[3]	Ending Spendable Fund Balance
	F007889		F007890			
F007889 / 90	$ 1,988,345	2000	$ 3,438	$ (9,625)	$ -	$ (6,188)
	$ 1,988,345	2001	$ 99,417	$ -	$ (62)	$ 93,167
	$ 2,017,380	2002	$ 100,869	$ (7,810)	$ (1,258)	$ 184,968
	$ 3,447,965	2003	$ 125,768	$ (52,502)	$ 237,079	$ 495,313
	$ 3,866,391	2004	$ 124,127	$ (7,810)	$ 14,191	$ 625,820
	$ 4,068,286	2005	$ 127,813	$ -	$ 4,602	$ 758,235
	$ 4,435,787	2006	$ 134,384	$ (150,000)	$ 19,578	$ 762,197
	$ 5,054,277	2007	$ 161,019	$ (150,000)	$ 19,448	$ 792,663
	$ 4,980,774	2008	$ 178,827	$ (200,000)	$ 14,387	$ 785,877
	$ 3,895,655	2009	$ 165,660	$ (450,000)	$ (38,922)	$ 462,615
	$ 4,100,525	2010	$ 143,584	$ (499,000)	$ 739	$ 107,938
	$ 4,602,508	2011	$ 148,182	$ -	$ -	$ 256,121
	$ 4,396,479	2012	$ 156,485	$ (200,000)	$ -	$ 212,606
	$ 4,550,752	2013	$ 156,803	$ (126,670)	$ -	$ 242,739
	$ 5,001,352	2014	$ 162,162	$ (250,000)	$ -	$ 154,901
	$ 5,006,025	2015	$ 85,063	$ (197,412)	$ -	$ 42,551 [1]
Life-to-date Totals			**$ 2,073,600**	**$ (2,300,830)**	**$ 269,781**	

[1]Endowment market value balance as of Sept. 30, 2014. All other balances as of Dec. 31, 2014.

UF Foundation Endowment Reports

Evelyn F. McKnight Brain Research Grant

BOOK VALUE as of 09/30/14	**$25,967,781**
MARKET VALUE as of 09/30/14	**$32,831,771**
PROJECTED SPENDABLE INCOME for 2014/15	**$1,116,280**

ENDOWMENT MANAGEMENT

Endowment assets are invested through the University of Florida Investment Corporation (UFICO), created in 2004 to manage UF's investment portfolios. UFICO is headed by a Chief Investments Officer who reports to a volunteer Board of Directors and to the President of the University of Florida.

(Fund # 008057)

Evelyn F. McKnight Chair for Brain Research in Memory Loss

BOOK VALUE as of 09/30/14	**$3,995,677**
MARKET VALUE as of 09/30/14	**$5,006,025**
PROJECTED SPENDABLE INCOME for 2014/15	**$170,205**

ENDOWMENT MANAGEMENT

Endowment assets are invested through the University of Florida Investment Corporation (UFICO), created in 2004 to manage UF's investment portfolios. UFICO is headed by a Chief Investments Officer who reports to a volunteer Board of Directors and to the President of the University of Florida.

(Fund # 007889)

William G. Luttge Lectureship in Neuroscience

BOOK VALUE as of 09/30/14	**$250,170**
MARKET VALUE as of 09/30/14	**$275,701**
PROJECTED SPENDABLE INCOME for 2014/15	**$9,374**

ENDOWMENT MANAGEMENT

Endowment assets are invested through the University of Florida Investment Corporation (UFICO), created in 2004 to manage UF's investment portfolios. UFICO is headed by a Chief Investments Officer who reports to a volunteer Board of Directors and to the President of the University of Florida.

(Fund # 018093)

McKnight Brain Research Foundation

Evelyn F. McKnight Brain Research Grant (008057)

Spendable Fund Transfers since endowment inception

FY 2014/2015	**$278,810**	**(09/30/14 YTD)**
FY 2013/2014	**$1,063,533**	
FY 2012/2013	**$1,028,384**	
FY 2011/2012	**$1,026,301**	
FY 2010/2011	**$971,846**	
FY 2009/2010	**$941,689**	
FY 2008/2009	**$1,086,475**	
FY 2007/2008	**$1,172,824**	
FY 2006/2007	**$1,056,031**	
FY 2005/2006	**$881,347**	
FY 2004/2005	**$843,131**	
FY 2003/2004	**$729,335**	
FY 2002/2003	**$651,801**	
FY 2001/2002	**$657,852**	
FY 2000/2001	**$648,384**	
TOTAL	**$13,037,743**	

Evelyn F. McKnight Chair for Brain Research in Memory Loss (007889)

Spendable Fund Transfers since endowment inception

FY 2014/2015	**$42,511**	**(09/30/14 YTD)**
FY 2013/2014	**$162,162**	
FY 2012/2013	**$156,803**	
FY 2011/2012	**$156,485**	
FY 2010/2011	**$148,182**	
FY 2009/2010	**$143,584**	
FY 2008/2009	**$165,660**	
FY 2007/2008	**$178,827**	
FY 2006/2007	**$161,019**	
FY 2005/2006	**$134,384**	
FY 2004/2005	**$127,813**	
FY 2003/2004	**$124,127**	
FY 2002/2003	**$125,768**	
FY 2001/2002	**$100,869**	
FY 2000/2001	**$99,417**	
FY 1999/2000	**$3,438**	
TOTAL	**$2,031,049**	

McKnight Brain Research Foundation

William G. Luttge Lectureship in Neuroscience (018093)

Spendable Fund Transfers since endowment inception

FY 2014/2015	**$2,341 (09/30/14 YTD)**
FY 2013/2014	**$9,074**
FY 2012/2013	**$6,754**
TOTAL	**$18,169**

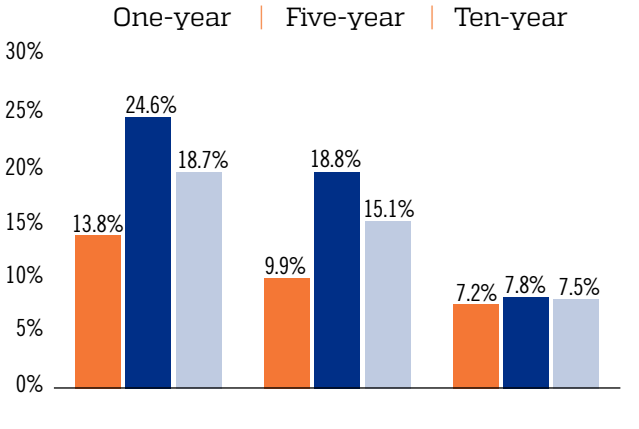
The University of Florida

INVESTMENT PERFORMANCE REPORT

Endowments are an irreplaceable source of quality, stability, productivity and creativity for the University of Florida. The thoughtful individuals and organizations who create endowments provide security and confidence for our students and faculty, now and in the future. As such, the University of Florida Foundation invests your gift assets to protect the ability of the endowment to provide, in perpetuity, an income stream sufficient to support the university activity you designated, and to ensure the proceeds thereof are used in accordance with your designation.

The endowment investment pool is managed by the University of Florida Investment Corporation, a direct support organization. The long-term goal for the endowment investment pool is to earn a total return of 8.2%, sufficient to provide a 4.0% income stream to support the university activity you designated, fund the Office of Development and Alumni Affairs through a 1.2% administrative fee and provide 3% to protect against inflation. The endowment investment pool's growth and investment returns are summarized in the charts below.

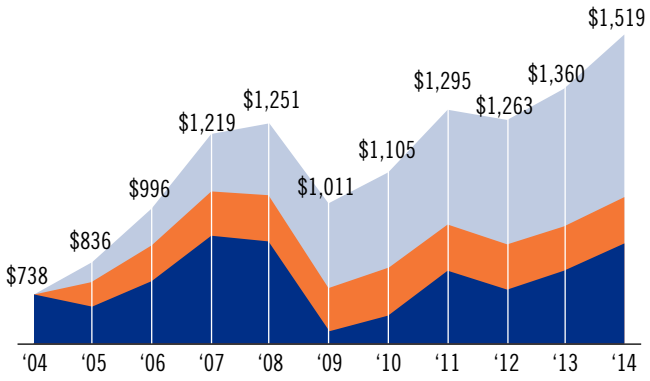
Endowment Investment Pool Annualized Return*



Returns are net of investment manager fees, before endowment spending

Endowment Growth

(in $ millions)
Fiscal years ending June 30th



*Net of fees and distributions

Questions? 352-846-3444 (Donor Relations) • DonorRelations@uff.ufl.edu

UF | UNIVERSITY of FLORIDA INVESTMENT CORPORATION

Quarterly Performance Report

UF Foundation - Endowment

September 30, 2014

UF Foundation - Endowment

September 30, 2014

Endowment Pool

Since the founding of the University of Florida (UF) in 1853, generous alumni, corporations, foundations, parents and friends have contributed financial resources to assist UF in achieving its long-term mission of providing a superb education for undergraduates while maintaining excellent graduate programs and professional schools. As a result, UF's total endowment market value is among the largest public university endowments in the United States.

The UF endowment assets reside with the University of Florida Foundation (UFF). UFF is a private, not-for-profit, 501(c)(3) direct support organization of UF that raises and manages all gift money for the benefit of UF. UFF's management of the Endowment Pool is designed to accomplish two goals:

1. Provide a total return from assets invested that will preserve or increase the purchasing power of the endowment capital, and;
2. Generate the maximum current spendable income stream to support activities of funds held for colleges and units of UF.

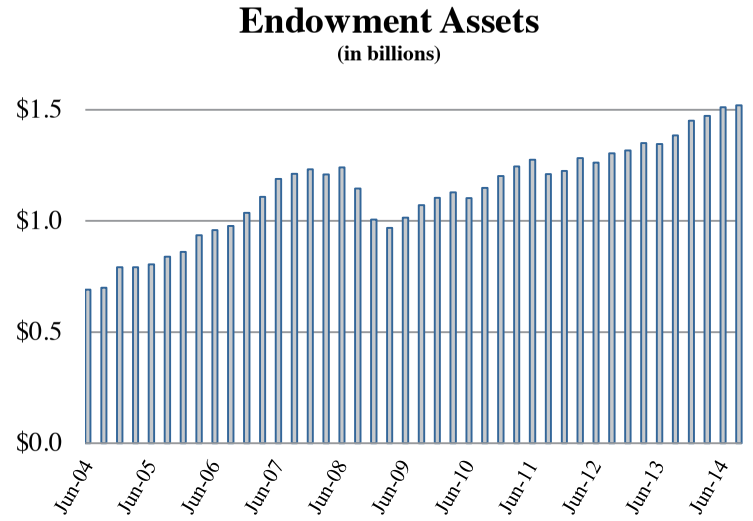
Since the inception of the University of Florida Investment Corporation (UFICO) in June 2004, the investment of the Endowment Pool has been managed by UFICO and overseen by the Finance Committee of the UFF Board of Directors, which establishes the goals and performance benchmarks for the pool.

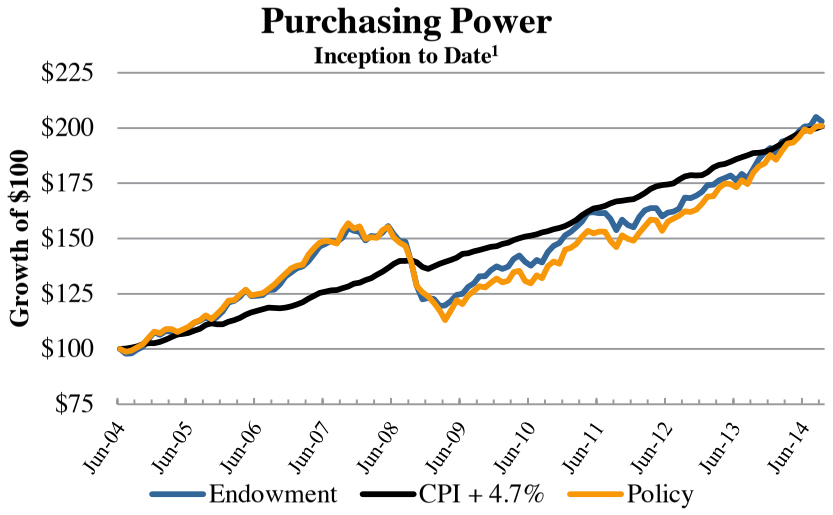
Investment Objective

Through UFICO's management of the Endowment Pool, UFF seeks to achieve an annualized real rate of return of at least 4.7% net of fees to preserve and enhance the purchasing power of the endowment. To measure performance results, returns are compared against the following benchmarks:

- CPI + 4.7% Benchmark – The consumer price index plus the average gross spending rate for the endowment. This is a measure of the purchasing power of the endowment over time considering the effects of inflation.
- UFICO Policy Benchmark – This is an asset-weighted composite index which represents a passive implementation of the Pool's strategic asset allocation.

Returns are measured over the long-term as the Endowment Pool is able to tolerate variability in the short and intermediate-term given its long investment horizon.





[1] UFICO inception of June 2004.

UF Foundation - Endowment

Financial Recap

September 30, 2014

Financial Recap

Fiscal Year Period	Beginning NAV	New Endowments	Endowment Spending	UFF Overhead Fees	UFICO Fees	Investment Income	Ending NAV	Investment Return
Q1- 15	$ 1,511,974	$ 7,334	$ (12,458)	$ (3,746)	$ (564)	$ 18,035	$ 1,520,575	1.2%
FY- 14	$ 1,345,840	$ 42,431	$ (47,131)	$ (14,110)	$ (2,157)	$ 187,101	$ 1,511,974	13.8%
FY- 13	$ 1,262,971	$ 28,263	$ (44,609)	$ (13,694)	$ (1,756)	$ 114,665	$ 1,345,840	9.1%
FY- 12	$ 1,276,322	$ 42,312	$ (43,162)	$ (14,100)	$ (1,959)	$ 3,558	$ 1,262,971	0.1%
FY-11	$ 1,103,464	$ 34,830	$ (37,588)	$ (12,719)	$ (1,601)	$ 189,936	$ 1,276,322	17.3%
FY-10	$ 1,014,335	$ 34,521	$ (36,547)	$ (11,414)	$ (1,831)	$ 104,401	$ 1,103,464	10.2%
FY- 09	$ 1,241,570	$ 48,478	$ (43,907)	$ (11,011)	$ (1,983)	$ (218,812)	$ 1,014,335	-17.7%
FY-08	$ 1,189,657	$ 68,324	$ (41,713)	$ (10,256)	$ (1,866)	$ 37,424	$ 1,241,570	3.0%
FY-07	$ 958,861	$ 88,977	$ (33,659)	$ (8,448)	$ (1,435)	$ 185,361	$ 1,189,657	18.8%
FY-06	$ 804,240	$ 79,233	$ (27,090)	$ (6,702)	$ (1,107)	$ 110,287	$ 958,861	13.3%
FY-05	$ 691,172	$ 72,316	$ (24,062)	$ (5,904)	$ (933)	$ 71,651	$ 804,240	9.5%

Note: All values in $ 000's

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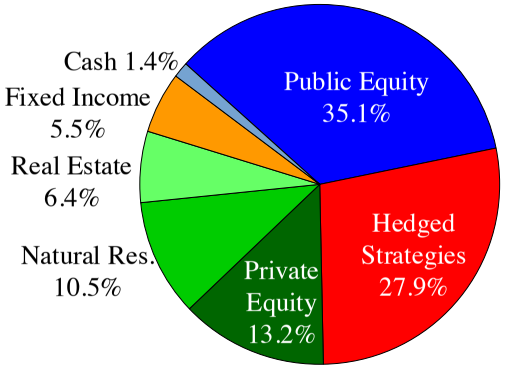
UF Foundation - Endowment

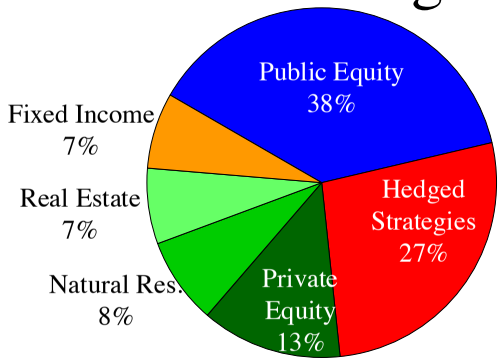
Asset Allocation

September 30, 2014

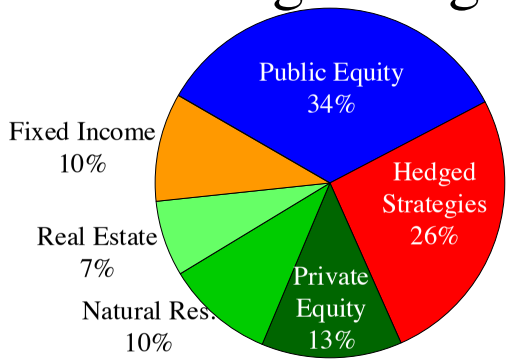
Actual



Active Target



Strategic Target



88

Asset Allocation	Actual 9/30/14	Active Target	Strategic Target
Public Equity	35.1%	38.0%	34.0%
Hedged Strategies	27.9%	27.0%	26.0%
Private Equity	13.2%	13.0%	13.0%
Natural Resources	10.5%	8.0%	10.0%
Real Estate	6.4%	7.0%	7.0%
Fixed Income	5.5%	7.0%	10.0%
Cash	1.4%	0.0%	0.0%
Total	100.0%	100.0%	100.0%

UF Foundation - Endowment

Quarterly Performance Report

Performance Commentary

September 30, 2014

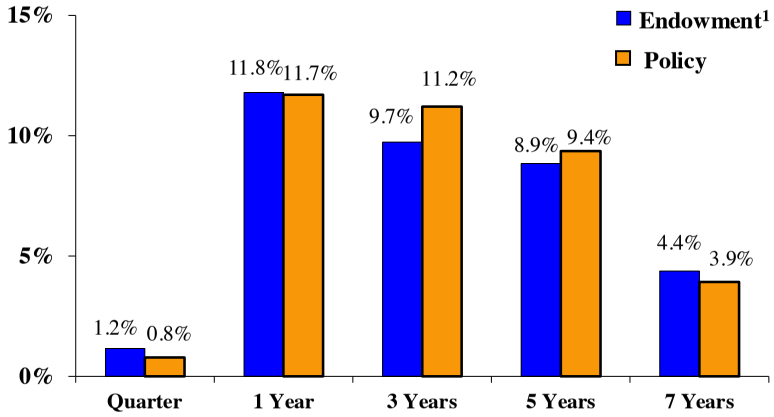
The quarter ended September 30th was marked by growing global concerns. An increase in geopolitical disruptions abroad and signals of slower global economic growth contributed to the higher volatility experienced during the quarter. Although U.S. stocks hit new highs in September, the S&P 500 Index was up only slightly at 1.1% for the quarter. Developed international markets did not fare as well. The MSCI EAFE Index was down -5.9% for the quarter with a strengthening dollar and growth concerns pressuring valuations. Emerging markets also experienced headwinds in the quarter as credit conditions have tightened. The MSCI Emerging Markets Index was down -3.5% for the quarter. The fixed income markets saw an uptick in interest rate volatility during the quarter but showed little movement with the Barclays Aggregate Bond Index up only 0.2%.

The UFF Endowment Pool gained 1.2% for the quarter, outperforming its Policy Benchmark return of 0.8%. The Endowment benefited from its overweight position to risk assets versus fixed income during the quarter and from the strong relative performance of the Public Equity, Hedged Strategies, Private Equity and Real Estate asset classes. The Public Equity portfolio returned -1.8% for the quarter, ahead of its respective benchmark return of -2.3%. The outperformance in the Public Equity portfolio was primarily driven by the active management in the emerging markets portfolio. The Hedged Strategies portfolio has continued to outperform returning 0.2%, ahead of its benchmark return of -0.1% for the quarter. Global macro and relative value strategies drove the outperformance in the quarter. The Fixed Income portfolio struggled some returning -1.3% for the quarter versus -0.9% for its respective benchmark due primarily to the portfolio's shorter duration stance.

The Private Equity and Real Estate portfolios, with returns of 5.1% and 3.8%, respectively, for the quarter, both outperformed their respective benchmark returns of 4.1% and 3.0%. Returns in the Private Equity portfolio were driven by the venture growth equity space. The Natural Resources portfolio had a strong absolute return of 8.8% during the quarter driven by infrastructure with energy also being a major contributor. While accretive to the overall Endowment return, the Natural Resources portfolio did however trail its respective benchmark which returned 9.2% for the quarter.

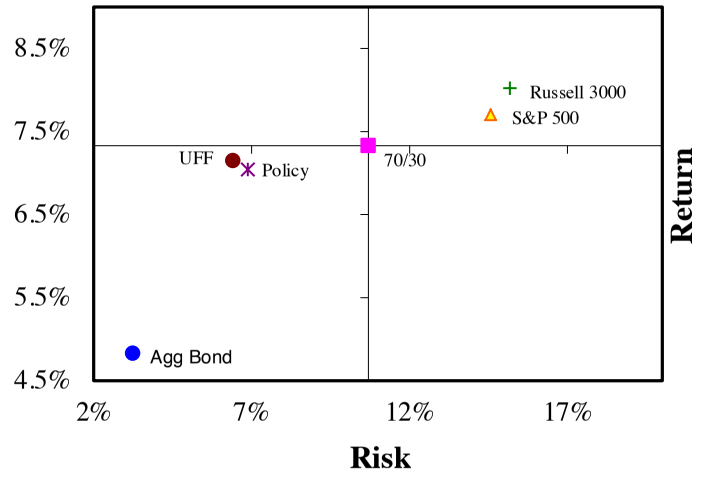
For the 12 month period ended September 30th, the UFF Endowment Pool returned 11.8%, ahead of the portfolio's Policy Benchmark return of 11.7% for the same period. During the trailing three-, five-, and seven-year periods, the UFF Endowment Pool was up 9.7%, 8.9%, and 4.4%, respectively, versus the Policy Benchmark returns of 11.2%, 9.4%, and 3.9% over the same periods.

Endowment Pool Returns



Risk / Return

Inception to Date[2]



[1] Actual returns are net of all investment management fees, but gross of UFF annual management fees.
[2] UFICO inception of June 2004.

UF Foundation - Endowment

Quarterly Performance Report

September 30, 2014

	Inception Date[1]	(000's) NAV	Allocation Actual	Allocation Target[2]	Fiscal Year[3] Q1	Calendar YTD	1 Year	Annualized 3 Year	5 Year	7 Year	10 Year	ITD
UFF Endowment	**Jul-04**	**$1,520,575**	**100.0%**	**100.0%**	**1.16%**	**6.32%**	**11.80%**	**9.73%**	**8.85%**	**4.38%**	**7.37%**	**7.15%**
UFF Endowment Policy Benchmark					*0.79%*	*7.01%*	*11.75%*	*11.21%*	*9.36%*	*3.92%*	*7.15%*	*7.04%*
UFF Endowment ex Privates	**Jul-04**	**$1,061,237**			**-0.96%**	**3.58%**	**9.91%**	**9.74%**	**7.50%**	**3.21%**	**6.39%**	**6.18%**
UFF Endowment ex Privates Benchmark					*-1.27%*	*3.43%*	*8.43%*	*10.47%*	*7.32%*	*2.74%*	*5.73%*	*5.64%*
Public Equity	Jul-04	**$534,846**	**35.1%**	**38.0%**	**-1.79%**	**2.24%**	**10.94%**	**14.92%**	**10.80%**	**3.63%**	**8.02%**	**7.49%**
MSCI ACWI Free					*-2.30%*	*3.73%*	*11.32%*	*16.61%*	*10.07%*	*2.40%*	*7.28%*	*7.03%*
Hedged Strategies	Jul-04	**$423,782**	**27.9%**	**27.0%**	**0.23%**	**6.56%**	**12.15%**	**5.93%**	**4.79%**	**2.19%**	**5.49%**	**5.42%**
HFRI FoF Strategic Index +1%					*-0.06%*	*2.81%*	*7.12%*	*6.10%*	*4.52%*	*1.71%*	*4.50%*	*4.44%*
Fixed Income	Jul-04	**$82,874**	**5.5%**	**7.0%**	**-1.32%**	**1.91%**	**1.49%**	**1.78%**	**4.38%**	**4.28%**	**4.52%**	**4.81%**
Fixed Income Benchmark					*-0.86%*	*3.60%*	*2.12%*	*1.24%*	*3.92%*	*4.66%*	*4.54%*	*4.77%*
Private Equity	Jul-04	**$201,325**	**13.2%**	**13.0%**	**5.13%**	**13.74%**	**15.96%**	**11.00%**	**14.34%**	**9.11%**	**12.45%**	**12.20%**
Cambridge Private Equity Index					*4.08%*	*15.73%*	*22.13%*	*12.99%*	*16.45%*	*8.12%*	*14.00%*	*13.92%*
Natural Resources	Jul-04	**$160,379**	**10.5%**	**8.0%**	**8.75%**	**13.12%**	**17.92%**	**12.31%**	**13.52%**	**11.01%**	**9.76%**	**9.62%**
Cambridge Natural Resources Index					*9.15%*	*15.89%*	*18.11%*	*13.17%*	*14.42%*	*11.88%*	*11.93%*	*10.41%*
Real Estate	Jul-04	**$97,634**	**6.4%**	**7.0%**	**3.77%**	**13.20%**	**17.07%**	**8.82%**	**6.46%**	**1.06%**	**4.78%**	**4.98%**
Real Estate Benchmark					*3.01%*	*11.27%*	*14.47%*	*10.88%*	*6.38%*	*-2.94%*	*2.17%*	*2.25%*
Cash	Jul-04	**$19,735**	**1.4%**	**0.0%**	**0.06%**	**0.11%**	**0.11%**	**0.22%**	**0.27%**	**0.86%**	**1.79%**	**1.82%**
Citi 3 Month Treasury Bill					*0.01%*	*0.03%*	*0.04%*	*0.05%*	*0.08%*	*0.47%*	*1.51%*	*1.50%*

Benchmark Composites

UFF Endowment: 34% MSCI ACWI, 26% HFRI FoF Strategic + 1%, 13% Cambridge Private Equity, 10% Cambridge Natural Resources, 5.95% Cambridge Real Estate, 1.05% Wilshire US RESI, 5% Barclays Government Index, 5% Barclays US Inflation-Linked Bond Index

UFF Endowment ex Private Investments: 49% MSCI ACWI, 36% HFRI FoF Diversified +1%, 7.5% Barclays Government Index, 7.5% Barclays US Inflation-Linked Bond Index

Fixed Income Benchmark: 7/1/04-6/30/11 - 100% Barclays Universal; As of 7/1/11 - 50% Barclays Gov't Index / 50% Barclays US Inflation Protected

Real Estate Benchmark: 7/1/04-12/31/13 - 100% Cambridge Real Estate Index; As of 1/1/14 - 85% Cambridge Real Estate Index / 15% Wilshire US Real Estate Securities Index

Note: Investor Pool returns are net of all UFICO and investment management fees. Asset class returns are gross of UFICO fees and net of investment management fees.

[1] Note: As of UFICO's inception date (7/1/2004)

[2] Active Target

[3] Fiscal year-end is June 30.

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Faculty Biographical Sketches

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Anton, Stephen Douglas	Associate Professor & Clinical Research Division Chief
eRA COMMONS USER NAME (credential, e.g., agency login) antonsd	

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)*	MM/YY	FIELD OF STUDY
Florida State University, Tallahassee, FL	BA	1997	Psychology
University of Florida, Gainesville FL	MS	1999	Clinical & Health Psychology
University of Florida, Gainesville FL	Ph.D.	2003	Clinical & Health Psychology
Louisiana State University, Baton Rouge, LA Pennington Biomedical Research Center	Postdoctoral Fellow	2006	Behavioral Medicine

A. Personal Statement

Dr. Anton completed his graduate degree in Clinical and Health Psychology at the University of Florida, where he received training in health promotion and the delivery of lifestyle interventions designed to modify eating and exercise behaviors. Following his graduate training, he completed a post-doctoral fellowship at the Pennington Biomedical Research Center, where he gained direct experience in the treatment of obesity and age-related disease conditions. Dr. Anton currently serves as an Associate Professor, Chief of the Clinical Research Division in the Department of Aging and Geriatric Research, and has a joint appointment in the Department of Clinical and Health Psychology within the College of Public Health and Health Professions. He is also leader of the Clinical Research Core for both the National Institute on Aging (NIA) funded Claude D. Pepper Older Americans Independence Center (OAIC) and the McKnight Brain Institute's Cognitive Aging and Memory (CAM) Program. In this capacity, Dr. Anton assists both OAIC and CAM faculty in the development and conduct of clinical trials conducted within the University of Florida's Institute on Aging. Specifically, the Clinical Research Core provides assistance to OAIC and CAM faculty members in the development of study budgets and protocols, including study specific recruitment and retention plans, data capture and security procedures, as well as regulatory oversight prior to study IRB approval. For approved study protocols, the Clinical Research Core provides assistance with all aspects of study operations management, including participant recruitment and retention, provision of safety and regulatory services, biospecimen collection, and data collection and management. Since joining the University of Florida as an Assistant Professor in 2007, Dr. Anton has been the Principal Investigator on numerous NIH and other peer-reviewed grants. His specific research interests are in the role that lifestyle factors, such as diet and exercise, and natural compounds have in influencing biological mechanisms related to the aging process, as well as age-related disease conditions. Dr. Anton currently serves as the Principal Investigator of five active clinical trials. Among his honors, Dr. Anton was selected as one of two Outstanding Young Alumni honorees for the College of Public Health and Health Professions in 2009. He was also awarded the prestigious Thomas H. Maren Junior Investigator Award in 2010, which is provided to one junior faculty member within the College of Medicine each year. Dr. Anton has served as the primary mentor or committee member for eleven doctoral students, nine of whom have graduated. He currently serves on the mentoring committee for three junior faculty members within the Department of Aging and Geriatric Research and as the primary mentor for two doctoral students enrolled in the Clinical and Health Psychology doctoral program

B. Positions and Honors

Positions and Employment

1997-2002	Research Assistant, University of Florida
1999	Instructor, Santa Fe Community College
2002-2003	Pre-doctoral Psychology Intern, Medical University of South Carolina, Charleston, SC
2003-2006	Post-doctoral Fellow of Psychology, Pennington Biomedical Research Center, Louisiana State University
2007-2014	Assistant Professor, Department of Aging and Geriatric Research & Department of Clinical and Health Psychology, University of Florida

2011-2012	Interim Clinical Research Division Chief, Department of Aging and Geriatric Research, College of Medicine, University of Florida
2013–present	Clinical Research Division Chief, Department of Aging and Geriatric Research, College of Medicine, University of Florida
2014-present	Associate Professor, Department of Aging and Geriatric Research & Department of Clinical and Health Psychology, University of Florida

Professional Awards and Honors

2000	UF Clinical & Health Psychology Award for Outstanding Research (Nomination)
2001	Society of Behavioral Medicine Paper Citation – "Effects of exercise prescriptions on exercise adherence"
1997-2001	J. Hillis Miller Presidential Fellowship, awarded each year to a small number of students based on campus wide competition, University of Florida, Gainesville, FL
2008	Research Travel Award, National Institute on Aging Conference on Idiopathic Fatigue and Aging
2009	Research Travel Award, National Institute on Aging Bench to Bedside Conference on Inflammation and Nutrient Metabolism
2009	Outstanding Young Alumni honoree, College of Public Health and Health Professions, University of Florida, Gainesville, FL
2009	Thomas H. Maren Junior Investigator Award Recipient, Awarded each year to one Assistant Professor in College of Medicine, University of Florida, Gainesville, FL
2013	Invited Member of University of Florida's Leadership Academy

C. Selected Peer-reviewed Publications (15 of 80, listed in chronological order from past five years):

1. Hofer, T., Fontana, L., **Anton, S.D.**, Weiss, E. P., Villareal, D. T., Malayappan, B., & Leeuwenburgh, C. (2008). Long-term effects of caloric restriction or exercise on DNA and RNA oxidation levels in white blood cells and urine in humans. *Rejuvenation Research*, 11(4), 793-799. PMID: 18729811
2. Sacks, F.M., Bray, G.A., Carey, V.J., Smith, S.R., Ryan, D.H., **Anton, S.D.** et al. (2009). Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *New England Journal of Medicine*. 360, 859-873. PMID: 19246357
3. Chung, H.Y., Cesari, M., **Anton, S.D.**, Marzetti, E., Giovannini, S., Seo, A.Y., Carter, C., Yu, B.P., & Leeuwenburgh, C. (2009). Molecular inflammation: Underpinnings of aging and age-related diseases. *Ageing Research Reviews*, 8(1), 18-30. PMID: 18692159
4. Buford, T. W., **Anton, S.D.**, Judge, A. R., Marzetti, E., Wohlgemuth, S. E., Carter, C., Leeuwenburgh, C., Pahor, M., & Manini, T. (2010). Models of accelerated sarcopenia: Critical pieces for solving the puzzle of age-related muscle atrophy. *Aging Research Reviews*, 9(4), 369-383. PMID: 20438881
5. Wohlgemuth S. E., Marzetti E., Manini T. M., Aranda, J. M., Daniels, M. J., Pahor, M., Perri, M. G., Leeuwenburgh, C., & **Anton, S.D.** (2011). An Exploratory Analysis of the Effects of a Weight Loss plus Exercise Program on Cellular Quality Control Mechanisms in Older Overweight Women. *Rejuvenation Research*, 14(3), 315-24. PMID: 21631380
6. **Anton S.D.**, Manini T. M., Milsom V. A., Dubyak, P., Cesari, M., Cheng, J., Daniels, M. J., Marsiske, M. Pahor, M., Leeuwenburgh, C., & Perri, M. G. (2011). Effects of a Weight Loss Plus Exercise Program on Physical Function in Overweight, Older Women: A Randomized Controlled Trial. *Clinical Interventions in Aging*., 6, 141-9. PMID: 21753869
7. Nocera, J., Buford, T., Manini, T.M., Naugle, K., Leeuwenburgh, C., Pahor, M., Perri, M.G., & **Anton S.D.** (2011). The impact of behavioral intervention on obesity mediated declines in mobility function: Implications for longevity. *Journal of Aging Research*, 392510. PMID: 22013527
8. **Anton, S.D.**, Duncan, G.E., Limacher, MC. Martin, A.D., Perri, M.G. (2011). How much walking Is needed to improve cardiorespiratory fitness? An examination of the 2007 ACSM/AHA physical activity recommendations. *Research Quarterly for Exercise and Sport*, 82, 365-370. PMID: 21699118
9. **Anton, S.D.**, & Leeuwenburgh, C. L. (2013). Fasting or caloric restriction for healthy aging? *Experimental Gerontology*. 48, 1003-1005. PMID: 23639403
10. **Anton, S.D.**, Karabetian, C., Heekin, K., & Leeuwenburgh, C. (2013). Caloric Restriction to Moderate Senescence: Mechanisms and Clinical Utility. *Current Translational Geriatrics and Experimental Gerontology Reports*. 13, 239-246. PMID: 24466503
11. Nackers, L.M., Middleton, K.R., Dubyak, P.J., Daniels, M.J., **Anton, S.D.**, & Perri, M.G. (2013). Effects of prescribing 1,000 versus 1,500 kilocalories per day in the behavioral treatment of obesity: a randomized trial. *Obesity*. 21, 2481-2487. PMID: 23512956
12. Buford, TW, **Anton, SD**, Clark, DJ, Higgins, TJ, & Cooke, MB. (2014). Optimizing the Benefits of Exercise on Physical Function in Older Adults. *Journal of Aging and Physical Activity*. 6, 528-543. PMID: 24361365
13. Manini T.M., Lott D., Vandenborne K., Buford T., Knaggs J., Leeuwenburgh C., Pahor M., Perri M.G., 60. **Anton S.D.** (2014). Body composition changes with weight loss and exercise in older obese women with mild physical impairments. *Journal of Gerontology Medical Sciences*, 69, 101-108. PMID: 23682155

14. Botoseneanu, A., Ambrosius, W. T., Beavers, D., Rekeneire, N. D., **Anton, S.D.**, Church, T., Folta, S.C., et. al. (in press). Prevalence of Metabolic Syndrome and Its Association with Physical Capacity, Disability, and Self-Rated Health among Lifestyle Interventions and Independence for Elders (LIFE) Study Participants. *Journal of the American Geriatrics Society*.
15. **Anton SD**, Karabetian, C.K., Naugle K., and Buford T (in press). Obesity and diabetes as accelerators of functional decline: can lifestyle interventions maintain functional status in high risk older adults?. *Experimental Gerontology*. PMID: 23832077

D. Research Support:

Ongoing Research Support:

Active

1 R01 AT007564-01 Anton (PI) 09/01/13 - 05/31/17

REVIVE – Resveratrol to Enhance Vitality and Vigor in Elders (REVIVE)

The proposed clinical trial will test whether daily supplementation with 1000mg of resveratrol will improve mitochondrial function and physical performance in generally healthy but moderately functioning older men and women. The central hypothesis is that resveratrol treatment will improve mitochondrial function by activating key genes involved in mitochondrial biogenesis and metabolism, and that these biological/cellular changes can enhance physical performance among both low to moderately-functioning older adults.

Role: Principal Investigator

1 U01 AG022376 Pahor (PI) 12/01/08 - 11/30/14 NIH/NIA

Physical Exercise to Prevent Disability

The major goal of this project is to assess whether a physical activity intervention prevents mobility disability in older persons.

Role: Investigator

NIH/NIA 1 U01 AG030644-01A1 Snyder (PI) 05/15/09 - 04/30/15

The Testosterone Trial

The major goal of this project is to evaluate the effects of testosterone replacement on physical activity, sexual function and vitality in older men.

Role: Investigator

NIH/NIA P01 AG028740-06 Pahor (PI) 04/01/12 - 03/31/17

Claude D. Pepper Older Americans Independence Center (OAIC)

The major goals of this program are to assess the mechanisms leading to sarcopenia and functional decline as well as to develop and test interventions for the treatment and prevention of physical disability in older adults.

Role: Core Leader

NIH/NIA 1U01AG029824-01A2 Williams (PI) 07/01/10 - 01/31/17

ASpirin IN Reducing the Effects on the Elderly

The major goal of this project is to examine whether the potential benefits of low dose aspirin (particularly preventing heart disease, stroke, certain cancers and dementia) outweigh the risks (particularly bleeding) in people over age 70. ASPREE will determine whether taking a daily low-dose aspirin will extend the length of a disability-free life in healthy participants aged 70 years and above.

Role: Sub-Project PI

NIH/NIA P01 AG028740-06 Pahor (PI) 04/01/13 - 03/31/14

Effects of Vitamin D on Fall Risk and Functional Outcomes in Older Adults with Insufficient Vitamin D Levels: A Pilot Study

The major goal of this project is to examine whether daily vitamin D supplementation at the dose recommended by the Institute of Medicine improves functional outcomes and reduces fall risk in older adults with insufficient vitamin D levels.

Role: PI (Pilot Study)

NIH 1P50 GM000052-01 Moore (PI) 09/01/14 - 05/31/15

Epidemiology of Chronic Critical Illness in Surgical ICU Patients after Sepsis

This project proposes to investigate and describe the epidemiology of CCI and PICS in sepsis patients, identify early biomarkers that can predict its incidence and outcome, explore mechanisms that drive this process, and examine potential interventions to prevent the development of PICS in septic CCI patients.

Role: Co-I – Project 1 and Core B – Human Subjects

Completed Research Support:

1K23AT004251 Anton (PI) 09/01/09 - 08/30/14 NIH/NCCAM

Investigations of Botanicals on Food Intake, Satiety, and Weight Loss

The proposed line of research will explore the role that botanical compounds have in affecting food intake, gastrointestinal signals, satiety, and weight loss. The central hypothesis is that botanical compounds will reduce food intake in humans by stimulating neuroendocrine pathways related to satiety.

Role: Principal Investigator

(No Grant Number) Anton (Dual-PI) 02/01/08 - 12/31/11

The Evelyn F. and William L. McKnight Brain Institute

Resveratrol supplementation to improve oxidative stress, inflammation, and memory function in older adults

This Phase I double-blind, placebo controlled trial will determine whether three months of daily resveratrol supplementation affect oxidative stress and inflammatory pathways, as well as memory function, among non-impaired older adults.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Jennifer L. Bizon	POSITION TITLE Associate Professor
eRA COMMONS USER NAME (credential, e.g., agency login) jbizon	

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)*	MM/YY	FIELD OF STUDY
University of North Carolina at Chapel Hill	BS	1993	Psychology
University of California, Irvine	PhD	1998	Neurobiology and Behavior
Johns Hopkins University	Post-doc	1998-2002	Neuroscience

A. Personal Statement

My research program is broadly focused on understanding brain aging and its implications for cognitive functions, including learning, memory, and executive processes. Research within my NIH-funded laboratory integrates neuroanatomical, biochemical, and/or pharmacological techniques with cognitive/behavioral variables to better understand how aging alters corticolimbic inhibitory and neuromodulatory circuits, and how such alterations contribute to decline of function across multiple cognitive domains. We are particularly interested in how changes in these systems contribute to age-related decline of prefrontal cortical-supported executive functions, including working memory, cognitive flexibility, and decision making. A key element of our approach involves the consideration of individual differences in cognitive aging, which can be leveraged to identify and to better understand the relevant cognitive and neural mechanisms that underlie both impaired and successful cognitive outcomes. Our ultimate goal is to target effective compensatory strategies and to develop new approaches for promoting successful cognitive aging.

B. Positions and Honors

Positions & Employment

1993	Research Assistant at University of North Carolina at Chapel Hill
1993-1998	Graduate Student Assistant, University of California, Irvine, Laboratory of Dr. Christine Gall
1998-2003	Postdoctoral Fellow, Johns Hopkins University, Laboratory of Dr. Michela Gallagher
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-present	Associate Professor of Neuroscience and Psychiatry, University of Florida College of Medicine
2011-2013	Co-director, Neuroscience Concentration, Interdisciplinary Graduate Program, University of Florida College of Medicine
2013-present	Director, Neuroscience Concentration, Interdisciplinary Graduate Program, University of Florida College of Medicine

Honors and Professional Activities

Graduated with Highest Honors (Psychology) UNC-Chapel Hill (1993)
Individual NRSA, NIMH F31 pre-doctoral award (1995-1998)
Individual NRSA, NIA F32 post-doctoral award (2001-2003)
Leadership and Service Award, Faculty of Neuroscience, Texas A&M University (2008)
Montague Center for Teaching Excellence Award (2008), College of Liberal Arts, Texas A&M University
Editor, Animal Models of Human Cognitive Aging (2008), Humana (Wiley) Press
Editorial Board, Neurobiology of Aging (2008-present)
Advisory Board, Alzheimer's Drug Discovery Foundation (2010-present)

McKnight Cognitive Test Battery Working Group (2011-present)
NIH Special Emphasis Review Panel (ZAG1 ZIJ-5), Bethesda, MD (2009)
NSF Review Panel (Modulatory Brain Systems), Rockville MD (2011)
NIH Review Panel (CNND) Washington DC (2010, 2011)
NIH Review Panel (CDIN) Washington DC (2012)
NIH Review Panel (F03A), 2013-present
NIH Review Panel (F02B), Bethesda, MD (2013)
NIH Special Emphasis Review Panel (ZES1 LWJ-K), Chapel Hill, NC (2014)
NIH Review Panel (F03A), co-Chair, 2014-present
Section Editor, Behavior, Cognition and Physiology Section, Neurobiology of Aging (2014-present)

C. Selected Peer-reviewed Publications (2014 and <u>selected</u> from 2012-2013):

1. Orsini, CA, Trotta, R, **Bizon, JL** & Setlow, B. Dissociable roles for the basolateral amygdala and orbitofrontal cortex in decision-making under risk of punishment. In Press *J. Neurosci*.
2. Beas, BS, Setlow, B, Samanez-Larkin, GR, **Bizon, JL** Modeling cost-benefit decision making in aged rodents. In Hess, TM, Loeckenhoff, CE, Sttrough (Eds.) *Aging and Decision-Making: Empirical and Applied Perspectives*, Elsevier Press
3. Shimp, KM, Mitchell, MR, Beas, BS, **Bizon, JL**, & Setlow, B Affective and cognitive mechanisms of risky decision making. *Neurobiol Learn Mem*. 2014 Mar 15. pii: S1074-7427(14)00048-3. doi: 10.1016/j.nlm.2014.03.002. [Epub ahead of print]
4. Bañuelos, C, Beas, BS, McQuail, JA, Gilbert, RJ, Frazier, CJ, Setlow, B, & **Bizon, JL** Altered GABAergic signaling contributes to age-related impairments in working memory. *J Neurosci*. 2014 Mar 5;34(10):3457-66. doi: 10.1523/JNEUROSCI.5192-13.2014
5. Adolescent Risk Taking, Cocaine Self-Administration, and Striatal Dopamine Signaling. Mitchell MR, Weiss VG, Beas BS, Morgan D, **Bizon JL**, Setlow B. *Neuropsychopharmacology*. 2014 Mar;39(4):955-62. doi: 10.1038/npp.2013.295.
6. Yoder, W. M., Setlow, B., **Bizon, JL**, & Smith, *DW Characterizing olfactory perceptual similarity using carbon chain discrimination in behaviorally-trained Fischer 344 rats*. May;39(4):323-31. doi: 10.1093/chemse/bju001.
7. Centrally administered angiotensin-(1-7) increases the survival of stroke prone spontaneously hypertensive rats. Regenhardt RW, Mecca AP, Desland F, Ritucci-Chinni PF, Ludin JA, Greenstein D, Banuelos C, **Bizon JL**, Reinhard MK, Sumners C. *Exp Physiol*. 2014 Feb;99(2):442-53. doi: 10.1113/expphysiol.2013.075242.
8. Characterization of age-related changes in synaptic transmission onto F344 rat basal forebrain cholinergic neurons using a reduced synaptic preparation. Griffith WH, Dubois DW, Fincher A, Peebles KA, **Bizon JL**, Murchison DA. *Neurophysiol*. 2014 Jan;111(2):273-86. doi: 10.1152/jn.00129.2013.
9. Beas BS, Setlow B, **Bizon JL** (2013) Distinct manifestations of executive decline in aged rats. *Neurobiol Aging*. 2013 Sep; 34(9): 2164-74. doi: 10.1016/j.neurobiolaging.2013.03.019.
10. Simon NW, Beas BS, Montgomery KS, Haberman RP, **Bizon JL**, Setlow B. (2013) Prefrontal cortical-striatal dopamine receptor mRNA expression predicts distinct forms of impulsivity. *European Journal of Neuroscience* 37(11): 1779-88. doi: 10.1111/ejn.12191.
11. Mendez IA, Damborsky JC, Winzer-Serhan UH, **Bizon JL**, Setlow B (2013) A4β2 and α7 nicotinic acetylcholine receptor binding predicts choice preference in two cost benefit decision-making tasks. *Neuroscience*. 230:121-31. doi: 10.1016/j. neuroscience.2012.10.067.
12. Bañuelos, C, LaSarge, CL, McQuail, JA, Hartman, JA, Gilbert, RJ, Ormerod, BK, **Bizon, JL** (2013) Age-related changes in basal forebrain cholingergic and GABAergic neuron number: Relationship with spatial impairment. *Neurobiology of Aging*. 34(3):845-62. doi: 10.1016/j.neurobiolaging.2012.06.013.
13. Alexander, G.E., Ryan, L., Bowers, D. Foster, TC, **Bizon, JL**, Geldmacher, D.S., Glisky, E.L. (2012) Characterizing cognitive aging in humans with links to animal models. *Frontiers in Aging Neuroscience*. 4:21. doi: 10.3389/fnagi.2012.00021.
14. **Bizon, JL**, Foster, TC, Alexander, GE, Glisky, EL (2012) Characterizing Cognitive Aging of Working memory and executive function in animal models. *Frontiers in Aging Neuroscience*. 4:19. doi: 10.3389/fnagi.2012.00019.
15. Foster, T.C., DeFazio, **Bizon, JL**, Characterizing cognitive aging of spatial and contextual memory in animal models. (2012). *Frontiers in Aging Neuroscience*. doi: 10.3389/fnagi.2012.00012.
16. Roberson, ED, DeFazio, RA, Barnes, CA, Alexander GE, **Bizon, JL**, Bowers, D, Foster, TC, Glisky, EL, Levin, BE, Ryan, L, Wright, CB, Geldmacher, DS. Challenges and Opportunities for characterizing cognitive aging across species. (2012) *Frontiers in Aging Neuroscience*. doi: 10.3389/fnagi.2012.00006.
17. Mendez, I, Gilbert, RJ, **Bizon, JL**, Setlow, B. (2012) Effects of acute administration of nicotinic and muscarinic cholinergic agonists and antagonists on different forms of cost-benefit decision making. Psychopharmacology. 224(4):489-99. doi: 10.1007/s00213-012-2777-y.
18. McQuail, JA, Bañuelos, LaSarge, CL, Nicolle, MM, **Bizon, JL** (2012) GABAB receptor GTP-binding is decreased in the prefrontal cortex but not the hippocampus of aged rats. Neurobiology of Aging. 33(6):1124.e1-12. doi: 0.1016/j. neurobiolaging.2011.11.011.

D. Research Support:

Ongoing

2R01 AG029421-07 (NIH-NIA) 5/15/14-3/15/19 35% effort
"Neural mechanisms of cognitive decline in aging"
Bizon, PI
The goal of this project is to determine how age-related alterations in GABAergic signaling mechanisms in prefrontal cortex contribute to impairments in executive functions. No overlap.

AG029421-07S1 (NIH-NIA) 8/1/14-8/1/16
"Neural mechanisms of cognitive decline in aging"
This award is to support the graduate training of Sofia Beas who will be conducting work under the parent award.

UF Project 00088113 (Bizon PI) 10/1/14-10/1/15
McKnight Brain Research Foundation $144,000 direct
These funds support studies investigating the neural mechanisms of learning, memory, and decision-making and the decline of these cognitive functions across the lifespan.

5R37AG036800-03 (Foster PI, Bizon, co-I) 6/1/14-6/1/17 20% effort
National Institute on Aging
"Signaling cascades and memory deficits during aging"
The goal of this project is to understand the influence of Ca2+ signaling on spatial and working memory deficits that emerge in normal aging.

R01 DA024671 (B. Setlow PI, Bizon co-I) 7/1/09-3/31/14 (no-cost extension) 15% effort
National Institute on Drug Abuse
"Neural mechanisms of enduring cocaine effects on impulsive choice"
The goal of this project is to understand the long-term effects of cocaine use on decision making and to begin to elucidate the neurobiology associated with impulsivity resulting from psychostimulant drug use.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Dr. Sara N. Burke	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) SBURKE	

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)*	MM/YY	FIELD OF STUDY
University of Oregon, Eugene, OR, USA	B.Sc./M.Sc.	12/2000	Psychology
University of Arizona, Tucson, AZ, USA	Ph.D.	05/2009	Neuroscience
University of Arizona, Tucson, AZ, USA	Postdoctoral	09/2013	Neurobiology of Aging

B. Positions and Honors

Positions & Employment

1997-1999	Undergraduate Research Assistant in Dr. Richard Marrocco's Visual-Attention laboratory (U of O)
1999-2000	Graduate Research Associate in Dr. Richard Marrocco's Visual-Attention laboratory (U of O)
2000-2002	Research Associate in Dr. Alvin Eisner's Visual Adaptation laboratory (Oregon Health & Science University, Portland, OR)
2002-2009	Graduate Research Associate in Dr. Carol Banes Neural Systems, Memory and Aging Laboratory (U of Arizona)
2003-2004	Graduate Teaching Assistant for MSB407: Cellular, Molecular Neuroscience (U of Arizona)
2006-2011	Teaching Assistant for NRSC4/524: Gerontology (University of Arizona)
2009-2013	Postdoctoral Research Associate in Evelyn F. McKnight Brain Institute (U of Arizona)
Since 10/2013	Assistant Professor, Department of Neuroscience, University of Florida

Awards/Honors

1999	Phi Beta Kappa, inducted Departmental honors in Psychology, University of Oregon Magna Cum Laude, University of Oregon
2002-2004	Recipient of National Institute of Health Training Grant
2006	Recipient of the Society for Neuroscience Travel Award
2006-2009	Recipient of the Ruth L. Kirschstein National Research Service Award
2008	Recipient of the D.B. Marquis Behavioral Neuroscience Award
2010	Recipient of the D.B. Marquis Behavioral Neuroscience Award

Committees and Service

2008	Mentor and small group leader for University of Arizona Undergraduate Biology Research Program
2010-2011	Society for Neuroscience Membership Survey Advisory Group
2010-2011	Mentor for the University of Arizona Assurance Program
2014-present	HHMI Science for Life Mentor
2014-present	University of Florida Scholar Award Mentor

C. Selected Peer-reviewed Publications (2013)

Most recent and relevant to the current application (in chronological order)

1. **Burke SN**, Maurer AP, Nematollahi S, Uprety A, Wallace JL, Barnes CA (2014). Advanced age has dissociative effects on dual functions of the perirhinal cortex. *Journal of Neuroscience*, 34(2): 467-480. PMID: 24403147; PMCID: PMC3870932
2. **Burke SN**, Thome A, Plange K, Engle JR, Trouard TP, Gothard KM, Barnes CA (2014). Orbitofrontal cortex and basolateral amygdala volume show a dissociable relationship with reward devaluation in young and aged monkeys. *Journal of Neuroscience*, 34(30): 9905-16.
3. **Burke SN**, Barnes CA (2014). The Neural Representation of 3-Dimensional Objects in Rodent Memory Circuits. In press, *Behavioural Brain Research*. PMID: 25256648
4. Topper NC, **Burke SN**, Maurer AP (2014). Multiple Frequency Audio Signal Communication as a Mechanism for Neurophysiology and Video Data Synchronization. In press, Journal of Neuroscience Methods. PMID: 25205370

5. Maurer AP, Lester AW, **Burke SN**, Ferng J, Barnes CA (2014). Back to the Future: Preserved hippocampal network activity during reverse ambulation. *Journal of Neuroscience*, 5;34(45):15022-31.

Additional publications of importance to the field (in chronological order)

1. **Burke SN**, Chawla MK, Penner MR, Crowell BE, Worley PF, Barnes CA, McNaughton BL (2005). Differential encoding of behavior and spatial context in deep and superficial layers of the neocortex. *Neuron* 45, 667-674. PMID: 15748843.
2. **Burke SN**, Barnes CA (2006). Neural plasticity in the ageing brain. *Nature Reviews Neuroscience*, 7, 30-40. PMID: 16371948.
3. **Burke SN**, Maurer AP, Zhiyoung Y, Navratilova Z, Barnes CA (2008). Glutamate receptor-mediated restoration of experience-dependent place field expansion plasticity in aged rats. *Behavioral Neuroscience*, 122(3), 535-548. PMID: 18513124 ; PMCID: PMC2773228.
4. Gerrard JL, **Burke SN**, McNaughton BL, Barnes CA. (2008). Sequence reactivation in the hippocampus is impaired in aged rats. *Journal of Neuroscience*, 28(31):7883-90. PMID: 18667620; PMCID: PMC2703197.
5. **Burke SN**, Wallace JL, Nematollahi S, Uprety AR and Barnes CA (2010). Pattern separation deficits may contribute to age-associated recognition deficits. *Behavioral Neuroscience*, 24(5): 559-573. PMID: 20939657; PMCID: PMC3071152.
6. **Burke SN** and Barnes CA (2010). Senescent synapses and hippocampal circuit dynamics. *Trends in Neurosciences*, 33(3): 153-61. PMID: 20071039; PMCID: PMC3076741.
7. **Burke SN**, Maurer AP, Nematollahi S, Uprety AR, Wallace JL and Barnes CA (2011). The influence of objects on place field expression and size in distal hippocampal CA1. *Hippocampus*, 21(7):783-801. PMID: 21365714; PMCID: PMC3314262.
8. **Burke SN**, Maurer AP, Hartzell AL, Nematollahi S, Uprety A, Wallace JL and Barnes CA (2012). Representation of three-dimensional objects by the rat perirhinal cortex. *Hippocampus*, 22(10):2032-44. PMID: 22987680; PMCID: PMC3447635.
9. **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. PMID: 22987683; PMCID: PMC3523702.
10. **Burke SN**, Ryan L, Barnes CA (2012). Characterizing cognitive aging of recognition memory and related processes in animal models and in humans. *Frontiers in Aging Neuroscience*, 4(15). PMID: 22988437; PMCID: PMC3439640.
11. Maurer AP, **Burke SN**, Lipa P, Skaggs WE, Barnes CA (2012). Greater running speeds result in altered hippocampal phase sequence dynamics. *Hippocampus*, 22(4):737-47. PMID: 21538659; PMCID: PMC3367321.
12. Takehara-Nishiuchi K, Insel N, Hoang LT, Wagner Z, Olson K, Chawla MK, **Burke SN**, Barnes CA (2012). Activation patterns in superficial layers of neocortex change between experiences independent of behavior, environment, or the hippocampus. *Cerebral Cortex*, 23(9):2225-34. PMID: 22806267; PMCID: PMC3733063.
13. Hartzell AL, **Burke SN**, Hoang LT, Lister JP, Rodriguez CN, Barnes CA (2013). Transcription of the immediate-early gene Arc in CA1 of the hippocampus reveals activity differences along the proximodistal Axis that are attenuated by advanced age. *Journal of Neuroscience*, 33(8):3424-33. PMID: 23426670; PMCID: PMC3711759.

D. Research Support

Current

Institutional Startup Funds 10/01/2013 – 6/30/2018

2014 University of Florida Research Opportunity Seed Fund Award 6/01/2014 – 5/31/2016

Neurogenesis and Memory Network Dynamics during Normal Aging

The major goal of this award is to collect pilot data regarding the impact of reduced neurogenesis with age on the changes in activity pattern dynamics within the hippocampus. These data will be used to generate future NIH proposal. No overlap.

Role: P.I. (15% effort)

Completed Support

NIH – F31 NS054465 01/2007 – 01/2009

Aging and Neural Ensembles in the Perirhinal Cortex

The major goal of this project was to investigate the neurobiology of age-associated impairments in object recognition using high-density single cell recordings and single-cell imaging in young and old rats.

Role: Primary investigator under the mentorship of Carol A. Barnes.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Carter, Christy S.	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) chrcarte	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Colorado at Colorado Springs	B.A.	1991	Psychology
University of North Carolina at Chapel Hill	Ph.D.	1998	Experimental and Biological Psychology with minor in Neurobiology

A. Personal Statement

I currently serve the CAM-CTRP as facilitator of pilot projects and seminar directors. In addition, my primary research focuses on the development of preclinical rodent models for assessing the efficacy of preventative treatments for age-related physical, cognitive and cardiac decline. These interventions include diet, exercise, as well and nutritional and pharmaceutical approaches. These preclinical findings have been translated to humans through my collaboration with clinical researchers in our department. To fund these studies, I have been PI and co-PI on several NIH and foundation grants. I am currently Leader of the Pilot and Exploratory Core of the UF Older Americans Independence Center/CAM-CTRP, a core that fosters translational research between our clinical and preclinical researchers that has supported collection of data for this application.

B. Positions and Honors

1992-1994	Research Assistant, Center for Environmental Medicine and Lung Biology, University of North Carolina at Chapel Hill, North Carolina.
1994-1995	Trainee, Toxicology Training Grant, University of North Carolina at Chapel Hill, North Carolina
1995-1998	NIMH Pre-doctoral Fellow, NRSA (#MH11292 F31), University of North Carolina at Chapel Hill, North Carolina
9/99-10/01	Research Associate, Department of Internal Medicine/Geriatrics and Gerontology, Wake Forest University School of Medicine, Winston-Salem, North Carolina.
10/01-06/04	Instructor, Department of Internal Medicine/Geriatrics and Gerontology, Wake Forest University School of Medicine
10/03-03/05	Co-Director Pepper Center Pilot and Exploratory Core Wake Forest University School of Medicine
07/04-03/05	Assistant Professor, Departments of Internal Medicine/Geriatrics & Gerontology and Physiology & Pharmacology Wake Forest University School of Medicine
09/06-12/08	Associate Director for Research North Florida/South Georgia VMAC GRECC
06/07-12/08	Chair Research and Development Committee North Florida/South Georgia VMAC
04/05-present	Assistant Professor, College of Medicine, Department of Aging and Geriatric Research, University of Florida, Gainesville FL
04/05-present	Leader Institute on Aging Pilot and Exploratory Core, University of Florida

Other Experience and Professional Memberships

2009-present	National Scientific Advisory Board, AFAR
2003-present	Member American Association for the Advancement of Science
2002-present	Member American Aging Association
2001-present	Member American Geriatrics Society
2001-present	Member Gerontological Society of America
1993-present	Member Society for Neuroscience

Selected Honors

1995 NRSA predoctoral Fellowship awarded November.
1996 Travel Award to Neurobehavioral Teratology Society, Keystone, Colorado.
2001 Austin Bloch Post-Doctoral Fellow Award from the Gerontological Society of America.
2003 New Investigator Award from the American Geriatrics Society
2004 Travel Award to the American Aging Association Annual Meeting
2014 Fellow, Gerontological Society of America

C. Selected peer-reviewed publications (of > 50 peer-reviewed publications)

Most relevant to the current application

1. Buford TW, Hsu FC, Brinkley TE, **Carter CS**, Church TS, Dodson JA, Goodpaster BH, McDermott MM, Nicklas BJ, Yank V, Johnson JA, Pahor M; LIFE Research Group. Genetic influence on exercise-induced changes in physical function among mobility-limited older adults. Physiol. *Genomics*, 2014; 46 (5): 149-58.
2. Marzetti E, Calvani R, Dupree J, Lees HA, Giovannini S, Seo D, Buford TW, Sweet K, Morgan D, Strehler KYE, Diz D, Borst SE, Moningka N, Krotova K, **Carter CS**. Late-life enalapril administration induces nitric oxide-dependent and independent metabolic adaptation in the rat skeletal muscle. *Age* (Dordr.), 2013; 35(4): 1061-75.
3. Buford TW, Manini TM, Hsu FC, Cesari M, Anton SD, Nayfield S, Stafford RS, Church TS, Pahor M, **Carter CS**. Angiotensin-converting enzyme inhibitor use by older adults is associated with greater functional responses to exercise.
4. **Carter CS**, Giovaninni S, Seo DO, Dupree J, Morgan D, Chung HY, Lees H, Daniels M, Hubbard GB, Lee S, Ikeno Y, Foster TC, Buford TW, Marzetti E. Differential effects of enalapril and losartan on body composition and indices of muscle quality in aged male Fischer 344 x Brown Norway rats. 2011; 33: 167-83. *J Am Geriatr Soc*. 2012 Jul; 60:1244-52.
5. **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 Series A: Biol Sci.* 2004; 59:416-23.

Other publications of importance to the field

6. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, NadonNL, 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; 460: 392-395.
7. **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; 67: 17-27.
8. **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; 64: 850-859.
9. **Carter CS**, Groban L. Role of the renin-angiotensin system in age-related sarcopenia and diastolic dysfunction. *Aging Health* 2008; 4: 37-46.
10. You T, Sonntag WE, Leng X, **Carter CS**. Lifelong caloric restriction and interleukin-6 secretion from adipose tissue: effects on physical performance decline in aged rats. *J Gerontol A Biol Sci Med Sci* 2007; 62: 1082-1087.
11. **Carter CS**, Sonntag WE. "Growth Hormone, Insulin-Like Growth Factor-1 and the Biology of Aging" (Chapter 20) In: Masoro E.J. and Austad S. N. eds., *Handbook of the biology of aging, sixth edition*, 2005, Elsevier, United Kingdom.
12. Sonntag WE, **Carter CS**, Ikeno Y, Ekenstedt K, Carlson CS, Loeser RF, Chakrabarty S, Lee S, Bennett C, Ingram R, Moore T, Ramsey M. Adult-onset growth hormone and insulin-like growth factor I deficiency reduces neoplastic disease, modifies age-related pathology, and increases life span. *Endocrinology*, 2005;14: 920-32.
13. *Carter CS*, Sonntag WE, Ramsey M. A critical analysis of the role of growth hormone and IGF-1 in aging and lifespan. *Trends in Genetics*. 2002; 18: 295-301.
14. Onder G, Penninx BW, Balkrishnan P, Fried LP, Chaves PHM, Williamson JD, **Carter CS**, DiBari M, Guralnik JM, Pahor M. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. *Lancet*. 2002; 359: 926-930.
15. **Carter CS**, Sonntag WE, Onder G, Pahor M. Physical performance and longevity in aged rats. *J Gerontol Series A: Biol Sci*. 2002; 57: B193-197.

D. Research Support

1 P30 AG028740-01 Pahor (PI) 6/1/2012 – 3/31/2017 NIH/NIA

Claude D. Pepper Older Americans Independence Center (OAIC)

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, Co-Leader of the Preclinical Core, Co-Leader of Development Projects in the Preclinical and Biostatistics Core, and Leader of a Small Exploratory Study.

Completed (last three years)

1 P30 AG028740-01 Carter (PI) 7/1/2012 – 3/31/2014 NIH/NIA
Claude D. Pepper Older Americans Independence Center (OAIC) Development Project.
This development project is designed to validate the use of MALDI MS/MS in the identification of intracellular lipid moieties in aging skeletal muscle.

1R21DA023022-01 Morgan (PI) 07/01/07 – 05/31/10 NIDA/NIH
Chronic opioids and aging.
The primary purpose of this grant is to study the effects of chronic opioid treatment in a rodent model of age-related pain.

R01 AG024526-03 Carter (PI) 9/15/2005-7/31/2010 NIH/NIA
(supplement 8/1/2008-7/31/2010)
Title: ACE inhibition and physical performance in aged rats.
This grant is designed to assess the effects of inhibition of the renin-angiotensin system on physical performance, body composition and biological parameters in aged rats. A Translational Supplement has also been awarded with this grant.

Carter (PI) 07/01/05-06/31/10
ACE inhibition and longevity in mice. NIA Interventions Testing Program (ITP).
NIA initiated the ITP to evaluate compounds or diets thought to extend longevity in mice by delaying or decelerating the aging process.

Veterans Administration Tumer (PI) 10/1/07- 9/30/2010
Rehabilitation and R&D Service Obesity and Age Impaired Physical Performance; Gene Therapy Interventions.
The major goals of this project are: Objective 1. Are older rats more susceptible to high-fat feeding and will this accelerate the decline in physical performance or physical activity? Objective 2. Does central gene therapy mediated weight loss enhance physical function in aged rats?
Role: Co-I

(No grant number assigned) Carter (PI) 05/14/07-09/01/07
North Florida/South Georgia VA Research Investment Fund (RIF) pilot project.
Adiposity, aging and declining physical performance: Attenuation through targeted gene therapy
This grant is designed to test the effect of Wnt10b gene therapy on whole body and tissue specific adiposity in aged rats as measured by NMR spectroscopy.

P30 NIH/NIA Pahor (PI) 10/01/03-09/30/07
Pilot and Exploratory Core, Claude D. Pepper Older Americans Independence Center.
The goal of this core is to support pilot projects which will lead investigators toward a career in the field of aging. Dr. Carter withdrew from this grant on April 5, 2005, when she moved to the University of Florida.
Role: Investigator, Co-Leader

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Ronald A. Cohen, Ph.D.	Professor, Director CAM-CTRP
eRA COMMONS USER NAME (credential, e.g., agency login) RCOHEN1	

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)*	MM/YY	FIELD OF STUDY
Tulane University	BSc	1976	Psychology
Louisiana State University	Ph.D.	1982	Psychology
UCLA Medical Center: Neuropsychiatric Institute	Internship	1982	Psychology
University of Florida	Fellowship	1983	Neuropsychology

A. Personal Statement

Dr. Ron Cohen is the director of the Cognitive Aging and Memory-Clinical Translational Research Program, and an endowed professor in the Departments of Neurology, Psychiatry, and Aging-Geriatrics of the College of Medicine at the University of Florida. He leads efforts in clinical translational neuroscience of aging research. He came to UF to develop aims to translate basic neuroscience discoveries of researchers in the McKnight Brain Institute for study and clinical application in clinical, cognitive, and social-affective aspects of aging. An essential aspect of Dr. Cohen's research over the past two decades has involved the use of multimodal neuroimaging methods to study brain structure, function, and pathophysiology. He is an expert in the field of neuroimaging with over 100 of his 225 published studies involving neuroimaging methods, including FMRI, MRS, ASL, DTI and structural imaging. He has been continuously funded by NIH for many years, with most of his recent grants employing multimodal neuroimaging methods. He edited a book "Brain Imaging in Behavioral Medicine and Clinical Neuroscience" which covers the use of various neuroimaging methods for the cognitive and clinical neuroscience studies in these areas of focus. Prior to coming to UF, Dr. Cohen was a Professor in the Department of Psychiatry and Human Behavior and the Brain Science Institute at Brown University for 20 years, where he remains an adjunct professor. He played a pivotal role in developing the Magnetic Resonance Imaging Foundation, of which he was a member of the executive board that initially established research neuroimaging capabilities at Brown University.

Beyond this expertise in neuroimaging and aging, Dr. Cohen is a recognized expert in the cognitive and clinical neuroscience of attention. He wrote a seminal book on this topic "Neuropsychology of Attention", which just had a second edition published this year. He has published many papers and chapters on the neuropsychology of attention, including studies elucidating the component processes underlying attention. His research has also examined the relationships between attention, working memory and associative memory. Among his past research were important studies on the role of the anterior cingulate cortex in attention, intention, and emotional behavior. Supporting his current work in the area of cognitive aging, Dr. Cohen has expertise in several areas of clinical neuroscience, including the brain manifestations of cardiovascular disease and also HIV. Over the past 20 years, he co-directed a memory disorders clinic, which assessed a large number of patients with Alzheimer's disease, vascular dementia, and other neurodegenerative diseases affecting the elderly. His recent work has focused on vascular and metabolic factors affecting the aging brain, for which he recently was awarded a R01 grant to study the effects of weight loss after bariatric surgery on brain functions. He is actively involved in efforts directed at translating new technologies, particularly in the areas of neuroimaging and brain stimulation for application in humans. He also has a distinguished record of accomplishment as a teacher and mentor. He has trained over 25 post-doctoral fellows over the past 25 years, many of whom are now faculty members at universities around the country. He mentored 14 fellows who received F32 awards from NIH, and six career development (K) award recipients.

B. Positions and Honors

1992-1993 Associate Professor of Neurology, Univ. Mass. Medical School
1993-1996 Assistant Professor, Psychiatry-Human Behavior, Brown University
1996-2004 Associate Professor, Psychiatry-Human Behavior, Brown University
1993-2008 Director, Neuropsychology: The Miriam Hospital, Providence, RI
2002-2011 Permanent Member, NIH – BMIO Study Section
2008-2012 Director, Neuropsychological Research, The Miriam Hospital

1998-Current Editorial Boards: Journal of the International Neuropsychological Society; Brain Imaging and Behavior; the Clinical Neuropsychologist, Stroke, JCRP
2002-Current Member, Executive Committee, Brown University, Magnetic Resonance Foundation
2004-Current Professor, Brain Sciences Program, Brown University
2004-Current Professor of Psychiatry and Human Behavior, Brown University
2012-Current Director, Center for Cognitive Aging and Memory, The University of Florida
2012-Current Evelyn McKnight Endowed Professor, Departments of Neurology, Psychiatry and Aging, The University of Florida

C. Selected Peer-reviewed Publications

Selected Peer-reviewed Publications (selected from 225 peer-reviewed publications)

1) Seider TR, Luo X, Gongvatana A, Devlin KN, de la Monte SM, Chasman JD, Yan P, Tashima KT, Navia B, **Cohen RA**. (2014). Verbal memory declines more rapidly with age in HIV infected versus uninfected adults. *J Clin Exper Neuropsychol*. **PMID: 24645772.**
2) Woods AJ, **Cohen RA**, Pahor M. (2013). Commentary: cognitive frailty: frontiers and challenges. *J Nutr Health Aging*. Sep;17(9):741-743. **PMID: 24154645.**
3) Alosco ML, Gunstad J, Jerskey BA, Xu X, Clark US, Hassenstab J, Cote DM, Walsh EG, Labbe DR, Hoge R, **Cohen RA**, Sweet LH. (2013). The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease. *Brain Behav*. Nov;3(6):626-636. **PMID: 24363966**
4) Correia S, **Cohen RA**, Gongvatana A, et al. Relationship of plasma cytokines and clinical biomarkers to memory performance in HIV. *J Neuroimmunol*. 2013; 265(1-2):117-23. **PMID: 24210837**
5) Clark US, **Cohen RA**, Sweet LH, et al. Effects of HIV and early life stress on amygdala morphometry and neurocognitive function. *J Int Neuropsychol Soc*. Jul 2012;18(4):657-668. **PMCID: PMC3575741**
6) Clark US, **Cohen RA**, Westbrook ML, Devlin KN, Tashima KT. Facial emotion recognition impairments in individuals with HIV. *J Int Neuropsychol Soc*. Nov 2010;16(6):1127-1137. **PMCID: PMC3070304**
7) **Cohen RA**, Harezlak J, Gongvatana A, et al. Cerebral metabolite abnormalities in human immunodeficiency virus are associated with cortical and subcortical volumes. *J Neurovirol*. Nov 2010;16(6):435-444. **PMID 20961212**
8) **Cohen RA**, Harezlak J, Schifitto G, et al. Effects of nadir CD4 count and duration of human immunodeficiency virus infection on brain volumes in the highly active antiretroviral therapy era. *J Neurovirol*. Feb 2010;16(1):25-32. **PMCID: PMC2995252**
9) Ott BR, **Cohen RA**, Gongvatana A, et al. Brain ventricular volume and cerebrospinal fluid biomarkers of Alzheimer's disease. *J Alzheimers Dis*. 2010; 20(2):647-657. **PMCID: PMC3078034**
10) Paskavitz JF, Sweet LH, Helmer KG, Rao SM, **Cohen RA**. Recruitment and stabilization of brain activation within a working memory task; an FMRI study. *Brain Imaging and Behavior*. 2010; 4(1):5-21. **PMID 20503110**
11) Jefferson AL, Holland CM, Tate DF, Guttmann, Cohen RA. Atlas-derived perfusion correlates of white matter hyperintensities in patients with reduced cardiac output. *Neurobiol Aging*. 2011; 32(1): 133-9. **PMCID: PMC2889176**
12) **Cohen RA**, de la Monte S, Gongvatana A, et al. Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning. *J Neuroimmunol*. 2011;233(1-2):204-210. **PMCID: PMC3074016**
13) **Cohen RA**, Poppas A, Forman DE, Hoth KF, Haley AP, Gunstad J, Jefferson AL, Tate DF, Paul RH, Sweet LH, Ono M, Jerskey BA, Gerhard-Herman M. Vascular and cognitive functions associated with cardiovascular disease in the elderly. *J Clin Exp Neuropsychol*. 2009; 31(1):96-110. **PMC2739675**
14) **Cohen RA**, Grieve S, Hoth KF, Paul RH, Sweet L, Tate D, Gunstad J, Stroud L, McCaffery J, Hitsman B, Niaura R, Clark CR, MacFarlane A, Bryant R, Gordon E, and Williams LM. Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biol Psychiatry*. 2006; 59(10), 975-82. **PMID: 16616722.**
15) **Cohen RA**, Paul R, Lohr I. Impairments of attention in patients with major affective disorder. *J Neuropsychiatry Clinical Neurosci*. 2001; 13(3): 385-395. **PMID:11514646**

D. Research Support

Ongoing Research Support

1R01DK09933401A1 (Ronald Cohen, PI) 09/30/14 - 08/30/19
"Obesity and Type-2 Diabetes: Bariatric Surgery Effects on Brain Function"
The study will delineate mechanism underlying the effects of chronic obesity on brain functioning and determine if cognitive benefits of bariatric surgery and weight loss contribute to enhanced cerebral metabolic or hemodynamic function assessed using multimodal neuroimaging methods. 35% effort

1U54EB020403-01 Thompson (PI)
ENIGMA: Center for Worldwide Medicine, Imaging and Genomics
The Enigma Center for Worldwide Medicine, Imaging and Genomics is an unprecedented global effort bringing together 287 scientists and all their vast biomedical datasets, to work on 9 major human brain diseases: schizophrenia, bipolar disorder, major depression, ADHD, OCD, autism, 22q deletion syndrome, HIV/AIDS and addictions. Enigma integrates images, genomes,

connectomes and biomarkers on an unprecedented scale, with new kinds of computation for integration, clustering, and learning from complex biodata types. Enigma, founded in 2009, performed the largest brain imaging studies in history (N>26,000 subjects; Stein +207 authors, Nature Genetics, 2012) screening genomes and images at 125 institutions in 20 countries. Responding to the BD2K RFA, ENIGMA'S Working Groups target key programmatic goals of BD2K funders across the NIH, including NIMH, NIBIB, NICHD, NIA, NINDS, NIDA, NIAAA, NHGRI and FIC. Enigma creates novel computational algorithms and a new model for Consortium Science to revolutionize the way Big Data is handled, shared and optimized. We unleash the power of sparse machine learning, and high dimensional combinatorics, to cluster and inter-relate genomes, connectomes, and multimodal brain images to discover diagnostic and prognostic markers. The sheer computational power and unprecedented collaboration advances distributed computation on Big Data leveraging US and non-US infrastructure, talents and data. Our projects will better identify factors that resist and promote brain disease, that help diagnosis and prognosis, and identify new mechanisms and drug targets. Our Data Science Research Cores create new algorithms to handle Big Data from (1) Imaging Genomics, (2) Connectomics, and (3) Machine Learning & Clinical Prediction. Led by world leaders in the field who developed major software packages (e.g., Jieping Ye/SLEP), we prioritize trillions of computations for gene-image clustering, distributed multi-task machine learning, and new approaches to screen brain connections based on the Partition Problem in mathematics. Our Enigma Training Program offers a world class Summer School coordinated with other BD2K Centers, worldwide scientific exchanges. Challenge-based Workshops and hackathons stimulate innovation and Web Portals disseminate tools and engage scientists in Big Data science. Dr. Cohen is a co-I (10% effort) and director of HIV data initiative.
Role: Co-Investigator

U24 AA022002 Cook (PI) 09/01/13 - 08/31/15 NIAAA
Southern HIV Alcohol Research Consortium (SHARC) Admin and Research Support Cure
The objective of this proposal is to establish the administrative structure and to provide research support for the SHARC, a collaboration that links several universities and investigators with a common goal of supporting new research related to HIV and alcohol consumption.
Role: Co-Investigator

P01 AA019072 Monti (PI) 09/30/10 - 08/31/15 NIAAA
Alcohol and HIV: Biobehavioral Interactions and Intervention
One of two primary R01 projects in the Brown University HIV-Alcohol center grant, this study focuses on the interactive effects of HIV and alcohol use on metabolic-vascular disturbances underling brain dysfunction. We are longitudinally assessing HIV infected and seronegative controls who are stratified by alcohol use into three groups (heavy, moderate, none use) over a 36-month period. The study examines MRI-based neuroimaging biomarkers of brain dysfunction including diffusion tensor imaging (DTI), morphometry, and magnetic resonance spectroscopy (MRS) to measure cerebral metabolite abnormalities. Dr. Cohen is the principal investigator of this R01 project overseeing all aspects of the study.
Role: Co-Investigator

RO1 NS080655 Thompson (PI) 08/01/12 - 07/31/16 NINDS
Predicting Brain Changes in HIV/AIDS
This project greatly advances the ability to map, and predict, brain changes in people living with HIV/AIDS. HIV/AIDS is perhaps the greatest threat to public health worldwide in the 21st century. 40 million people are HIV-infected - a shocking 1 out of every 100 people aged 18-45 - and 40% have some neurological or cognitive impairment. This work offers 3 immediate public health consequences: (1) new methods to predict whether a person with HIV/AIDS will show imminent brain decline; (2) enhancing basic neuroscience, identifying brain circuits disrupted by the virus, and (3) a clear method to boost power for clinical trials of drugs to treat the brain in the millions of people now living with HIV/AIDS.
Role: Co-Investigator

Completed Support

U01 CA150387 Wing (PI) 09/28/09 - 08/31/14 NCI
Increasing Sleep Duration: A Novel Approach to Weight Control
The purpose of the project is to translate the basic science on sleep duration into a novel intervention to reduce obesity and obesity-related co-morbidities.
Role: Co-Investigator

R34 DA031057 Cohen (PI) 09/30/10 - 08/31/12 NIDA
Improving Adherence and Cognition in Substance-Using HIV Patients
Substance abuse in the context of HIV infection is a major problem that affects clinical outcome and interferes with adherence to treatment regimens. This study examines the value of a computer-based cognitive training program (Vigorous Mind) to enhance

attention and executive functioning as a means of improving organizational and planning ability and ultimately treatment adherence. The study focuses on further development of the program for use in this population and initial testing to determine its acceptability and whether a larger scale clinical trial is warranted.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Robert Lewis Cook	Professor of Epidemiology and Medicine
eRA COMMONS USER NAME cookrl	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of North Carolina at Chapel Hill, NC	BSPH	1982-86	Biostatistics
University of North Carolina at Chapel Hill, NC	MD, MPH	1986-91	Epidemiology
University of Virginia, Charlottesville, VA	Residency	1994-96	Internal Medicine
University of North Carolina at Chapel Hill, NC	Residency	1994-96	Preventive Medicine
University of North Carolina at Chapel Hill, NC	Fellowship	1994-96	RWJ Clinical Scholars

A. Personal Statement

I am a Professor in the Department of Epidemiology and Medicine at the University of Florida, Gainesville. For over a decade, I have studied the association of alcohol and drugs to clinical and behavioral outcomes in HIV infection. Much of my work has been in collaboration with large HIV cohort studies. In 2009, I received an R01 grant to develop a randomized clinical trial to study the prescription medication naltrexone as an intervention for women with HIV and high-risk drinking. In 2011, we received U01 funding from NIAAA/NIH to expand the naltrexone clinical trial into Miami, and we also received U24 funding from NIAAA/NIH to support the Southern HIV Alcohol Research Consortium (SHARC). Through SHARC we are now in the process of expanding a longitudinal study, the Florida Cohort to Monitor and Improve Health Outcomes, throughout the state of Florida. An anonymous pilot survey, which began in April 2013 is almost complete and Phase I of the survey is in full swing in 5 counties.

B. Positions and Honors

1994-1996	Clinical Instructor, University of North Carolina, Chapel Hill, NC.
1996-2006	Assistant Professor, Department of Medicine, Division of General Internal Medicine, and Department of Community and Behavioral Health Sciences, University of Pittsburgh, Pittsburgh, PA
2006	Associate Professor, Department of Medicine, University of Pittsburgh, Pittsburgh, PA
2007-2013	Associate Professor with Tenure. Department of Epidemiology, University of Florida, Gainesville Fl.
2007-present	Associate Director, Florida Center for Medicaid and the Uninsured, University of Florida
2010-2012	Director, PhD Program in Epidemiology, University of Florida
2012-present	Director, Southern HIV & Alcohol Research Consortium (SHARC), University of Florida, Gainesville, Fl.
2013- present	Professor (tenured), Departments of Epidemiology and Medicine, University of Florida, Gainesville FL.

Professional Societies

1993-present	Member, Society of General Internal Medicine
1996-present	Member, American Sexually Transmitted Disease Association
2007-present	Member, American Public Health Association, Florida Public Health Association
2009-present	Member, Research Society on Alcoholism

Awards/Professional Activities

1989-90	Delta Omega Undergraduate Award of Excellence, University of NC
1989-91	Holderness Medical Research Fellowship, University of NC School of Medicine.
1990	Cecil G. Sheps Award in Social Medicine, University of NC School of Medicine.
1999-2006	Co-Director, Bridging the Gaps Community Health Internship
2010	Delta Omega, Honorary Society of Public Health
2010	University of Florida College of Medicine Excellence in Teaching Award
2013-2016	UF Research Foundation (UFRF) Professor

C. Selected Peer-reviewed Publications (selected from 82 peer-reviewed publications)

Most relevant to the current application

1. **Cook RL**, Zhu F, Belnap BH, Weber K, Cook JA, Vlahov D, Wilson TE, Hessol NA, Plankey M, Howard AA, Cole SR. Sharp GB, Richardson JL, Cohen MH. Longitudinal trends in hazardous alcohol consumption in women with HIV infection: 1995-2006. *American Journal of Epidemiology* 2009;169(8):1025-32. **PMID: 19270052. PMC2727230.**
2. **Cook RL**, Zhu F, Belnap BH, Weber, KM, Cole SR, Vlahov D, Cook JA, Hessol NA, Wilson TE, Plankey M, Howard, AA, Sharp GB, Richardson JL, Cohen MH. Long-term trajectories of alcohol consumption in adult women with and without HIV infection. *AIDS and Behavior* 2013, 17(5), 1705-1712. initially published online July 27, 2012. **PMID: 22836592. PMC3534826. NIHMS396916.**
3. **Cook RL**, Clark DB. Is there an association between alcohol consumption and sexually transmitted diseases? A systematic review. *Sex Transm Dis* 2005: 32:156-64. **PMID: 15729152.**
4. Miguez-Burbano MJ, Espinoza L, Whitehead NE, Bryant VE, Vargas M, **Cook RL**, Quiros C, Lewis JE, Deshratan A. Brain derived neurotrophic factor and cognitive status: The delicate balance among people living with HIV, with and without alcohol abuse. *Curr HIV Res*. 2014;12(4):254-64. **PMID: 25053366**
5. **Cook RL**, Sereika SM, Hunt SC, Woodward WC, Erlen JA, Conigliaro JC. Problem drinking and medication adherence among persons with HIV infection. *J Gen Intern Med*. 2001; 16:83-88. **PMID: 11251758. PMC1495171.**

Additional recent publications of importance to the field

6. Hu X, Dodd VJ, Oliverio JC, **Cook RL**. Utilization of information and communication technology (ICT) among sexually transmitted disease clinics attendees with coexisting drinking problems. *BMC Research Notes* 2014, Mar 26;7:178. doi: 10.1186/1756-0500-7-178. **PMID: 24670037.**
7. **Cook RL**, Zhang J, Mullins J, Kauf T, Brumback B, Steingraber H, Mallison C. Factors associated with initiation and completion of HPV vaccine series among young women enrolled in Medicaid. 2010, *Journal of Adolescent Health*, 2010 Dec; 47(6):596-9. **PMID: 21094437.**
8. Bass M, Korthuis PT, Cofrancesco J, Berkenblit GV, Sullivan LE, Asch SM, Bashook PG, Edison M, Sosman JM, **Cook RL**. Provider and practice characteristics associated with use of rapid HIV testing by general internists. *J Gen Intern Med* 2011, 26(11):1258-64. **PMID: 21710314. PMC3208478.**
9. **Cook RL**, Thompson EL, Friary J, Hosford J, Barkley P, Dodd VJ, Abrahamsen M, Ajinkya S, Obesso PD, Rashid MH, Giuliano AR. Sexual behaviors and other risk factors for oral Human Papillomavirus (HPV) infections in young women. *Sexually Transmitted Diseases*, 2014 Aug;41(8):486-92. Doi: 10.1097/OLQ. **PMID: 25013976.**
10. Mohandas R, Casey MJ, **Cook RL**, Lamb KE, Wen X, Segal MS. Racial and socioeconomic disparities in the allocation of expand criteria donor kidneys. *Clin J Am Soc Nephrol*. 2013 Dec;8(12):2158-64. doi: 10.2215/CJN.01430213. Epub 2013 Oct 10.
11. **Cook RL**, Comer DM, Wiesenfeld HC, Chang CH, Tarter R, Lave JR, Clark DB. Alcohol and drug use and related disorders: an under recognized health issue among adolescents and young adults attending STD clinics. *Sex Transm Dis*. 2006; 33(9):565-70. **PMID: 16572042.**
12. **Cook RL**, McGinnis KA, Kraemer KL, Gordon AJ, Conigliaro J, Maisto SA, Samet JH, Crystal S, Rimland D, Bryant KJ, Braithwaite RS, Justice AC. Intoxication before intercourse and risky sexual behavior in male veterans with and without HIV infection. *Medical Care* 2006; 44(8 suppl 2):(S31-S36). **PMID: 16849966.**
13. **Cook RL**, McGinnis KA, Samet JH, Fiellin DA, Rodriguez-Barradas MC, Kraemer KL, Gibert CL, Braithwaite RS, Goulet JL, Mattocks K, Crystal S, Gordon AH, Oursler KA, Justice AC. Erectile dysfunction drug receipt, risky sexual behavior and sexually transmitted diseases (STDs) in men with and without HIV infection. *J Gen Intern Med*. 2010 Feb; 25(2):115-21. **PMID: 19921112. PMC2837496.**
14. Míguez-Burbano M, Espinoza L, **Cook RL**, Vargas M, Bueno D, et al. (2013) Alcohol, brain derived neurotrophic factor and obesity among people living with HIV. *J AIDS Clin Res* 4: 245. doi: 10.4172/2155-6113.1000245. published online September 20, 2013.
15. Malek AM, Chang JC, Clark DB, **Cook RL**. Delay in seeking care for sexually transmitted diseases in young men and women attending a public STD clinic. *Open AIDS J*. 2013 Jun 14;7:7-13. doi: 10.2174/1874613620130614002. eCollection 2013. **PMID: 24078858. PMCID: PMC3785038**

D. Research Support

Ongoing Research Support

NIAAA U24 AA022002 (Cook, PI) 9/1/12 – 8/31/17

Southern HIV & Alcohol Research Consortium (SHARC) The mission of the SHARC is to improve health outcomes and reduce HIV transmission among the diverse range of populations affected by alcohol and HIV infection in the Southeastern United States.

NIAAA 1U01AA020797-01 (Cook, PI) 9/25/11 – 9/24/16

Pharmacotherapy for alcohol consumption in HIV-infected women: Randomized trial

This study is a double-blind randomized clinical trial to determine the efficacy of the medication naltrexone to reduce alcohol consumption and complications in women with HIV.

NIAAA 1U01AA020800-01 Co-I (PI: Desai) 09/10/11 – 08/31/16
Immune Dys-regulation in HIV-infected Women with Heavy Alcohol Consumption
The major goal of this project is to examine whether chronic cumulative alcohol exposure is associated with more rapid CD4 T cell decline and immune dys-functionality (microbial translocation, immune activation, inflammation and immune senescence) leading to early advent of AIDS and non AIDS co-morbidities

NIAID Co-I (PI: Fischl) 2013-2018
Miami Women's Interagency HIV Study (WIHS)
The Miami Women's Interagency HIV Study is part of the national WIHS Cohort, which seeks to study long-term outcomes of HIV infection in women. As part of the Miami site, Dr. Cook will be involved with the behavioral working group and will study other long-term outcomes in HIV.

Completed Research Support (most relevant to current submission)
R01 Supplement, AA018934 (Cook, PI) 2009-2012
Pharmacotherapy to reduce hazardous drinking in HIV-infected women.
This study is a multi-site clinical trial, designed as a pilot study to determine the acceptability and feasibility of delivering pharmacologic treatment for hazardous alcohol consumption to women with HIV infection.

HRSA 1UB6HP2282 Co-I (PI: Peoples-Sheps) 2011-2014
Rural South Public Health Training Center
The Rural South Public Health Training Center seeks to expand training of public health professionals and to support community public health, with a focus on HIV infection and a focus on rural areas in Florida. Dr. Cook is involved in the center by co-teaching a course on HIV/AIDS, participating in supervision of interns and internship projects, and helping to evaluate the program.

NIAID, HHSN2662 00400074C 2007-2010
Home Screening for Bacterial Vaginosis to Prevent STD: A Study of the STI Clinical Trials Group
This study is a randomized controlled trial designed to determine whether regular screening and treatment of bacterial Vaginosis will reduce the risk of incident chlamydial and gonorrhea infections. We will recruit 1500 young women from 6 US cities. Subjects will obtain self-collected vaginal swabs and send them in every two months. Dr. Cook designed the protocol for the study, which began recruitment in the May, 2008, and is scheduled to finish in November, 2014.
Role: Protocol Chair

K23 AA000303-01 (Cook, PI) 1999-2003
Alcohol Use Disorders and Infectious Diseases among Youth
This study involved the recruitment of over 400 youth attending an STD clinic, completion of a behavioral risk survey, and linkage to clinical records of STD outcomes. We completed the project on schedule and the data have resulted in 5 peer-reviewed publications to date.

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	POSITION TITLE
Yenisel Cruz-Almeida	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) ycruzalmeida	

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)*	MM/YY	FIELD OF STUDY
University of Florida, Gainesville, FL	B.S.	05/01	Microbiology & Cell Science
University of Miami, Miami, FL	M.S.P.H.	08/04	Epidemiology & Public Health
University of Miami, Miami, FL	Ph.D.	12/11	Neuroscience
University of Florida, Gainesville, FL	Post-doctoral	12/12	Translational Pain Research

A. Personal Statement

My research interests are to elucidate the underlying nervous system mechanisms associated with age differences in endogenous pain modulation and associated functional implications. This area of interest stems from my previous research training in the field of Neuroscience. During my doctoral work, I studied brain metabolites associated with neuropathic pain phenotype profiles in persons with spinal cord injury combining Magnetic Resonance Spectroscopy and Quantitative Sensory testing. During my post-doctoral training, I was involved with several different studies that afforded me the opportunity to become very familiar with methods to assess endogenous pain inhibition and facilitation using more dynamic experimental stimuli. My career plans are to: 1) excel in an academic institution as an independent clinical/translational neuroscientist with expertise in the fields of pain and aging and 2) to contribute to the research and biomedical community through scholarship and education with the ultimate goal of improving the physical function and quality of life of older adults. My drive, self-motivation, previous training and research experience provide a solid foundation to achieve my long-term career objectives.

B. Positions and Honors

Positions and Employment

1997- 1999: Clinical Research Coordinator, Florida Ophthalmic Institute, Gainesville, FL
1999- 2000: Medical Laboratory Assistant, Shands Hospital, Gainesville, FL
2002- 2004: Research Associate, Miami Project to Cure Paralysis, University of Miami, Miami, FL
2004- 2006: Senior Research Associate, Miami Project to Cure Paralysis, University of Miami, FL
2006- 2011: PhD Student, Neuroscience Graduate Program, University of Miami, Miami, FL
2011- 2012: Postdoctoral Fellow, College of Dentistry, University of Florida, Gainesville, FL
2012- 2014: Research Assistant Professor, College of Dentistry, University of Florida, Gainesville, FL
2014-Present: Assistant Professor, College of Medicine, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

2003-Present Member, American Pain Society
2003-Present Member, International Association for the Study of Pain
2004-Present Member, National Neurotrauma Society
2009-Present Journal Reviewer, Pain Medicine
2009-Present Member, Society for Neuroscience
2012-Present Journal Reviewer, Journal of Pain
2013-Present Member, The Gerontological Society of America
2013-Present Journal Reviewer, Clinical Journal of Pain
2013-Present Editorial Board Member, Journal of Geriatrics & Palliative Care
2014-2016 Elected Co-Chair, American Pain Society, Shared Interest Group: Measurement of Pain and its impact

Awards/Honors

1998 University of Florida Hispanic Student Association Award for Leadership
1999 University of Florida Outstanding Student Award in Community Service
2004 University of Miami Award for Academic Merit (Master's level)
2004 American Pain Society Young Investigator Travel Award
2006 NINDS/NIH Predoctoral Training Fellowship
2006 Lois Pope Life Fellowship, Neuroscience Program, University of Miami
2006 American Pain Society Young Investigator Travel Award
2007 Florida Graduate Academic Scholar Award, University of Miami, Graduate Studies
2008 Congress of Spinal Cord Medicine and Rehabilitation Scholarship
2010 Department of Veteran Affairs RR&D Predoctoral Fellowship Award
2010 Alpha Epsilon Lambda Graduate Honor Society
2011 Medical Faculty Association Margaret Whelan Graduate Student Scholarship Award
2011 Miami VA Medical Center Young Investigator Award
2011 Top Student Competition Finalist, National Neurotrauma Symposium
2011 American Pain Society Young Investigator Travel Award
2011 University of Miami Award for Academic Merit (PhD level)
2012 NIDCR/NIH Postdoctoral Training Fellowship
2012 National Institute on Aging Loan Repayment Program Recipient
2013 University of Florida Affiliated Junior Pepper Scholar
2013 American Pain Society Young Investigator Travel Award
2014 American Pain Society Annual Meeting Faculty, Tampa, Florida
2014 University of Florida Pepper Scholar, Institute on Aging
2015 American Pain Society Annual Meeting Faculty, Palm Springs, California

C. Selected Peer-reviewed Publications *(Selected from 30 peer-reviewed publications)*

1. Widerström-Noga EG, **Cruz-Almeida Y**, Krassioukov AV. Is There A Relationship Between Chronic Pain and Autonomic Dysreflexia in Persons with Cervical Spinal Cord Injury? *J Neurotrauma*. 2004. 21:2, 195-204.
2. **Cruz-Almeida Y**, Martinez-Arizala A, Widerström-Noga EG. Chronicity of Pain Associated With Spinal Cord Injury: A Longitudinal Analysis. *J Rehabil Res Dev*. 2005 Sep- Oct;42(5):585-94.
3. Felix ER, **Cruz-Almeida Y**, Widerström-Noga EG. Chronic pain after spinal cord injury: What characteristics make some pains more disturbing than others? *J Rehabil Res Dev*. 2007;44(5):703-16.
4. **Cruz-Almeida Y**, Alameda G, Widerström-Noga EG. Differentiation between pain-related interference and interference caused by the functional impairments of spinal cord injury. *Spinal Cord*. 2009 May;47(5):390-5. Epub 2008 Nov 25.
5. **Cruz-Almeida Y**, Felix ER, Martinez-Arizala A, Widerström-Noga EG. Pain symptom profiles in persons with spinal cord injury. *Pain Med*. 2009 Oct;10(7):1246-59.
6. Widerström-Noga EG, Pattany P, **Cruz-Almeida Y**, Felix ER, Martinez-Arizala A, Cardenas D, Pérez S, Gómez-Marin O. Cortical neurochemical correlates of neuropathic pain severity and impact after spinal cord injury. *Pain*, 2012 Nov 7. Epub ahead of print. **PMCID:PMC3670594**
7. **Cruz-Almeida Y**, Wallet S, King CD, Riley III JL. Immune biomarker response depends on choice of experimental pain stimulus in healthy adults: A preliminary study. *Pain Res Treat*. 2012;2012:538739. Epub 2012 Nov 20. **PMCID: PMC3508574**
8. **Cruz-Almeida Y**, Felix ER, Martinez-Arizala A, Widerström-Noga EG. Decreased spinothalamic and dorsal column-medial lemniscus mediated sensory function is associated with neuropathic pain after spinal cord injury. *J Neurotrauma*. 2012 Nov 20;29(17):2706-15. Epub 2012 Aug 27.
9. Naugle KM, **Cruz-Almeida Y**, Fillingim RB, Riley JL. Offset analgesia in older adults. *Pain*. 2013 Nov;154(11):2381-7. doi: 10.1016/j.pain.2013.07.015. Epub 2013 Jul 16. **PMCID:PMC3894599**
10. **Cruz-Almeida Y**, King CD, Goodin BR, Sibille KT, Glover TL, Riley III JR Sotolongo A, Herbert MS, Fessler BJ, Redden DT, Staud R, Bradley LA, & Fillingim RB. Psychological profiles and pain characteristics of older adults with knee osteoarthritis. *Arthritis Care Res (Hoboken)*. 2013 Jul 16. doi: 10.1002/acr.22070. [Epub ahead of print] **PMCID: PMC3922880.**
11. **Cruz-Almeida Y**, Riley III JR, & Fillingim RB. Experimental pain phenotype profiles in a racially and ethnically diverse sample of healthy adults. *Pain Med*. 2013 Nov;14(11):1708-18. doi: 10.1111/pme.12203. Epub 2013 Jul 24. **NIHMSID #568518**
12. Riley JL, **Cruz-Almeida Y**, Glover TL, King CD, Goodin BR, Sibille KT, Bartley EJ, Herbert MS, Sotolongo A, Fessler BJ, Redden DT, Staud R, Bradley LA, Fillingim RB. Age and race effects on pain sensitivity and modulation among middle-aged and older adults. *J Pain*. 2013 Nov 13. [Epub ahead of print] **NIHMSID #565148**
13. **Cruz-Almeida Y**, Fillingim RB. Can Quantitative Sensory Testing Move Us Closer to Mechanism-Based Pain Management? *Pain Med*. 2013 Sep 6. doi: 10.1111/pme.12230. [Epub ahead of print] **NIHMSID #520249**

14. **Cruz-Almeida Y**, Goodin BR, Sibille KT, Glover TL, Riley III JR, Sotolongo A, Herbert MS, King CD, Fessler BJ, Redden DT, Staud R, Bradley LA, & Fillingim RB. (in press). Racial and ethnic differences in older adults with knee osteoarthritis. *Arthritis & Rheumatology*. **NIHMSID #568521**
15. **Cruz-Almeida Y**, Black ML, Christou EA, Clark DJ. Site-specific differences in the association between plantar tactile perception and mobility function in older adults. *Frontiers in Aging Neuroscience*, 2014 Apr 11;6:68. **PMCID: PMC3990110**

D. Research Support

Ongoing Research Support

University of Florida CTSI Junior Faculty Pilot Award Cruz-Almeida (PI) 06/01/14-12/30/16
Cortico-striatal connectivity in predicting widespread pain in older adults
The overall aim of the research project is to obtain pilot data to characterize cortico-striatal connectivity in older adults with and without widespread pain and its relation to physical performance.

NIH/NIA R01AG039659-02S1 Riley (PI) 11/21/12-11/20/14
The effects of aging on experimental models of pain inhibition and facilitation
The overall aim of the research project is to characterize alterations in pain perception and endogenous pain modulation associated with aging. The specific goals of the funded supplement are to provide the training and environment for preparing the candidate (Dr. Cruz-Almeida) to transition into the field of aging.
Role: Co-Principal Investigator

Pending Research Support

NIH/NIA 1K01AG048259-01A1 Cruz-Almeida (PI) 04/01/15-03/31/20
Neuroimaging age-related changes in pain modulation
The primary goal of this award is to provide the necessary training and mentoring for Dr. Cruz-Almeida to establish an independent neuroscience research program aimed at studying the neurobiological mechanisms underlying abnormal pain modulation in older adults that may account for increased clinical pain in this population.

Completed Research Support

University of Florida-CTSI Trainee Pilot Award Cruz-Almeida (PI) 06/01/12-12/31/13
Saliva as an alternative to plasma to measure biomarkers associated with pain mechanisms
The goal of this pilot study is to delineate and quantify the standard basal and pain- evoked changes in saliva concentrations of relevant biomarkers and validate their analysis with plasma samples in the context of experimental pain stimulation across various age groups in a sample of healthy adults.

VA RR&D Office of Academic Affiliations Cruz-Almeida (PI) 09/01/10-08/31/11
Utility of thalamic metabolites and sensory testing in neuropathic pain conditions after spinal cord injury using Magnetic Resonance Spectroscopy and Quantitative Sensory Testing.
The goal of the study was to assess the diagnostic utility of thalamic biomarkers in predicting clinical pain phenotypes in persons with pain after spinal cord injury.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Ding, Mingzhou	Pruitt Family Professor
eRA COMMONS USER NAME mingzhou_ding	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Peking University, China	B.S.	1982	Astrophysics
Institute of Theoretical Physics, China	----	1982-86	Theoretical Physics
University of Maryland, College Park, MD	Ph.D.	1990	Physics

A. Personal Statement

The long-term objective of my laboratory is to understand the neural basis of cognition and its impairments by neurological and psychiatric disorders. Trained as a theoretical physicist/applied mathematician, my initial encounter with cognitive neuroscience occurred in the early 1990s when I joined the faculty of the Center for Complex Systems and Brain Sciences at Florida Atlantic University. Subsequent appointments on various NIH study sections and NSF panels have broadened my understanding of this fascinating field and made me aware of its potential in helping address cognitive impairments in brain disorders. In 2004 I joined the faculty of the J Crayton Pruitt Family Department of Biomedical Engineering at the University of Florida. My current research interests include the mechanisms of attention and emotion, function and characterization of neuronal oscillations, cognitive fatigue in aging and in Parkinson's disease, etc. We achieve our scientific goals by utilizing advanced signal processing methods to model and understand multimodal neural data, including single unit spike trains, multiunit activities, local field potentials (LFP), electroencephalogram (EEG), electrocorticogram (ECOG), functional magnetic resonance imaging (fMRI), and simultaneous EEG-fMRI.

B. Positions and Honors

Positions and Employment

1990-1995 Assistant Professor, Center for Complex Systems and Brain Sciences and Department of Mathematical Sciences, Florida Atlantic University, Boca Raton, Florida
1995-2000 Associate Professor, Center for Complex Systems and Brain Sciences and Department of Mathematical Sciences, Florida Atlantic University, Boca Raton, Florida
2000-2004 Professor, Center for Complex Systems and Brain Sciences and Department of Mathematical Sciences, Florida Atlantic University, Boca Raton, Florida
2004-present Professor, Department of Biomedical Engineering, University of Florida
2008-present J. Crayton Pruitt Family Professor, Department of Biomedical Engineering, University of Florida

Honors

1989 University of Maryland Dissertation Fellowship
1992 First Prize for Natural Sciences, Chinese Academy of Sciences
1993 State Award of Second Rank in Natural Sciences, State Council, PRC
1998 Florida Atlantic University Researcher of the Year Award
1995-1998 Member, NIMH Study Section on Cognitive Functional Neuroscience (CFN)
2002-2006 Member, NIH Study Section on Cognitive Neuroscience (COG)
2003-2005 Associate Editor, Mathematical Biosciences and Engineering
2004-2005 Editor, Physica D
2005, 2006, 2012 Member, NIMH Study Section for the Conte Center for Neuroscience Research
2008-2012 Member, NIH Study Section on Cognitive Neuroscience (COG)
2008 Fellow, American Institute for Medical and Biological Engineering (AIMBE)
2013 University of Florida Research Foundation Professorship

C. Selected Peer-reviewed Publications (from more than 130)

Most relevant to the current application)

1. Liu Y, Bengson J, Huang H, Mangun GR, and **Ding M** (2014) Top-down Modulation of Neural Activity in Anticipatory Visual Attention: Control Mechanisms Revealed by Simultaneous EEG-fMRI, *Cerebral Cortex*, in press
2. Wang C, **Ding M**, and Kluger BM (2014) Change in intraindividual variability over time as a key metric for defining performance-based cognitive fatigability, *Brain and Cognition* 85:251-258 **PMC3980793**
3. Wen X, Yao L, Liu Y, and **Ding M** (2013) Top-down regulation of default mode activity in spatial visual attention, *Journal of Neuroscience* 33:6444-6453 **PMC3670184**
4. Wen X, Yao L, Liu Y, and **Ding M** (2012) Causal interactions in attention networks predict behavioral performance, *Journal of Neuroscience* 32:1284-1292 **PMID:22279213**
5. Wen X, Mo J, and **Ding M** (2012) Exploring Resting-State Functional Connectivity with Total Interdependence, *NeuroImage* 60:1587-1595 **PMC3516187**

Additional recent publications of importance to the field

1. Brovelli A, **Ding M**, Ledberg A, Chen Y, Nakamura R, and Bressler SL (2004) Beta Oscillations in a Large-Scale Sensorimotor Cortical Network: Directional Influences Revealed by Granger Causality, *Proc. Natl. Acad. Sci.* USA 101:9849-9854 **PMC470781**
2. Shah AS, Bressler SL, Knuth KH, **Ding M**, Mehta AD, and Schroeder CE (2004) Neural Dynamics and the Fundamental Mechanisms of Event-Related Brain Potentials, *Cerebral Cortex* 14:476-483 **PMID: 15054063**
3. Dhamala M, Rangarajan G and **Ding M** (2008) Analyzing Information Flow in Brain Networks with Nonparametric Granger Causality, *NeuroImage* 41:354-362 **PMC2685256**
4. Bollimunta A, Chen Y, Schroeder CE, and **Ding M** (2008) Neuronal Mechanisms of Cortical Alpha Oscillations in Awake-behaving Macaques, *Journal of Neuroscience* 28:9976-9988 **PMC2692971**
5. Keil A, Sabatinelli D, **Ding M**, Lang PJ, Ihssen N, and Heim, S (2009) Re-entrant Modulation of Visual Cortex during Affective Processing: Evidence from Granger Causality Analysis, *Human Brain Mapping* 30:532-540 **PMC3622724**
6. Wang X and **Ding M** (2011) Relation between P300 and event-related theta-band synchronization: A single-trial analysis, *Clinical Neurophysiology* 122:916-924 **PMID:20943435**
7. Rajagovindan R and **Ding M** (2011) From prestimulus alpha oscillation to visual evoked response: An inverted U function and its attentional modulation, *Journal of Cognitive Neuroscience* 23:1379-1394 **PMID:20459310**
8. Bollimunta A, Mo J, Schroeder CE, and **Ding M** (2011) Neuronal mechanisms and attentional modulation of corticothalamic alpha oscillations, *Journal of Neuroscience* 31:4935-4943 **PMC3505610**
9. Mo J, Schroeder CE and **Ding M** (2011) Attentional modulation of alpha oscillations in macaque inferotemporal cortex, *Journal of Neuroscience* 31:878-882 **PMID:21248111**
10. Liu Y, Huang H, McGinnis M, Keil A, and **Ding M** (2012) Neural substrate of the late positive potential in emotional processing, *Journal of Neuroscience* 32:14563–14572 **PMID:23077042**

D. Ongoing Research Support

NIMH R01 MH097320 Ding/Keil (PI) 04/02/12-02/28/17
Acquisition and Extinction of Affective Bias in Perception: A Single Trial Approach
Objective: To characterize and quantify – on a trial by trial basis – the temporal evolution of neural changes in the human visual system that accompanies the acquisition and extinction of conditioned fear.

NIMH R01 MH100820 Kocsis/Ding (PI) 04/01/14-03/31/19
Spatiotemporal Network Dynamics in a Rat Model of Schizophrenia
Objective: To study the spectral structure, anatomy, physiology and pharmacology in normal rats and pharmacological rat models of schizophrenia.

NIA R21 AG044862 Ding/Kluger (PI) 09/15/14-04/30/16
Measuring Cognitive Fatigability in Older Adults
Objective: To examine the relationship between an objective measure of cognitive performance fatigability and activity levels in older adults.

NSF BCS-1439188 Ding (PI) 09/01/14–08/31/17
Mechanisms of anticipatory attention
Objective: To study the neural basis of anticipatory attention in both humans and monkeys using electrophysiology and advanced computational methods.

NIMH R01 MH094386 Lang (PI) 04/04/12-03/31/17
Anxiety, comorbidity, negative affect, and fear circuit activation
Objective: To identify the pathophysiology underlying anxiety, fear and emotional dysregulation using multimodal brain imaging.

NIMH R01 MH098078 Lang (PI) 09/12/12-05/31/17
From fear to anxious misery: Developing a defense circuit dimensional classifier
Objective: To develop classifiers for mood disorders using parameters extracted from behavior and brain imaging.

NINR R01 NR014181 Price (PI) 09/26/12-05/31/17
Neuroimaging biomarkers for post-operative cognitive decline in older adults
Objective: To develop imaging biomarkers to predict cognitive outcomes in older adults undergoing orthopedic surgery.

NINDS R01 NS076665 Marino (PI) 09/27/12-06/30/17
Characterizing and predicting drug effects on cognition
Objective: To study the adverse effects of antiepileptic drug topiramate on cognition using behavior, genetics and electrophysiological methods.

NINDS R01 NS082386 Price (PI) 09/25/13-08/31/18
White Matter Connectivity and PD Cognitive Phenotypes
Objective: To examine white matter connectivity in PD patients and develop biomarkers for different cognitive phenotypes.

NSF BCS-1344285 Poeppel (PI) 09/15/13-08/31/16
INSPIRE Track 1: Crowd-sourcing neuroscience: Neural oscillations and human social dynamics
Objective: To study the neural basis of interpersonal communication using electrophysiology and advanced computational approaches.

NSF RX4235406 Wu (PI) 09/07/13-02/06/15
Brain activity maps of novelty detection
Objective: To study the neural basis of novelty detection using multi-modal neuroimaging and advanced computational approaches.

Completed Research Support

NIMH R01 MH060358 Schroeder (PI) 09/29/09-05/31/14
Neuronal Oscillations as Instruments for Sensory Selection
Objective: To identify the mechanistic contributions of neuronal oscillations to sensory processing.

NIMH R01 MH079388 Ding (PI) 07/01/07-06/30/13
Top-down Control of Attention
Objective: To investigate the role of oscillatory neural activity in implementing attentional control in the absence of sensory stimulation.

NIMH R21 MH087777 Kocsis (PI) 07/01/10-05/31/13
Information Flow in the Limbic Theta Circuit Revealed by Granger Causality
Objective: To investigate the mechanisms of theta oscillations in the rat limbic system.

NIMH R21 MH087275 Schroeder/Ding (PI) 04/01/10-12/31/12
Attentional Modulation of Neuronal Communication
Objective: To investigate the mechanisms of attentional enhancement of neuronal information transmission

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Vonetta M. Dotson	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) dotsonv	

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)*	MM/YY	FIELD OF STUDY
St. Mary's University	B.A.	5/99	Psychology
University of Florida	M.S., Ph.D.	5/02, 8/06	Psychology (Clinical)
James A. Haley Veterans Hospital	N/A	7/06-8/06	Predoctoral Internship
NIA Intramural Research Program	Postdoctoral	8/06-7/09	Cognitive Neuroscience of Aging and Depression

A. Personal Statement

Vonetta Dotson is an Assistant Professor in the Department of Clinical and Health Psychology (CHP) at the University of Florida, with a joint appointment in the Department of Neuroscience at the University of Florida. She is also a Claude C. Pepper scholar. She received her Ph.D. from CHP in 2006 with a specialization in neuropsychology and a certificate in gerontology. She completed her postdoctoral training in the Laboratory of Personality and Cognition in the National Institute on Aging Intramural Research Program under the mentorship of Drs. Susan Resnick and Alan Zonderman. Her research focuses on studying the interaction of psychological disorders such as depression with cognitive and brain aging using both neuroimaging and behavioral techniques. Her more recent work focuses on the impact of aerobic exercise on depression-related cognitive and brain changes in older adults.

B. Position and Honors

Positions

2006-2009 Postdoctoral Fellow, Laboratory of Personality and Cognition, National Institute on Aging Intramural Research Program, Baltimore, MD

8/2009-present Assistant Professor, Department of Clinical and Health Psychology, University of Florida, Gainesville, FL
Affiliate Faculty, Department of Neuroscience, University of Florida, Gainesville, FL

Honors

1997 ACCD Foundation Scholars Award
1997-1999 Dean's List, St. Mary's University
1998-1999 The National Dean's List
2000-2004 University of Florida Graduate Minority Fellowship
2003-2005 University of Florida Institute on Aging Trainee
2004-2005 National Institute on Aging funded Predoctoral Fellow
2004 Recipient of National Institute on Aging Technical Assistance Workshop travel fellowship
2005 Accepted into the Society for Neuroscience's Neuroscience Scholars Program
2006 Accepted to attend the American Psychological Association's Advanced Training Institute on Functional Magnetic Resonance Imaging
2006 Recipient of the Institute for Learning in Retirement Graduate Aging Research Award
2007 Accepted to attend the American Psychological Association's Advanced Training Institute on Structural Equation Modeling for Longitudinal Research
2007 Recipient of National Institute on Aging Summer Institute on Aging Research travel fellowship
2010 Claude D. Pepper Affiliated Scholar
2012-present Claude D. Pepper Scholar

Licensure: Licensed psychologist, State of Florida, License No. PY 8055

Professional Memberships: Society for Neuroscience, International Neuropsychological Society, American Psychological Association

C. Selected Peer-reviewed Publications

Peer-reviewed publications or manuscripts in press (in chronological order)

1. Perlstein, W.M., Larson, M.J., **Dotson, V.M.**, & Kelly, G.K. (2006). Temporal dissociation of components of cognitive control dysfunction in severe TBI: ERPs and the cued-Stroop task. *Neuropsychologia*, 44(2), 260-274. **PMID: 15979655**
2. Larson, M.J., Perlstein, W.M., Stigge-Kaufmann, D., Kelly, G.K., & **Dotson, V.M.** (2006). Affective context induced modulation of the error-related negativity. *Neuroreport*, 17(3), 329-33. **PMID: 16462607**
3. **Dotson, V.M.**, Singletary, F.S., Fuller, R., Koehler, S., Bacon Moore, A., Rothi, L.J.G., & Crosson, B. (2008). Treatment of word-finding deficits in fluent aphasia through the manipulation of spatial attention: Preliminary findings. *Aphasiology*, 22(1), 103–113.
4. **Dotson, V.M.**, Schinka, J.A., Brown, L, Borenstein, A.R., & Mortimer, J.A. (2008). Characteristics of the Florida Cognitive Activities Scale in older African Americans. *Assessment*, 15(1), 72-77. **PMID: 18258733**
5. **Dotson, V.M.**, Resnick, S.M., & Zonderman, A.B. (2008). Differential Association of Baseline, Concurrent, and Chronic Depressive Symptoms with Cognitive Decline in Older Adults. *American Journal of Geriatric Psychiatry*, 16, 318-330. **PMID: 18378557**
6. **Dotson, V.M.**, Kitner-Triolo, M., Evans, M.K., & Zonderman, A.B. (2008). Literacy-based normative data for low socioeconomic status African Americans. *The Clinical Neuropsychologist*, 22, 989–1017. **PMID: 18609322**
7. Pedraza, O., **Dotson, V.M.**, Willis, F.B., Graff-Radford, N.R., and Lucas, J.A. (2009). Internal Consistency and Test-Retest Reliability of the Geriatric Depression Scale-Short Form in African American Older Adults. *Journal of Psychopathology and Behavioral Assessment*, 31(4), 412-416. **PMID: 20161488**
8. **Dotson, V.M.**, Kitner-Triolo, M., Evans, M.K., & Zonderman, A.B. (2009). Effects of Race and Socioeconomic Status on the Relative Influence of Education and Literacy on Cognitive Functioning. *JINS*, 15, 580-589. **PMID: 19573276**
9. **Dotson, V.M.**, Beason-Held, L., Kraut, M.A., & Resnick, S.M. (2009). Longitudinal Study of Chronic Depressive Symptoms and Regional Cerebral Blood Flow in Older Men and Women. *International Journal of Geriatric Psychiatry*, 24(8), 809-19. **PMID: 19484709**
10. **Dotson, V.M.**, Davatzikos, C., Kraut, M.A., & Resnick, S.M. (2009). Depressive Symptoms and Brain Volumes in Older Adults: A Longitudinal MRI Study. *Journal of Psychiatry and Neuroscience*, 34(5), 367-375. **PMID: 19721847**
11. **Dotson, V.M.**, Zonderman, A.B., Davatzikos, C., Kraut, M.A., & Resnick, S.M. (2009). Frontal Atrophy and Immediate Memory Deficits in Older Adults with a History of Elevated Depressive Symptoms. *Brain Imaging and Behavior*, 3, 358–369. **PMID: 20161651**
12. **Dotson, V.M.**, Baydoun, M.A., & Zonderman, A.B. (2010). Recurrent depressive symptoms and the incidence of dementia and MCI. *Neurology*, 75, 27-34. **PMID: 20603482**
13. Sutin, A. R., Beason-Held, L. L., **Dotson, V. M.**, Resnick, S. M., & Costa, P. T. (2010). The neural correlates of neuroticism differ by sex and prospectively mediate depressive symptoms among older women. *Journal of Affective Disorders*, 127, 241-7. **PMID: 20599276**
14. Goveas, J.S., Espeland, M.A., Hogan, P., **Dotson, V.**, Tarima, S., Coker, L.H., Ockene, J., Brunner, R., Woods, N.F., Wassertheil-Smoller, S., Kotchen, J.M., Resnick, S. (2011). Depressive symptoms, brain volumes and subclinical cerebrovascular disease in postmenopausal women: the Women's Health Initiative MRI Study. *Journal of Affective Disorders*, 132, 275–284. **PMID: 21349587**
15. **Dotson, V.M.**, Zonderman, A.B., Kraut, M.A., & Resnick, S.M. (2013). Temporal Relationships between Depressive Symptoms and White Matter Hyperintensities in Older Men and Women. *International Journal of Geriatric Psychiatry*, 28, 66–74. DOI: 10.1002/gps.3791.
16. **Dotson, V.M.**, Sozda, C.N., Marsiske, M., & Perlstein, W.M. (2013). Within-session Practice Eliminates Age Differences in Cognitive Control. *Aging, Neuropsychology and Cognition: A Journal on Normal and Dysfunctional Development*, 20 (5), 522-531. DOI:10.108 0/13825585.2012.736469.
17. Kirton, J. W., Resnick, S. M., Davatzikos, C. Kraut, M. A. & **Dotson, V. M.** (2013). Depressive Symptoms, Symptom Dimensions and White Matter Lesion Volume in Older Adults: A Longitudinal Study. *American Journal of Geriatric Psychiatry*. DOI: 10.1016/j.jagp.2013.10.005.
18. **Dotson, V.M.**, Szymkowicz, S.M., Kirton, J.W., McLaren, M.E., Green, M., & Rohani, J.Y. (2014). Unique and interactive effect of anxiety and depressive symptoms on cognitive and brain function in young and older adults. *Journal of Depression and Anxiety*. DOI: doi: 10.4172/2167-1044.S1-003
19. **Dotson, V.M.**, Green, M.L., Kirton, J.W., Szymkowicz , S.M., Sozda, C.N., Perlstein, W.M., Anton, S.D., & Manini, T.M. (in press). Adult age differences in fMRI activity during memory encoding. *Psychology & Aging*.
20. Bryant, V.E., Whitehead, N.E., Burrell, L.E., **Dotson, V.M.**, Cook, R.L., & Cohen, R.A. (provisional accepance). Depression and apathy among people living with HIV: substance use and cognitive performance differences and the implications for treatment of HIV Associated Neurocognitive Disorders. *AIDS and Behavior*.

D. Research Support

Research Support

R01 DA942367-03 Hunt (PI) 09/01/08-08/31/13

Health trajectories and behavioral interventions among older substance abusers

The goal of this study is to compare the effects of two substance abuse interventions on health outcomes in an urban population of older opiate addicts.

Role: PI

Completed Research Support

5T32AG020499-07 Marsiske (PI) 05/01/03-04/30/08 National Institute on Aging

Physical, Cognitive and Mental Health in Social Context

The major goals of this project were to train pre-doctoral researchers in the behavioral theories, methodologies and analyses needed to address questions of health, independence and functioning in older adults.

Role: Research Fellow/Trainee (2004-2005)

R03 AG024539-01 Dotson (PI) 09/30/04-06/30/06 National Institute on Aging

Double Jeopardy: Cognitive Decline in Depression and Aging

The major goals of this project were to determine whether the combined effect of aging and depression were associated with additive or synergistic effects on executive functioning and brain activity measured by event-related potentials.

Role: PI

No number assigned Dotson (PI) 03/01/11-8/31/13 McKnight Brain Research Foundation

Effect of Exercise on Memory in Geriatric Depression: An fMRI Pilot Study

The major goals of this project were to determine whether aerobic exercise leads to improved memory and changes in memory-related brain activity in older depressed adults.

Role: PI

U01 AG022376 Pahor (PI) 2/01/12-11/30/13 National Institute on Aging

Diversity Supplement to the Lifestyle Interventions and Independence for Elders (LIFE) Study (PI)

The major goals of this project were to examine the impact of physical activity on depressive symptoms in older adults and to determine if genetic variation moderated the effect.

Role: PI for diversity supplement

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Natalie C. Ebner	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) NATALIE.EBNER	

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)*	MM/YY	FIELD OF STUDY
Free University Berlin, Berlin, Germany	B.A.	04/1998	Psychology
Free University Berlin, Berlin, Germany	M.A.	03/2001	Psychology
Free University Berlin & Max Planck Institute for Human Development, Berlin, Germany	Ph.D.	04/2005	Psychology
Max Planck Institute for Human Development, Berlin, Germany	Postdoctoral	06/2007	Psychology
Yale University, New Haven, USA	Postdoctoral	07/2010	Psychology

A. Personal Statement

My laboratory primarily focuses on cognitive, social, and affective experimental aging research using behavioral, eye-tracking, and neuroimaging methods. I have a broad background in psychology, with specific training and expertise in research areas that are central for this application as well as its future extensions: Lifespan development and cognitive and socioemotional aging, behavioral, eye-tracking and brain imaging (fMRI) experimental research with adult samples, and modeling approaches (e.g., multi-level modeling, structural equation modeling). For example, as a pre- and postdoctoral fellow at the Free University Berlin and the Max Planck Institute for Human Development, I supervised research on age-group differences in cognition and emotion, and motivation using cognitive-behavioral measures. As a postdoctoral fellow and later as Associate Research Scientist at Yale University and as faculty at UF, I expanded my research to examine neuropsychological changes associated with cognition-motivation-emotion interactions in adulthood using fMRI and eye tracking. Currently, in addition to my primary appointment in the Department of Psychology at UF, I am scholar of the UF Pepper Center Research Career Development Core and adjunct faculty in the Center for Cognitive Aging and Memory (CAM) in the Aging Department at the College of Medicine at UF. Both of these additional appointments offer various educational opportunities and institutional support tailored towards junior faculty.

I successfully coordinated various projects, collaborated with other researchers, and produced several peer-reviewed publications from each project. As a result of these previous experiences, I am aware of the importance of constructing a realistic research plan, timeline, and budget, and working closely with collaborators and project members towards the shared goal.

In sum, combining the skills and expertise of my collaborator with my own research training and background, our team is optimally equipped to successfully carry out the work. My prior experiences have prepared me well to lead the human data collection of the proposed project, and I have demonstrated successful and productive research conduct in an area of high relevance for the aging population and health.

B. Positions and Honors

Positions

2001-2005	Predoctoral Fellow, Free University Berlin & Max Planck Institute for Human Development, Berlin, Germany
2005-2007	Postdoctoral Fellow, Max Planck Institute for Human Development, Berlin, Germany
2007-2010	Postdoctoral Fellow, Department of Psychology, Yale University, New Haven, USA
2010-2011	Associate Research Scientist, Department of Psychology, Yale University, New Haven, USA
08/2011-	Assistant Professor, Department of Psychology, University of Florida, Gainesville, USA
06/2013-	Adjunct Faculty at Cognitive Aging and Memory Clinical Translational Research Program; CAM-CTRP, University of Florida, Gainesville, USA

Other Experience and Professional Memberships

2000- Member, German Psychological Association
2003- Member, American Psychological Association
2003- Member, Society for Personality and Social Psychology
2008- Member, Association for Psychological Science
2008- Member, Social and Affective Neuroscience Society
2009 Reviewer for Retirement Research Foundation Doctoral Dissertation Award in the Psychology of Aging (American Psychological Association)
2010- Member, Society for Social Neuroscience
2012- Member, Cognitive Neuroscience Society
2012- Reviewer for the Swiss National Fond
2012- Early Career Reviewer (ECR) at the Center for Scientific Review (CSR), National Institute of Health
2014- Member, Society for Affective Science

Awards

2003 Student Research Award, American Psychological Association (Division 20)
2004 Graduate Student Poster Award, Society for Personality and Social Psychology
2006 Heinz-Heckhausen-Jungwissenschaftlerpreis (Young Research Scientist Award), German Psychological Association
2014 International Max Planck Research School on the Life Course (LIFE) Outstanding Alumni Award

C. Selected Peer-reviewed Publications (Selected from 94 peer-reviewed publications, * Senior / Corresponding author)

Most relevant to the current application (In chronological order)

1. **Ebner, N. C.**, & Fischer, H. (2014a). Studying the various facets of emotional aging: Introduction to the current Frontiers research topic. *Frontiers in Emotion Science*. DOI: 10.3389/fpsyg.2014.01007
2. **Ebner, N. C.**, & Fischer, H. (2014b). Emotion and aging: Recent evidence from brain and behavior. Invited paper to introduce special issue. *Frontiers in Emotion Science*.
3. Voelkle, M. C., **Ebner, N. C.**, Lindenberger, U., & Riediger, M. (2014). A note on age differences in mood-congruent versus mood-incongruent information processing in faces. *Frontiers in Emotion Science*.
4. **Ebner, N. C.**, Johnson, M. R., Rieckmann, A., Durbin, K., Johnson, M. K., & Fischer, H. (2013). Processing own-age vs. other-age faces: Neuro-behavioral correlates and effects of emotion. *NeuroImage*. DOI: 10.1016/j.neuroimage.2013.04.029. **PMCID: PMC3684564**
5. **Ebner, N. C.**, Maura, G., MacDonald, K., Westberg, L., & Fischer, H. (2013). Oxytocin and socioemotional aging – Current knowledge and future trends. [Research topic] *Frontiers in Human Neuroscience*, 7(487), 1-14. DOI: 10.3389/fnhum.2013.00487. **PMCID: PMC3755210**
6. Voelkle, M. C., **Ebner, N. C.**, Lindenberger, U., & Riediger, M. (2013). Here we go again: Anticipatory and reactive mood responses to recurring unpleasant situations throughout adulthood. *Emotion*, 13(3), 424-433. DOI: 10.1037/a0031351
7. **Ebner, N. C.**, Johnson, M. K., & Fischer, H. (2012). Neural mechanisms of reading facial emotions in young and older adults. *Frontiers in Psychology*, 3(223), 1-19. DOI: 10.3389/fpsyg.2012.00223. **PMCID: PMC3394436**
8. **Ebner, N. C.**, Gluth, S., Johnson, M. R., Raye, C. L., Mitchell, K. M., & Johnson, M. K. (2011). Medial prefrontal cortex activity when thinking about others depends on their age. [Special issue] *Neurocase*, 17, 260-269. DOI:10.1080/13554794.2010.536953. **NIHMS ID: NIHMS251257 PMCID: PMC3322673**
9. **Ebner, N. C.**, He, Y., & Johnson, M. K. (2011). Age and emotion affect how we look at a face: Visual scan patterns differ for own-age versus other-age emotional faces. [Special section] *Cognition & Emotion*. Advance online publication. DOI:10.1080/02699931.2010.540817. **NIHMS ID: NIHMS303333 PMCID: PMC3339265**
10. Riediger, M., Voelkle, M., **Ebner, N. C.**, & Lindenberger, U. (2011). Beyond "happy, angry, or sad?": Age-of-poser and Age-of-rater effects on multi-dimensional emotion perception. [Special section] Cognition & Emotion. Advance online publication. DOI:10.1080/02699931.2010.540812
11. **Ebner, N. C.**, & Johnson, M. K. (2010). Age-group differences in interference from young and older emotional faces. *Cognition & Emotion*, 24, 1095-1116. DOI:10.1080/02699930903128395. **PMCID: PMC3030265**
12. **Ebner, N. C.**, Riediger, M., & Lindenberger, U. (2010). FACES—A database of facial expressions in young, middle-aged, and older women and men: Development and validation. *Behavior Research Methods*, 42, 351-362. DOI:10.3758/BRM.42.1.351. **PMID: 20160315**
13. **Ebner, N. C.**, & Johnson, M. K. (2009). Young and older emotional faces: Are there age-group differences in expression identification and memory? *Emotion*, 9, 329-339. DOI: 10.1037/a0015179. **PMCID: PMC2859895**

14. Mitchell, K. J., Raye, C. L., **Ebner, N. C.**, Tubridy, S. M., Frankel, H., & Johnson, M. K. (2009). Age-group differences in medial cortex activity associated with thinking about self-relevant agendas. *Psychology and Aging*, 24, 438-449. DOI:10.1037/a0015181. **PMCID: PMC2859896**

Additional recent publications of importance to the field (In chronological order)

1. Lovén, J., Svärd, J., **Ebner, N. C.**, Herlitz, A., & Fischer, H., (2013). Face gender modulates women's brain activity during face encoding. *Social Cognitive and Affective Neuroscience*. [Epub ahead of print]
2. **Ebner, N. C.**, He, Y., Fichtenholtz, H. M., McCarthy, G., & Johnson, M. K. (2010). Electrophysiological correlates of processing faces of younger and older individuals. Social Cognitive and Affective Neuroscience. *Advance online publication*. DOI:10.1093/scan/nsq074. **PMCID: PMC3150862**
3. **Ebner, N. C.** (2008). Age of face matters: Age-group differences in ratings for young and old faces. *Behavior Research Methods*, 40, 130-136. DOI:10.3758/BRM.40.1.130. **PMID: 18411535**
4. **Ebner, N. C.**, Freund, A. M., & Baltes, P. B. (2006). Developmental changes in personal goal orientation from young to late adulthood: From striving for gains to maintenance and prevention of losses. *Psychology and Aging*, 21, 664-678. DOI:10.1037/0882-7974.21.4.664. **PMID: 17201488**

D. Research Support

Ongoing Research Support

National Science Foundation SaTC EAGERs NSF 13-037; Ebner (PI; co-PI: Dr. Daniela Oliveira)
09/01/14-08/31/2016
Age-Targeted Automated Security Cueing Against Web-Based Social Engineering Attacks
The goal of this project is to develop and validate an open-source browser extension that provides visual security cues in an age-targeted fashion to protect older adults from web-based social engineering attacks during their everyday internet use.

Scientific Research Network on Decision Neuroscience and Aging (SRNDNA; sponsored by NIH/NIA; Ebner (PI; co-PI: Dr. Steve Chang) 09/01/14-03/31/2015
The Role of Oxytocin in Prosocial Decision Making in Aging Across Humans and Monkeys
The goal of this project is to compare the effects of the neuropeptide oxytocin on social preferences and altruism in young and older primates and humans.

University of Florida Center for Cognitive Aging and Memory & Claude D. Pepper Older Americans Independence Center (sponsor: NIH/NIA); Ebner (PI) 08/01/14-07/31/15
Neurofeedback and Aging
The goal of this project is to examine trainability of volitional control over brain regions associated with emotion processing via use of neurofeedback and subsequent benefits for emotion perception in aging.

NIH/NIAAA (1R01AA022456-01); Ebner (Co-I; PI: Dr. Sara Jo Nixon) 10/01/13-09/01/17
Neurobehavioral and Emotional Deficits in Male and Female Alcoholics
The goal of this project is to examine gender differences in deficits in cognitive and emotional functioning in alcoholics.

University of Florida Claude D. Pepper Older Americans Independence Center (sponsor: NIH/NIA); Ebner (PI) 08/01/13-07/01/15
Effects of Oxytocin on Physical and Cognitive Functioning in the Elders
The goal of clinical trial is to examine the effects of intranasal oxytocin administration on cognition, health, and socioemotional functioning in aging over time.

University of Florida University of Florida McKnight Brain Institute; Ebner (Co-I; PI: Dr. Adam Woods)
11/01/13
Acquiring Human Whole-Brain Phosphorous Magnetic Resonance Imaging Capabilities in the McKnight Brain Institute
The goal of this project is to implement a system for Human Whole-Brain Phosphorous Magnetic Resonance Imaging

Scientific Research Network on Decision Neuroscience and Aging (SRNDNA) Pilot Project Award (sponsor: NIH/NIA); Ebner (PI) 08/01/13-7/31/14
Effects of oxytocin on health-related decision making in aging
The goal of this project is to determine neuroendocrine and socio-behavioral effects of oxytocin on health-related decision making in aging.

Completed Research Support

University of Florida Clinical and Translational Science Institute (CTSI) Pilot Project Award (sponsor: NIH/NCATS Clinical and Translational Science Award to the University of Florida UL1 TR000064); Ebner (PI) 01/01/13-12/31/13
Neuro-behavioral effects of oxytocin on decisions of trust in aging
The goal of this project was to determine neuroendocrine and socio-behavioral effects of oxytocin on decisions of trust in aging.

Department of Psychology 2011 Michael L. & Judith D. Woodruff Research Competition Gant; Ebner (PI) 08/15/11-06/02/1
Neural mechanisms of social memory in young and older adults
The goal of this project was to determine the neural correlates for older adults' increased schema reliance and to examine whether self-relevance of information counteracts memory biases arising from schemas.

DFG EB 436/1-1 (sponsor: German Science Foundation); Fellowship; Ebner (PI) 07/01/07-06/30/10
Motivational orientation in adulthood
The goal of this project was to assess behavioral and neural correlates of age-related differences in processing motivationally and socially relevant information.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Falchook, Adam Dov	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) ADAM15	

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)*	MM/YY	FIELD OF STUDY
University of Florida	B. Music.	05/02	Music
Mount Sinai School of Medicine	M.D.	05/06	Medicine
University of Florida	Internship	06/07	Medicine
University of Florida	Residency	06/10	Neurology (Chief resident 7/09-6/10)
University of Florida	Fellowship	06/11	Behavioral Neurology

A. Personal statement

As a neurologist with specialization in behavioral neurology, my research focuses on how cognitive-motor control and attention are affected by healthy aging and neurological disease. Cognitive-motor disorders include impairments of praxis (how to perform learned skill movements and deft fine finger movements), action-intentional systems (when to start, continue, stop, and inhibit actions) and bimanual coordination. I completed a fellowship with Dr. Kenneth M. Heilman, and with his ongoing mentorship, in July 2013 I began a Career Development Award 1 from the Department of Veterans Affairs Office of Rehabilitation Research and Development. The goal of this study, "Motor Impairments after Traumatic Brain Injury: Effects of Callosal Disconnection," is to learn how interhemispheric disconnection from damage to the corpus callosum induces cognitive-motor impairments in people with a history of traumatic brain injury. Our research has demonstrated that cognitive-motor signs of interhemispheric disconnection are common after severe traumatic brain injury, and continued studies are planned to understand the mechanisms and rehabilitation for these cognitive-motor impairments. I am also performing research to learn how cognitive-motor networks change with healthy aging. Preliminary results from this ongoing research suggest that cognitive-motor changes with aging may be related to interhemispheric disconnection. In addition to my work as a researcher, I care for patients in the University of Florida Cognitive and Memory Disorders Clinic. 90% of my time is devoted to research, including an 8/8 research appointment at the Malcom Randall VAMC, 8% is devoted to patient care, and 2% is devoted to education.

B. Positions and Honors

Positions and Employment

2006-2007	University of Florida, Dept of Medicine, Director: N. Lawrence Edwards MD, Intern
2007-2010	University of Florida, Dept of Neurology, Director: Glen R. Finney MD, Resident
2009-2010	University of Florida, Dept of Neurology, Director: Glen R. Finney MD, Chief Resident
2010-2011	University of Florida, Dept of Neurology, Director: Kenneth M. Heilman MD, Behavioral Neurology Fellow
2011-2012	University of Florida, Dept of Neurology, Chairman: Tetsuo Ashizawa MD, Visiting Clinical Lecturer
2012-present	University of Florida, Dept of Neurology, Chairman: Tetsuo Ashizawa MD, Assistant Professor
2013-present	Gainesville Veterans Affairs Medical Center Research Service and Brain Rehabilitation Research Center, Director: Janis Daly PhD, Health Science Specialist

Honors

2003	Mount Sinai Alumni Summer Research Fellowship
2007, 2009	Customer Service is Key Award, Shands Hospital
2008	Excellence in Medical Education Award

2008 Department of Neurology Resident Teacher of the Year
2008, 2009, 2010 Program Director's Award for Academic Excellence
2009 Chairman's Award for Excellence in Patient Care
2013 Department of Veterans Affairs Outstanding Rating Certificate

Advisory

2012-3 Invited to review scientific abstracts for the 2013 annual meeting of the American Academy of Neurology
2013 Invited manuscript reviewer, Brain and Cognition
2014-5 Invited to review scientific abstracts for the 2015 annual meeting of the American Academy of Neurology

Other Experience and Professional Memberships

2007-present Member of the American Academy of Neurology
2009 Elected to Alpha Omega Alpha
2010-present Diplomat, American Board of Psychiatry and Neurology
2010-present Society for Cognitive and Behavioral Neurology
2011 Co-mentor for a student in the University of Florida University Scholars Program
2012 Co-mentor for a student in the American Academy of Neurology Medical Student Summer Research Scholarship Program

C. Selected Peer-reviewed Publications

Papers

1. **Falchook AD**, Salazar L, Neal D, Kesayan T, Williamson JB, Malaty IA, McFarland NR, Okun MS, Rodriguez RL, Wagle Shukla A, Heilman KM. Global attentional neglect of segmented lines in Parkinson's disease. *Neurocase*, 2014;1-8 [Epub ahead of print].
2. Pundik S, **Falchook AD**, McCabe J, Litinas K, Daly JJ. Functional Brain Correlates of Upper Limb Spasticity and Its Mitigation following Rehabilitation in Chronic Stroke Survivors. Stroke Res Treat, 2014; 2014:306325 [Epub ahead of print]. doi: 10.1155/2014/306325. **PMCID: PMC4101928**.
3. **Falchook AD**, Heilman KM, Finney GR, Gonzalez-Rothi LJ, Nadeau SE. Neuroplasticity, Neurotransmitters, and New Directions for Treatment of Anomia in Alzheimer Disease, Aphasiology, 2014; 28: 219-235. 4. Falchook AD, Burtis DB, Acosta LM, Salazar L, Hedna VS, Khanna AY, Heilman KM. Praxis and Writing in a Right-Hander with Crossed Aphasia, *Neurocase*, 2014; 20: 317-27. **PMCID: PMC3732537** [Available on 2015/6/1].
5. Kabasakalian A, Kesayan T, Skidmore F, Williamson JB, **Falchook AD**, Harciarek M, Heilman KM. Hypometric Allocentric and Egocentric Distance Estimates in Parkinson's Disease, *Cognitive and Behavioral Neurology*, 2013; 26: 133-9.
6. Hedna VS, Bodhit AN, Ansari S, **Falchook AD**, Stead L, Heilman KM, Waters MF. Hemispheric differences in ischemic stroke: is left-hemisphere stroke more common? *Journal of Clinical Neurology*, 2013; 9:97-102. **PMCID: PMC3633197**.
7. **Falchook AD**, Mody MD, Srivastava AB, Williamson JB, Heilman KM. Vertical line quadrisection: "what" it represents, and who gets the upper hand. *Brain and Language*, 2013; 127: 284-8.
8. **Falchook AD**, Mayberry RI, Poizner H, Burtis DB, Doty L, Heilman KM. Sign language aphasia from a neurodegenerative disease. *Neurocase*, 2013; 19: 434-44. **PMCID: PMC3501578** [Available on 2014/10/1].
9. **Falchook AD**, Mosquera D, Finney GR, Williamson JB, Heilman KM. The Relationship between Semantic Knowledge and Conceptual Apraxia in Alzheimer's Disease. *Cognitive and Behavioral Neurology*, 2012; 25: 167-174.
10. Claunch JD, **Falchook AD**, Williamson JB, Fischler I, Jones EM, Baum JB, Heilman KM. Famous faces but not remembered spaces influence vertical line bisections. *Journal of Clinical and Experimental Neuropsychology*, 2012; 34: 919-24.
11. Suavansri K, **Falchook AD**, Williamson JB, Heilman KM. Right up there: hemispatial and hand asymmetries of altitudinal pseudoneglect. *Brain and Cognition*, 2012; 79: 216-20.
12. **Falchook AD**, Decio D, Williamson J, Okun M, Malaty I, Rodriguez R, Heilman KM. Alternate but Do Not Swim: A Test for Executive Motor Dysfunction in Parkinson Disease. *Journal of the International Neuropsychological Society*, 2011; 17:1-7.
13. Decker DA, **Falchook AD**, Yachnis AT, Waters MF. Radiographic and pathologic findings in a atypical brainstem variant of reversible posterior leukoencephalopathy syndrome. *Neurologist*, 2009; 15:364-6.
14. **Falchook AD**. On Being a Doctor: The name of a champion. *Annals of Internal Medicine*, 2009; 150: 734.

D. Research Support

Ongoing Research Support

RR&D N0961-M Falchook (PI); Heilman (mentor) 07/28/13 – 07/27/15
Department of Veterans Affairs Office of Rehabilitation Research and Development
Motor Impairments in Traumatic Brain Injury: Effects of Callosal Disconnection
This research support allows us to learn about specific types of upper extremity cognitive-motor impairment that are predicted to result from damage to the corpus callosum induced by traumatic brain injury.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Glen R. Finney, M.D.	POSITION TITLE Assistant Professor of Neurology
eRA COMMONS USER NAME (credential, e.g., agency login)	

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)*	MM/YY	FIELD OF STUDY
Florida State University, Tallahassee, FL	B.S.	1989-1993	Biological Sciences
Temple University SOM, Philadelphia, PA	M.D.	1995-1999	Medicine

A. Personal Statement

As a fellowship trained behavioral neurologist I have a fascination with higher cortical function and brain/behavior relationships. My areas of research interest include early diagnosis and differentiation between different forms of neurodegenerative diseases impacting cognitive functions, as well as the brain-behavior relationship between creativity and the brain, including creativity in the setting of neurologic disease. My clinical practice is devoted to those suffering from memory and cognitive disorders. These make me eminently suitable for the role of PI in the project investigating IP6 in Alzheimer's disease. I fully anticipate that the results of this initial human study, demarcating the safety parameters of IP6 in the elderly and assessing effect by our measures in the study, will be of vital use as preliminary data for a full grant application to the NIH for a clinical phase II study of this substance. It will also result in a paper in the dementia field, my chosen clinical research area of interest. Both future grant support and important first person authorship will count in my favor for career advancement and promotion, when coupled with my other activities and achievements. This will be an important step in demonstrating my development into an independent researcher. This is an already produced product and we are not seeking further commercial development.

B. Positions and Honors

Positions and Employment

1999-2000	Internal Medicine Internship, Abington Memorial Hospital, Abington, PA
2000-2003	Neurology Residency, University of Miami/Jackson Memorial Hospital, Miami, FL
2003-2005	Behavioral Neurology Fellowship, Malcom Randall VAMC & University of Florida, Gainesville, FL
2005-Present	Assistant Professor, Memory and Cognitive Disorders Program University of Florida Department of Neurology, Gainesville, FL
2008-2009	Associate Residency Director, University of Florida Department of Neurology

Awards/Honors

2001	Excellence in Medical Student Education Award, University of Miami Department of Neurology
2002-2003	Teaching Resident Coordinator for Neurology Clerkship, University of Miami Department of Neurology
2003-2004	Course Director and Lecturer, Center for Neuropsychological Studies Seminar Series, University of Florida
2004	Donald M. Palatucci Advocacy Leadership Fellow, American Academy of Neurology
2004	Representative for University of Florida Memory Disorders Clinic, Third Annual Florida Alzheimer's Summit
2004	Behavioral Neurology Section Director, Clinical Neuroscience Presentation Series for Medical Students, University of Florida
2004	Course Director and Lecturer, 30th Annual Course in Behavioral Neurology & Neuropsychology: Florida Society of Neurology & Orlando Regional Healthcare System
2005	Donald M. Palatucci Advocacy Leadership Mentor, American Academy of Neurology
2005	Member of the Legislative Affairs Committee for the American Academy of Neurology
2005-2008	Member of the Board of Directors for the Florida Society of Neurology

2006-Present	Florida Society of Neurology Liaison for the Florida Neuroalliance Working Group
2007	Donald M. Palatucci Advocacy Leadership Advisor, American Academy of Neurology
2007-2008	Florida Society of Neurology Treasurer
2007-Present	Program Director, Florida Society of Neurology Annual Course in Behavioral Neurology & Neuropsychology
2008	Program Director, Practice Colloquium: Healthcare at a Crossroads: A Perspective on the Current Climate and How the 2008 Elections Will Impact You, American Academy of Neurology 60th Annual Meeting
2008	Clinical Teacher of the Year, University of Florida Department of Neurology
2008-2009	Associate Program Director Neurology Residency Program, University of Florida Department of Neurology
2008-2011	Florida Society of Neurology Secretary
2008-2010	Resident as Teacher Committee, University of Florida College of Medicine
2009-Present	AANPA BrainPAC Executive Committee
2009-2011	AAN.com Advocacy Editor
2009-2013	Residency Program Director, University of Florida Department of Neurology
2009-2013	University of Florida Graduate Medical Education Committee
2010-2011	Chair, Member Relations Workgroup, AAN Government Relations Committee
2010	Graduate, University of Florida Master Educator Fellowship Program
2010-2011	Florida Society of Neurology delegate to Florida Medical Association House of Delegates
2010-2012	Florida Medical Association Specialty Society Section Governing Council
2010-2012	Florida Medical Association Board of Governors
2010	Master of Ceremonies, AAN State Society Leadership Roundtable
2010-Present	Neurology Clerkship Director, University of Florida Department of Neurology
2010-2013	Organizer for Course Track, Introduction to Clinical Neurology, University of Florida COM
2011-Present	Division Chief, Behavioral Neurology, University of Florida Department of Neurology
2011	Exemplary Teacher, University of Florida College of Medicine
2011-2013	President-Elect, Florida Society of Neurology
2012	Florida Medical Association Vice-Chair, Council on Medical Education
2012-Present	Member, Florida Medical Association Task Force on the Future
2012	Nominated for American Academy of Neurology Program Director Award
2012	Finalist for American Academy of Neurology Clerkship Director Award
2013-Present	Florida Medical Association Chair, Council on Medical Education and Science
2013-Present	American Academy of Neurology Cost of Care Work Group
2013-Present	Clinical Lead, University of Florida College of Medicine Neuroscience Course
2013	Finalist for American Academy of Neurology Clerkship Director Award
2013-Present	Chair, University of Florida Neurology Residency Clinical Competency Committee
2013-Present	President, Florida Society of Neurology
2013-Present	Fellow of the Florida Society of Neurology
2014-Present	Member, State University System of Florida Board of Governors' Health Initiatives Committee Advisory Group
2014-Present	Counselor, American Academy of Neurology Behavioral Section and Behavioral and Cognitive Neurology Society
2014-Present	Member, Behavioral Neurology Division Search Committee, University of Florida Department of Neurology

C. Selected Peer-reviewed Publications and Presentations

1. Rivera-Gutierrez, D., Kopper, R., Kleinsmith, A., Cendan, J., **Finney, G.**, Lok B. "Exploring Gender Biases with Virtual Patients for High Stakes Interpersonal Skills Training" 14th Intelligent Virtual Agents Conference (IVA), 27-29 August 2014, Boston.
2. **Finney GR**. Rapidly Progressive Dementia Clinical Pathological Case Discussion. University of Miami Department of Neurology Grand Rounds. May 16, 2014.
3. **Finney GR**. Neurology Advocacy Update. Consortium of Neurology Program Directors. American Academy of Neurology 66th Annual Meeting. April 27, 2014.
4. **Finney GR**, Kleinsmith A, Rivera-Gutierrez D, Borish M, Cendan J, Velazquez M, Stalvey C, Lok B. Virtual Patient Cranial Neuropathy Simulator – Preliminary Results of the UF Nerve Study. Clerkship and Program Directors Conference, American Academy of Neurology 66th Annual Meeting April 26, 2014.
5. Falchook AD, Heilman KM, **Finney GR**, Gonzalez-Rothi LJ, Nadeau SE. Neuroplasticity, Neurotransmitters, and New Directions for Treatment of Anomia in Alzheimer Disease, *Aphasiology*, 2014; 28: 219-235.
6. **Finney GR**. The Dementias. University of South Florida Department of Neurology Grand Rounds. January 17, 2014.
7. **Finney GR**. Organized Neurology. University of South Florida Department of Neurology Grand Rounds. January 17, 2014.
8. **Finney GR**. Organized Neurology. University of Florida Department of Neurology Grand Rounds. October 29, 2013.

9. Foster PS, Roosa KM, Drago V, Branch K, **Finney G**, Heilman KM. Recall of word lists is enhanced with increased spreading activation. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2013;20(5):553-66.
10. Falchook AD, Mosquera DM, **Finney GR**, Williamson JB, Heilman KM. The relationship between semantic knowledge and conceptual apraxia in Alzheimer disease. *Cogn Behav Neurol*. 2012 Dec;25(4):167-74.
11. Loring DW, Marino SE, Parfitt D, **Finney GR**, Meador KJ. Acute lorazepam effects on neurocognitive performance. *Epilepsy Behav*. 2012 Nov;25(3):329-33.
12. **Finney GR**, Martin-Schild S. Learning standardized sign-outs: Handoff help just in time! *Neurology*. 2012 Sep 4;79(10):967-8.
13. Falchook AD, Mosquera DM, **Finney GR**, Williamson JB, Heilman KM. Conceptual Apraxia in Alzheimer Disease: Impaired Mechanical Knowledge with Preserved Tool Selection Associative Knowledge. 40th Annual Meeting of the International Neuropsychological Society. February 2012. Montreal, Quebec, Canada.
14. Falchook AD, Mosquera DM, **Finney GR**, Williamson JB, Heilman KM. Conceptual Apraxia in Alzheimer Disease: Impaired Mechanical Knowledge with Preserved Tool Selection Associative Knowledge. 2012 Annual Meeting of the American Academy of Neurology. March 2012. New Orleans, LA.
15. Schuh LA, Khan MA, Harle H, Southerland AM, Hicks WJ, Falchook A, Schultz L, **Finney GR**. Pilot trial of IOM duty hour recommendations in neurology residency programs: unintended consequences. *Neurology*. 2011 Aug 30;77(9):883-7. Epub 2011 Jul 27. Erratum in: *Neurology*. 2011 Nov 1;77(18):1712.

D. Research Support

Florida Department of Elders Affairs Contract Meador (PI) 2009 - 2014
Clinical Correlates of Leukoaraiosis in Alzheimer's Disease
The goal of this study was to identify clinical symptoms and signs that correlate with the amount and location of leukoaraiosis in patients with a diagnosis of Alzheimer's disease.
Role: Co-Principal Investigator

GSK Pharmaceutical Finney (PI) 2007 - 2013
Differential Age Effects of Lorazepam on Cognitive Functions
The goal of this study is to investigate the use of computer assessment in detecting and characterizing cognitive side effects from pharmacologic interventions with lorazepam as our model drug.
Role: Site Principal Investigator

Novartis Pharmaceuticals Finney (PI) 2007 – 2011
48 week placebo controlled randomized trial of Rivastigmine 15 cm2 patch in Alzheimer's disease decliners
The goal of this study is to investigate whether increasing dose of rivastigmine provides added benefit for those that are already on standard of care treatment in the face of cognitive decline.
Role: Site Principal Investigator

National Institutes of Health Finney (PI) 2010
Present Gene polymorphisms in motor recovery from stroke
The goal of this study was to identify genetic factors that predict recovery level from strokes.
Role: Site Principal Investigator

Myriad Pharmaceuticals Finney (PI) 2008 – 2009
R-Flurbiprofen in Alzheimer's Disease
The goal of this study is to determine whether r-flurbiprofen which in vitro is known to inihibit amyloid formation would have ameliorative effects in Alzheimer's disease.
Role: Site Principal Investigator

University of Florida McKnight Brain Institute Heilman (PI) 2004 - 2006
Treatment of Motor Learning Deficits associated w/ Aging
The goal of this project is to investigate the parameters of motor learning (procedural learning) in a healthy elderly population sample versus those of younger participants.
Role: Co-Author

Behavioral Neurology Heilman (PI) 2003 - 2005
VA Associate Investigator Award
The goal of this project is to investigate the different aspects of hemispatial neglect in man that occur from insult to the brain, more specifically non-dominant hemispheric damage.
Role: Clinical Scientist

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Thomas Foster	Professor of Neuroscience
eRA COMMONS USER NAME (credential, e.g., agency login) Tom_Foster	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Arizona, Tucson AZ	BS	1981	Psychology
Bowman Gray, School of Medicine, W-S, NC	PhD	1987	Physio/Pharm
University of Colorado, Boulder CO	Postdoctoral	1991	Neurophysiology and behavior

A. Personal Statement

My research focuses on understanding brain mechanisms of aging and their relationship with age-related cognitive decline and neurodegenerative disease of aging. My long-term goal is the amelioration of memory deficits associated with aging and Alzheimer's disease. My research program utilizes a combination of behavioral characterization with biochemical, molecular, and electrophysiological techniques and treatments (behavioral, pharmacological and viral) to obtain a vertically integrated perspective on neural aging, from the molecular to the cognitive level. I have been continuously funded through NIH as a principle investigator since 1992 and my work includes 108 publications on memory mechanisms and the aging brain. We have developed a battery of behavioral tasks that are sensitive to the onset and trajectory of age-related cognitive decline. Techniques include electrophysiological methods for examining NMDAR function and protocols for next generation RNA sequencing (Ion Proton) and transcription profile analysis. Our published research demonstrates that age-related memory impairments are linked to changes in cell excitability (i.e. afterhyperpolarization), synaptic plasticity, and altered gene expression. As part of this work we are funded to examine transcriptional markers of aging in relation to hippocampal function. Other major projects in the lab examine the role of estrogen receptors in protecting against age-related cognitive decline.

B. Positions and Honors

Positions and Employment

Assistant Professor, 1991-1992 Dept. Psych. University of Connecticut
Assistant Professor, 1992-1998, Dept. Psych. University of Virginia
Associate Professor, 1998-2003, Dept. Pharmacology, University of Kentucky Medical School
Associate Professor, 2003-2006, Dept Neurosci, University of Florida
Professor 2006-present, Dept Neurosci, University of Florida

Academic Honors and Awards

National Advisory Council on Aging NIH Method to Extend Research in Time (MERIT) Award (2011-present)
McKnight Chair for Research on Aging and Memory, University of Florida 2003-present
Member of the planning Committee for the Cognitive Aging Summits I (2006) & II (2010)
Associate Editor Frontiers in Aging Neuroscience 2009-present
Member for > 10 NIH Special Emphasis Review Panels (2001-2014)
Member, NIH IFCN-7 Study Section 1999-2004
Member NIH Learning and Memory study section (7/2014-6/201
Shannon Investigators Award, 1992

C. Selected Peer-Reviewed Publications (selected 15 most relevant or recent of 108 total)

1. Guidi, M., Kumar, A., Rani, A., **Foster, TC**. Assessing the emergence and reliability of cognitive decline over the life span in Fisher 344 rats using the spatial water maze. *Front Aging Neurosci*, 2014 6:2. **PMID:3896816**.
2. Lee WH, Kumar A, Rani A, **Foster TC**. Role of antioxidant enzymes in redox regulation of N-methyl-Daspartate receptor function and memory in middle-aged rats. *Neurobiol Aging* 2014,35 1459-68. **PM: 3961498**

3. Kumar A and **Foster TC**. Linking redox regulation of NMDAR synaptic function to cognitive decline during aging. *Journal of Neuroscience* 2013; 33: 15710-15715. **PMID: 24089479**
4. Han X, Aenlle KK, Bean LA, Rani A, Semple-Rowland SL, Kumar A, and **Foster TC**. Role of estrogen receptor alpha and beta in preserving hippocampal function during aging. *Journal of Neuroscience* 2013; 33: 2671-2683, **PMID: 23392694**.
5. Speisman RB, Kumar A, Rani A, **Foster TC**, Ormerod BK. Daily exercise improves memory, stimulates hippocampal neurogenesis and modulates immune and neuroimmune cytokines in aging rats. *Brain Behav Immun* 2013; 28:25-43. **PM:23078985**.
6. **Foster, T.C.** (2012) Dissecting the age-related decline on learning and memory tasks in rodent models: N-methyl-D-aspartate receptors and voltage-dependent Ca2+ channels in senescent synaptic plasticity. *Prog Neurobiol* 96:283-302. **PMID: 22307057**.
7. **Foster TC**, Defazio RA, Bizon JL. Characterizing cognitive aging of spatial and contextual memory in animal models. *Front Aging Neurosci* 2012; 4:12. **PM:22988436**.
8. Zeier, Z. Madorsky, I., Xu, Y., Ogle, W. O., Notterpek, L., **Foster, T. C.** (2012) Regionally specific gene expression in the hippocampus; effect of aging and caloric restriction. *Mechanisms of Ageing and Development*, 132: 8-19, **PMID 21055414**.
9. Craft S, **Foster TC**, Landfield PW, Maier SF, Resnick SM, Yaffe K. Session III: Mechanisms of agerelated cognitive change and targets for intervention: inflammatory, oxidative, and metabolic processes. *J Gerontol A Biol Sci Med Sci* 2012; 67(7):754-759. **PM:22570133**
10. Lee, W-H. Kumar, A., Rani, A., Herrera, J. and **Foster, T.C.** (2011) Influence of viral vector-mediated delivery of superoxide dismutase and catalase to the hippocampus on spatial learning and memory over the course of aging, *Antioxidants & Redox Signaling*, 16 (4): 339-50, **PMID: 21942371**.
11. Bodhinathan, K., Kumar, A., and **Foster, T.C.** (2010) Intracellular redox state alters NMDA receptor response during aging through Ca2+/calmodulin-dependent protein kinase II, *Journal of Neuroscience* 30: 1914-1924, **PMID 20130200**.
12. Jackson, T.C., Rani, A., Kumar, A., and **Foster, T.C.** (2010) Regional hippocampal differences in AKT survival signaling across the lifespan: implications for CA1 vulnerability with aging. *Cell Death and Differentiation*, 16: 439-448, **PMID 20161206**.
13. Aenlle KK, **Foster TC**. Aging alters the expression of genes for neuroprotection and synaptic function following acute estradiol treatment. *Hippocampus* 2010; 20(9):1047-1060, **PMID:19790252**.
14. **Foster, T.C.** (2007) Calcium homeostasis and modulation of synaptic plasticity in the aged brain. *Aging Cell* 6:319-325, **PMID 17517041**.
15. Blalock, E.M., Chen, K.C., Sharrow, K., Herman, J.P., Porter, N.M., **Foster, T.C.**, Landfield, P.W. (2003) Gene microarray analysis of hippocampal aging: Statistical profiling identifies novel expression programs correlated with cognitive impairment. *Journal of Neuroscience* 23: 3807-3819, **PMID 12736351**.

D. Research Support

Ongoing Research Support

R37 AG036800 Foster (PI) 10/05/10 to 08/31/14

The major goals of this project are to examine the hypothesis that age-related changes in NMDAR signaling mediate memory deficits and changes in synaptic plasticity.

OVERLAP None.

Role: PI

R01 AG037984 Foster (PI) 09/15/10 to 07/31/16

Examines the hypothesis that estrogen exerts its effects on memory function and in delaying brain aging through regulation transcription via the α-estrogen receptor.

OVERLAP None.

Role: PI

R01AG029421-07A1 Bizon (PI) 4/1/2014-3/31/2019

The goal of this project is to determine the contributions of GABAergic and cholinergic basal forebrain projection neurons and their cortical targets to age-related cognitive decline.

OVERLAP None.

Role: advice on electrophysiological studies

NIA P30AG028740 Pahor (PI) 7/1/2006-3/31/2017

Claude D. Pepper Older Americans Independence Center

The mission of the University of Florida Older Americans Independence Center (OAIC) is to assess the risk factors of physical disability in older adults, develop and test effective prevention therapies, and train new investigators in research on aging and disability, while developing their leadership qualities.

OVERLAP None.

Role: advice on animals models of aging and age-related cognitive decline

Completed Research Support

R01 AG14979 Foster (PI) 6/01/07 to 5/31/12

The major goals of this project are to examine the hypothesis that age-related changes in Ca2+ homeostasis mediate senescent neurophysiology leading to memory deficits.

Role: PI

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Frazier, Charles Jason	Associate Professor
eRA COMMONS USER NAME (credential, e.g., agency login) CJFRAZIER	

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)*	MM/YY	FIELD OF STUDY
Oberlin College, Oberlin, OH	B.A.	1991	Neuroscience
University of Colorado HSC, Denver, CO	Ph.D.	1997	Neuroscience

A. Personal Statement

My lab specializes in cellular neurophysiology and optical imaging. I have over 15 years of experience designing, running, and analyzing data from in vitro electrophysiological experiments that involve whole-cell patch clamp recordings and epifluorescence microscopy in acute tissue preparations. My lab has also published one previous study that relied on two-photon guided minimal stimulation, and we have recently developed the technology necessary to support quantitative two-photon based imaging of NMDA receptor mediated calcium influx into individual dendritic spines of both young and aged CA1 pyramidal cells. Although my lab has not previously been directly involved in aging research, this project is one that I believe my lab and I are well suited for, and it is one that I am personally very excited about. In fact, I can honestly say that I originally got into neuroscience (and ultimately acetylcholine receptor function) motivated in large part by an interest in how aging impairs cognition. I changed the focus of my effort away from aging only when I realized (as a graduate student in the mid 1990's) that I lacked the tools to study it with the level of mechanistic detail that I desired. So, some 17 years later, it seems appropriate to me that my lab would be among the first to attempt to leverage new technologies and abilities to directly address detailed mechanistic questions about how aging effects subcellular and synaptic physiology in the brain.

B. Positions and Honors

Positions and Employment

1998 – 2000	Postdoctoral Fellow, Department of Physiology and Biophysics, Case-Western Reserve
2000 – 2003	Postdoctoral Fellow, Department of Pharmacology and Therapeutics, University of Florida
2003 – 2010	Assistant Professor, Department of Pharmacodynamics, University of Florida
2003 – 2010	Adjunct Assistant Professor, Department of Neuroscience, University of Florida
2010 - present	Associate Professor, Department of Pharmacodynamics, University of Florida
2010 - present	Adjunct Associate Professor, Department of Neuroscience, University of Florida

Other Experience and Professional Memberships

1993-present	Member, Society for Neuroscience
1998-2000	Member, Biophysical Society
2006-2009	Course Director, GMS6022, Cell signaling in the nervous system. Required course in the Neuroscience graduate program in UF College of Medicine.
2006-2009	Member, UF HSC Student Conduct Committee
2008-present	Member, COP Academic and Professional Standards Committee

Honors

2006	Nominated, College of Pharmacy Teacher of the Year
2007	Nominated, College of Pharmacy Teacher of the Year
2009	Nominated, College of Pharmacy Teacher of the Year
2010	Jack Wessel Award for Excellence as an Assistant Professor

C. Selected peer-reviewed publications

1. **Frazier CJ**, Rollins YD, Breese CR, Leonard S, Freedman R, Dunwiddie TV (1998) Acetylcholine activates an α-bungarotoxin-sensitive nicotinic current in rat hippocampal interneurons, but not pyramidal cells. *Journal of Neuroscience* 18(4):1187-1195. **PMID: 9454829**.
2. **Frazier CJ**, Buhler AV, Weiner JL, Dunwiddie TV (1998) Synaptic Potentials Mediated via alpha- Bungarotoxin-Sensitive Nicotinic Acetylcholine Receptors in Rat Hippocampal Interneurons. *Journal of Neuroscience* 18(20):8228-8235. **PMID: 9763468**.
3. **Frazier CJ**, Strowbridge BW, Papke RL (2003) Nicotinic receptors on local circuit neurons in dentate gyrus: a potential role in regulation of granule cell excitability. *Journal of Neurophysiology* 89(6):3018-28. **PMID: 12611982**.
4. Hofmann ME, Nahir B, **Frazier CJ** (2006) Endocannabinoid mediated depolarization-induced suppression of inhibition in hilar mossy cells of the rat dentate gyrus. *J. Neurophysiology* 96(5):2501-12. **PMID: 16807350**.
5. Nahir B, Bhatia C, **Frazier CJ** (2007) Presynaptic inhibition of excitatory afferents to hilar mossy cells. *J. Neurophysiology* 97(6):4036-47. **PMID: 17442771**.
6. Hofmann ME, Nahir B, **Frazier CJ** (2008) Excitatory afferents to CA3 pyramidal cells display differential sensitivity to CB1 dependent inhibition of synaptic transmission. *Neuropharmacology* 55(7):1140-1146. **PMCID: PMC2610849**.
7. Nahir B, Lindsly C, **Frazier CJ** (2010) mGluR-Mediated and endocannabinoid-dependent long-term depression in the hilar region of the rat dentate gyrus. *Neuropharmacology*, 58(4-5):712-721. **PMCID: PMC2850117**
8. Hofmann ME and **Frazier CJ** (2010) Muscarinic receptor activation modulates the excitability of hilar mossy cells through the induction of an afterdepolarization. *Brain Research*, 1318:42-51. **PMCID: PMC2850114**
9. Lindsly C and **Frazier CJ** (2010) Two distinct and activity dependent mechanisms contribute to autoreceptor-mediated inhibition of GABAergic afferents to hilar mossy cells. *Journal of Physiology*, 588(Pt 15):2801-2822. **PMCID: PMC2956900**.
10. Hofmann ME, Bhatia C, **Frazier CJ** (2011) Cannabinoid receptor agonists potentiate action potential independent release of GABA in the dentate gyrus through a CB1 receptor independent mechanism. *Journal of Physiology*, 589:3801-3821. **PMCID: PMC3171887**.
11. Hofmann ME, **Frazier CJ** (2013) Marijuana, endocannabinoids, and epilepsy: Potential and challenges for improved therapeutic intervention. *Exp Neurol* 244:43-50. **PMCID: PMC3332149**.
12. De Kloet AD, Pati D, Wang L, Hiller H, Sumners C, **Frazier CJ**, Seeley RJ, Herman JP, Woods SC, Krause EG (2013) Angiotensin type 1a receptors in the paraventricular nucleus of the hypothalamus protect against diet-induced obesity. *Journal of Neuroscience*, 33(11):4825-4823. **PMCID: PMC3638262**.
13. **Frazier CJ**, Pati D, Hiler J, Nguyen D, Wang L, MacFadyen K, de Kloet AD, Krause EG (2013) Acute hypernatremia exerts an inhibitory oxytocinergic tone that is associated with anxiolytic mood in male rats. *Endocrinology*, **PMCID: PMC3689277**.
14. **Frazier CJ** (2013) Preformed vs. on-demand: Molecular economics of endocannabinoid signaling. *Journal of Physiology*, 59(Pt 19):4683-4684. **PMCID: PMC3800445**
15. 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. *J Neurosci* 34:3457-3466. **PMCID: PMC3942567**.

Ongoing Research Support

UF 0119176 7/1/2014 – 6/30/2015
McKnight Brain Institute (UF Intramural) $20,000 (subcontract to Frazier)
Title: Pilot studies to support the submission of NIH/NINDS Morris K. Udall Center of Excellence for Parkinson's disease research.
Role: Co-Investigator (PI: T. Golde).

Pending Research Support

R01MH104641-01A1 03/01/2015-02/28/2020
NIH/NIMH
Title: Novel aspects of central oxytocin signaling relevant to mood/anxiety disorders.
Role: Principle Investigator - Percentile: 8.0

R01HL122494-A1 10/01/2014-09/30/2019
NIH/NHLBI
Title: Central Mechanisms Underlying the Stress Dampening Effects of Acute Hypernatremia (no overlap)
Role: Co-Investigator (PI: E. Krause) – Percentile: 13.0

Completed Research Support (last 4 years)

R21DA029828-01A1 03/01/2011-06/30/2014
NIH/NIDA
Title: CB1R independent effects of cannabinoids on synaptic physiology in the CNS.
Role: Principal Investigator

Evelyn F. McKnight Brain Research Grant Program via the University of Florida 2011-2014
Title: The role of calcium activated potassium channels in geriatric memory dysfunction
Role: Principal Investigator

R01 DA019576 7/01/2005-06/30/2010
NIH/NIDA
Title: Endocannabinoids and tonic GABA in the dentate gyrus.
Role: Principal Investigator

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Heilman, Kenneth M.	Distinguished Professor of Neurology, University of Florida
eRA COMMONS USER NAME (credential, e.g., agency login)	Neurologist, NF/SG VAMC, Gainesville FL
KMHEILMAN	

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Virginia, Charlottesville VA		05/59	Chemistry
University of Virginia, College of Medicine, Charlottesville VA	M.D.	06/63	Medicine
Cornell Medical Div. Bellevue Hospital, NY	Intern and Assistant Resident (PGY1 & 2)	6/65	Internal Medicine
Harvard Neurological Unit, Boston City Hospital, Boston MA	Resident, Chief Resident and Fellow (PGY 3,4, 5)	6/70	Neurology

A. Personal Statement

Since joining the faculty at the University of Florida in 1970, I have established and maintained a productive research program and trained about 100 fellows, most of whom have gone on to prestigious academic leadership positions throughout the world. Research in my lab includes studies on the neurological basis and disorders of language, skilled purposeful movements (praxis), frontal-action-intentional systems, attention and neglect, emotion, and creativity. Forty-two percent of my time is with the VA (51% research, 10% education, 39% clinical) and 58% with the University of Florida Department of Neurology (21% teaching + 72% research + 7% patient care).

B. Positions and Honors

Positions and Employment

1998-present	Distinguished Professor, University of Florida College Medicine, Gainesville, FL.
1996-2008	Chief of Neurology, North Florida/South Georgia Veterans Affairs Medical Center, Gainesville, FL
1990-2008	James E. Rooks Jr., Professor of Neurology
2009-present	James E. Rooks Jr., Professor of Neurology
1988-present	Director Cognitive and Memory Disorder Clinic
1984-present	Director, Center for Neuropsychological Studies University of Florida College of Medicine, Gainesville, Florida
1977-present	Professor, Department of Clinical Psychology University of Florida Gainesville, Florida
1977-1996	Staff Physician @ VA Medical Center, Gainesville, FL
2009-present	Staff Physician and Member of GRECC @ VA Medical Center Gainesville, Florida
1973-1977	Associate Professor of Clinical Psychology University of Florida College of Medicine, Gainesville, Florida
1975-1998	Professor, Department of Neurology University of Florida, Gainesville, Florida
1973-1975	Associate Professor of Neurology, University of Florida College of Medicine, Gainesville, Florida
1970-1973	Assistant Professor of Medicine, Division of Neurology University of Florida College of Medicine Gainesville, Florida

Other Experience and Professional Memberships

Board Certification

1973-present	American Board of Psychiatry and Neurology
1994-2004	American Society of Neurorehabilitation

2006-present United Council for Neurologic Subspecialties-Behavioral Neurology

Advisory

1986-1992 American Board of Psychiatry and Neurology, Part I Neurology Committee (Minor Subcommittee)
1981-1984 National Institutes of Health: Study Sections: Neurobiology Review Group (Study Section)
1976-7, 1984-5 University of Florida Senate
1976 Presentation to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research - Psychosurgery

Memberships and Honors

1970- Alachua County Medical Society
1987-1990 American Academy of Aphasia (Governing Board)
1997-9, 2005-7 University of Florida Research Foundation Professorship (Award)"
1994-2004 American Society of Neurorehabilitation
1993 Faculty Research Award in Clinical Science, College of Medicine, University of Florida
1989 National Aphasia Association; Advisory Board
1984 International Society for Research of Emotion; Board of Directors
Phi Kappa Phi
1982-1983 Society for Behavioral and Cognitive Neurology; President
1996 Society for Behavioral and Cognitive Neurology; Outstanding Achievement Award
Aphasia Research Group of the World Federation of Neurology
1982 Alpha Omega
Alpha Sigma Xi
1974-1977 International Neuropsychology Society (Member, Executive Committee)
1982-1983 International Neuropsychology Society (President)
2009 International Neuropsychology Society Lifetime Achievement Award
Florida Society of Neurology
Florida Medical Society
Association of University Professors
1976-2008 American Neurological Association Active Member
2008-present American Neurological Association Honorary Member
1970-present American Academy of Neurology (Fellow from 1975-present)
2003- The Dana Foundation Alliance
2003 The American Speech and Hearing Association, Distinguished Service Award for Scientific and Educational Contributions
2008 University of Florida, College of Medicine, Lifetime Achievement Award
2009 American VA Speech and Language Pathologists' President's Award
2009 American Academy of Neurology, Wartenberg Award and Keynote Lecture

C. Selected Peer-Reviewed Publications

(Dr. Heilman has published over 500 peer-reviewed publications. The following are 15 selected publications from the prior year (2013):

1. Williamson JB, **Heilman KM**, Porges EC, Lamb DG, Porges SW. A possible mechanism for PTSD symptoms in patients with traumatic brain injury: central autonomic network disruption. *Front. Neuroeng.*, 19 December 2013 | doi: 10.3389/fneng.2013.00013
2. Acosta L, Goodman IJ, **Heilman KM**. Unilateral perseverationnnn. *Cogn Behav Neurol*. 2013 Dec;26(4):181-8.
3. Behforuzi H, Burtis DB, Williamson JB, Stamps JJ, **Heilman KM**. Impaired initial vowel versus consonant letter-word fluency in dementia of the Alzheimer type. *Cogn Neurosci*. 2013 Sep-Dec;4(3-4):163-70. doi: 10.1080/17588928.2013.854200.
4. Kabasakalian A, Kesayan T, Williamson JB, Skidmore FM, Falchook AD, Harciarek M, **Heilman KM**. Hypometric allocentric and egocentric distance estimates in Parkinson disease. *Cogn Behav Neurol*. 2013 Sep;26(3):133-9. doi: 0.1097/WNN.0000000000000007.
5. Acosta LM, Bennett JA, **Heilman KM**. Callosal disconnection and limb-kinetic apraxia. *Neurocase*. 2013 Aug 23. [Epub ahead of print]
6. **Heilman KM**. Locked-In or Locked-Out, But Present. *JAMA Neurol*. 2013 Aug 12. doi: 10.1001/jamaneurol.2013.3694. [Epub ahead of print]
7. Stamps JJ, Bartoshuk LM, **Heilman KM**. .A brief olfactory test for Alzheimer's disease. *J Neurol Sci*. 2013 Aug 5. doi:pii: S0022-510X(13)00311-0. 10.1016/j.jns.2013.06.033. [Epub ahead of print]

8. Kim EJ, Lee B, Jo MK, Jung K, You H, Lee BH, Cho HJ, Sung SM, Jung DS, **Heilman KM**, Na DL. Directional and spatial motor intentional disorders in patients with right versus left hemisphere strokes. *Neuropsychology*. 2013 Jul;27(4):428-37. doi: 10.1037/a0032824.
9. Foster PS, Drago V, Yung RC, Pearson J, Stringer K, Giovannetti T, Libon D, **Heilman KM**. Differential Lexical and Semantic Spreading Activation in Alzheimer's Disease. *Am J Alzheimers Dis Other Demen*. 2013 Jun 25. [Epub ahead of print].
10. Falchook AD, **Heilman KM**, Finney GR, Gonzalez-Rothi LJ & Nadeau SE (2013): Neuroplasticity, neurotransmitters and new directions for treatment of anomia in Alzheimer disease, *Aphasiology*, doi:10.1080/02687038.2013.793283.
11. Foster PS, Yung RC, Drago V, Crucian GP, **Heilman KM**. Working memory in Parkinson's disease: The effects of depression and side of onset of motor symptoms. *Neuropsychology*. 2013 May;27(3):303-13. doi: 10.1037/a0032265.
12. Hedna VS, Bodhit AN, Ansari S, Falchook AD, Stead L, **Heilman KM**, Waters MF. Hemispheric differences in ischemic stroke: is left-hemisphere stroke more common? *J Clin Neurol*. 2013 Apr;9(2):97-102. doi: 10.3988/jcn.2013.9.2.97.
13. Burtis DB, Williamson JB, Mishra M, **Heilman KM**.The blindside: Impact of monocular occlusion on spatial attention. *J Clin Exp Neuropsychol*. 2013 Mar;35(3):291-7.
14. Foster PS, Drago V, Mendez K, Witt JC, Crucian GP, **Heilman KM**. Mood disturbances and cognitive functioning in Parkinson's disease: The effects of disease duration and side of onset of motor symptoms. *J Clin Exp Neuropsychol*. 2013 Jan 16. [Epub ahead of print].
15. Falchook AD, Mayberry RI, Poizner H, Burtis DB, Doty L, **Heilman KM**. Sign language aphasia from a neurodegenerative disease. *Neurocase*. 2013 Oct;19(5):434-44.

D. Research Support

Ongoing Research Support

Active

VA Clinical Science Research & Development-Merit Review Heilman (PI) 10/01/12 – 09/30/16
Vertical Neglect
This grant provides support for research that is attempting to understand some of the neuropsychological mechanisms that may account for the signs of the 'neglect syndrome.'

XZ302 DOEA Heilman (PI) 07/01/88 – 06/30/14
State of Florida, Department of Elder Affairs Memory Disorder Clinics - Alzheimer's Disease Initiative
This support allows us to develop new assessments and behavioral treatments for the cognitive disorders associated with dementing diseases. It also provides funding for the training of neurologists, psychologist and speech pathologists in the care of patients with dementia.

NIH 1R21AG044449-01A1 Heilman (PI) 09/30/13 – 06/30/15
Disorders of Emotional Communication in Patient with Cerebellar Dysfunction
This research support allows us to learn how emotional communication is affected in adults with cerebellar disease.

Recently Concluded Research Support

VA Clinical Science Research & Development-Merit Review Heilman (PI) 2008–2012
Approach-Avoidance Neglect
This grant provides support for research that is attempting to understand some of the neuropsychological mechanisms that may account for the signs of the 'neglect syndrome.'

BIOGRAPHICAL SKETCH

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

NAME Ashok Kumar	POSITION TITLE Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login): Calcium	

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)*	MM/YY	FIELD OF STUDY
University of Lucknow, Lucknow	B.Sc.	1984	Life Sciences
University of Lucknow, Lucknow	M.Sc.	1986	Zoology
Central Drug Research Institute	Ph.D.	1992	Pharmacology
Yale University, New Haven	Postdoctoral	1998	Neuroscience/Neurobiology of Aging

A. Personal Statement

My research is directed towards understanding the mechanisms that regulate changes in cognitive function during aging. A central focus of my research involves the investigation of how treatments (pharmacological or viral mediated protein expression) or interventions, such as environmental enrichment and exercise, restore/improve age-associated impairment of learning and memory. I have technical expertise in electrophysiology with ~20 years' experience. As such, my published work examined how synaptic plasticity and cell excitability are related to cognitive function. I have published research demonstrating that environmental enrichment and exercise can influence memory and biological markers of aging including the level of cytokines in the serum and brain and senescent neurophysiology in the hippocampus, including cell excitability and synaptic plasticity. My recent work (Kumar and Foster, Journal of Neuroscience, 2013), which forms part of the foundation for the current proposal, provided a link between an early behavioral marker of cognitive decline, impaired spatial episodic memory, and a decrease in N-methyl-D-aspartate (NMDA) receptor function through an increase in oxidative redox state. I provided the preliminary data showing that systemic inflammation results a redox-mediated decrease in hippocampal NMDA receptor synaptic function. In addition, I have investigated the role of NMDA receptor function in the medial prefrontal cortex (mPFC). I provided the preliminary data showing that aged animals, which are impaired on the 5-choice serial reaction time attention task, exhibit a redox mediated decrease in NMDA receptor synaptic responses in the mPFC. Finally, my work has helped to define how age-related changes in G-protein coupled receptor signaling influence cell excitability and synaptic plasticity.

B. Positions and Honors

Positions and Employment

2011-Present Asst Prof, Dept of Neuroscience, Brain Institute, Univ of Florida, Gainesville, FL.
2003 - 2011 Res Asst Prof, Dept of Neurosci, Brain Institute, Univ of Florida, Gainesville, FL.
2000 - 2003 Sr Research Associate, Dept of Pharmacology, Univ of Kentucky, Lexington, KY.
1997-1999 Res Associate, Dept of Psychiatry, Yale University Sch of Med, New Haven, CT.
1995 -1997 Res Asso, Dept of Pharmacodynamics, Univ of Illinois at Chicago, Chicago, IL.
1987 -1994 Research Fellow, Dept of Pharmacology, Central Drug Res Inst, Lucknow.

Other Experience and Professional Memberships

1997- Member, Society for Neuroscience
1990- Life Member, Indian Society of Neuroscience
1990- Life Member, Indian Pharmacological Society

Review Editor: Frontiers in Aging Neuroscience

Ad hoc Reviewer: Journal of Neurophysiology, Neurobiology of Learning and Memory, Neurobiology of Aging, Synapse, Life Sciences, NeuroReport, Depression and Anxiety, Pharmacology, Biochemistry and Behavior, European Journal of Pharmacology, European Neuropsychopharmacology, Mechanisms of Aging and Development, Frontiers in Neuropharmacology, Hippocampus, Neuroscience, Brain Research, Neuroscience Letters, PLOS One

Honors

2007 Awarded travel grant by Southeast Neural Network, Wakula Spring, FL.
1997 Junior Scientist Award by ASIOA, FASEB, New Orleans, LA.
1993 Prof P.C. Dandiya Gold Medal for best paper presentation, Indian Pharmacological Society, Hissar

C. Selected Peer-reviewed Publications

Most relevant to the current application (15 out of 53)

1. M Guidi, **Ashok Kumar**, A. Rani, and T.C. Foster, Assessing the emergence and reliability of cognitive decline over the life span in Fisher 344 rats using the spatial water maze, *Frontiers in Aging Neuroscience*, Jan 21; 6:2 (2014) **PMID: 24478698**.
2. **Ashok Kumar** and Thomas C Foster, Interaction of DHPG-LTD and synaptic-LTD at senescent CA3-CA1 hippocampal synapses, *Hippocampus* (2014), **PMID: 24390964**.
3. **Ashok Kumar** and Thomas C Foster, Linking redox regulation of NMDAR synaptic function to cognitive decline during aging, *Journal of Neuroscience*, 40, 15710-15715 (2013), **PMID: 24089479**.
4. W.H. Lee, **Ashok Kumar**, A. Rani, and T.C. Foster, Role of antioxidant enzymes in redox regulation of NMDAR function and memory in middle-age rats, *Neurobiology of Aging*, (2013), **PMID: 24388786**.
5. X. Han, K. A. Aenlle, L. Bean, A. Rani, S. S. Rowland, **Ashok Kumar**, and T. C. Foster, Role of estrogen receptor alpha and beta in preserving hippocampal function during aging, *Journal of Neuroscience*, 33 (6) 2671-2683 (2013), **PMID: 23392694**.
6. Rachel. B. Speisman, **Ashok Kumar**, Asha Rani, Thomas C. Foster and Brandi K. Ormerod, Daily exercise improves memory, stimulates hippocampal neurogenesis and modulates immune and neuroimmune cytokines in aging rats, *Brain, Behavior, and Immunity*, 28, 25-43 (2013), **PMID: 23078985**.
7. K. Bodhinathan, **Ashok Kumar**, and T. C. Foster, Intracellular redox state alters NMDA receptor response during aging through Ca2+/Calmodulin-dependent protein kinase II, *Journal of Neuroscience* 30, 1914-24 (2010), **PMID: 20130200**.
8. **Ashok Kumar**, Asha Rani, and Thomas C Foster, Influence of exposure to enriched environment and exercise on learning and memory, synaptic plasticity, and neuronal excitability over the course of aging, *Neurobiology of Aging*, 33, 828.e1-828.e17 (2012), **PMID: 21820213**.
9. W.H. Lee, **Ashok Kumar**, A. Rani, J. Herrera, and T.C. Foster, Influence of viral vector-mediated delivery of superoxide dismutase and catalase to the hippocampus on spatial learning and memory during aging, *Antioxidant and Cell Signaling*, 16 (4) 339-350 (2012), **PMID: 21942371**.
10. **Ashok Kumar**, Long-term potentiation at CA3-CA1 hippocampal synapse with special emphasis on aging, disease, and stress, *Frontiers in Aging Neuroscience*, 3: 7 (2011), **PMID: 21647396**.
11. **Ashok Kumar**, Carbachol-induced long-term synaptic depression is enhanced during senescence at hippocampal CA3-CA1 synapses, *Journal of Neurophysiology*, 104 607-616 (2010), **PMID: 20505129**.
12. **Ashok Kumar**, K. Bodhinathan, and T. Foster, Susceptibility to calcium dysregulation during brain aging, *Frontiers in Aging Neuroscience*, 1 1-13 (2009), **PMID: 20552053**.
13. **Ashok Kumar** and T.C. Foster, Shift in induction mechanisms underlies an age-dependent increase in DHPG-induced synaptic depression at CA3-CA1 synapses, *Journal of Neurophysiology*, 98, 2729-2736 (2007), **PMID: 17898145**.
14. **Ashok Kumar**, J. S. Thinschmidt, T.C. Foster, and M.A. King, Aging effects on the limits and stability of long-term potentiation and depression in rat hippocampal area CA1, *Journal of Neurophysiology*, 98 (2), 594-601 (2007), **PMID: 17553951**.
15. **Ashok Kumar** and T.C. Foster, Environmental enrichment decreases the augmented hippocampal afterhyperpolarization in senescent rats, *Brain Research*, 1130 (1) 103-107 (2007), **PMID: 17169341**.

Ongoing Research Support

R01 AG037984 (Foster PI, Kumar Co-I) 09/15/10 to 07/31/16 50% effort NIA

Estrogen and cognition over the lifespan

Examines the hypothesis that estrogen exerts its effects on memory function and in delaying brain aging through regulation transcription via the α-estrogen receptor.

OVERLAP: None.

R01AG029421 (Bizon PI) 4/1/2014-3/31/2019 20% effort (year 1) NIA

Neural mechanisms of cognitive decline in aging

The goal of this project is to determine the contributions of GABAergic and cholinergic basal forebrain projection neurons and their cortical targets to age-related cognitive decline.

OVERLAP: None.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Lamb, Damon G.	Research Health Science Specialist (VAMC) Research Assistant Professor (Neurology, UF) Adjunct Research Assistant Professor (CAM/Aging,UF)
eRA COMMONS USER NAME dglamb	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Maryland, College Park, MD	BS	05/03	Mathematics
University of Maryland, College Park, MD	BS	12/03	Computer Engineering
University of Chicago, Chicago, IL	MS	12/05	Computer Science
MBL, Woods Hole, MA	~	08/09	Neural Sys. & Behavior
Emory University, Atlanta, GA	PhD	08/13	Neuroscience

A. Personal Statement

The goal of our proposed research is to investigate the neurophysiological basis of cognitive and emotional impairments from a range of conditions and disorders including stroke, TBI, HIV, and general aging. There are many putative mechanisms that may drive these impairments, and a better understanding of the basis for these will help guide future clinical recommendations and practice. My contribution to our research program is to provide analytical and modeling expertise, building on my diverse background in human and animal neuroscience as well as quantitative approaches. I have previously collaborated with the several CAM researchers on a wide range of projects over the past 8 years, including an investigation of the influence of stroke on white matter and cognition/executive function, post-surgical autonomic nervous system alterations, the influence of stroke on attention, and the relationship between mild TBI and PTSD.

B. Positions and Honors

Positions

2002-2004 Research Asst., Institute for Research in Electronics and Applied Physics University of Maryland
2001-2004 Research Software Developer University of Iowa & NIH
2003-2005 Acoustic Modeling Software Developer Acoustic Design Ahnert
2004-2007 Data Analyst, Brain-Body Center University of Illinois College of Medicine
2007-2013 Graduate Student, Neuroscience Program Emory University
2013-pres Research Health Science Specialist US Dept. of Veterans Affairs
2013-pres Research Assistant Professor (Neurology) University of Florida
2014-pres Adjunct Research Assistant Professor (Cognitive Aging & Memory/Institute on Aging) University of Florida

Honors

2005 Computer Science Faculty Commendation, University of Chicago
2007-2009 IGERT: Hybrid Neural Microsystems Fellow, National Science Foundation
2009 MBL Neural Systems and Behavior Fellow, Frank R. Lillie Fellowship and Scholarship
2009 Scholar, Burroughs Wellcome Fund
2011-2013 Research Partners Fellow, Howard Hughes Medical Institute

C. Selected Peer-reviewed Publications [1-15]

1. Williamson JB, Heilman KM, Porges EC, **Lamb DG**, Porges SW (2013) A possible mechanism for PTSD symptoms in patients with traumatic brain injury: Central autonomic network disruption. *Frontiers in neuroengineering 6*.
2. **Lamb DG**, Calabrese RL (2013) Correlated Conductance Parameters in Leech Heart Motor Neurons Contribute to Motor Pattern Formation. *PloS one* 8-11.
3. **Lamb DG**, Calabrese RL (2013) Once more unto the leech: production of functional motor patterns in leech heart motor neurons. *BMC Neuroscience* 14: P51.
4. **Lamb DG**, Calabrese RL (2012) Small is beautiful: models of small neuronal networks. *Current Opinion in Neurobiology* 22: 670-675.
5. **Lamb DG**, Calabrese RL (2012) Individual differences in leech heart motor neuron models. *BMC Neuroscience* 13: 1-2.

6. **Lamb DG**, Calabrese RL (2011) Neural circuits controlling behavior and autonomic functions in medicinal leeches. *Neural systems & circuits* 1: 1-10.
7. Williamson JB, Lewis G, Grippo AJ, **Lamb D**, Harden E, et al. (2010) Autonomic predictors of recovery following surgery: A comparative study. *Autonomic Neuroscience* 156: 60-66.
8. Williamson J, Nyenhuis D, Stebbins GT, **Lamb D**, Simkus V, et al. (2010) Regional differences in relationships between apparent white matter integrity, cognition and mood in patients with ischemic stroke. *Journal of Clinical and Experimental Neuropsychology* 32: 673-681.
9. Bal E, Harden E, **Lamb D**, Van Hecke AV, Denver JW, et al. (2010) Emotion recognition in children with autism spectrum disorders: relations to eye gaze and autonomic state. *Journal of autism and developmental disorders* 40: 358-370.
10. Van Hecke AV, Lebow J, Bal E, **Lamb D**, Harden E, et al. (2009) Electroencephalogram and heart rate regulation to familiar and unfamiliar people in children with autism spectrum disorders. *Child development* 80: 1118-1133.
11. Williamson JB, Lewis GF, Grippo AJ, **Lamb D**, Carter SC, et al. Autonomic predictors of survival post surgery: *An animal model*; 2008. Blackwell Publishing. pp. S79-S79.
12. Grippo AJ, **Lamb DG**, Carter CS, Porges SW (2007) Cardiac regulation in the socially monogamous prairie vole. *Physiology & behavior* 90: 386-393.
13. Grippo AJ, **Lamb DG**, Carter CS, Porges SW (2007) Social isolation disrupts autonomic regulation of the heart and influences negative affective behaviors. *Biological psychiatry* 62: 1162-1170.
14. Walter M, Quinn B, **Lamb D**, Bernal S, Godlove T, et al. (2005) Experimental tests of the injection Y on the University of Maryland Electron Ring. *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* 544: 374-377.
15. Bernal S, Beaudoin B, Cui Y, Glanzer M, Godlove T, et al. (2004) Intense beam transport experiments in a multi-bend system at the University of Maryland Electron Ring. *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* 519: 380-387.

D. Research Support (last 3 years)

LK2RX000707-01 Williamson (PI) 2012-2017

White matter changes and mild TBI: Emotional and autonomic consequences

Funded by the Department of Veterans Affairs to investigate the interaction of mTBI and PTSD as linked by structural damage to specific white matter tracts, resulting in dysregulation of autonomic nervous system function.

Role: Co-I

Merit Review Award Heilman (PI) 10/01/12 - 09/30/16

Vertical Neglect

Funded by the Department of Veterans Affairs to investigate the vertical organization of attention and in particular neglect in the vertical plane in both normal individuals and individuals with stroke.

Role: Co-I

R01 NS024072-28 Calabrese (PI)

Neuromodulatory influences on motor systems

Funded by the National Institute of Neurological Disease and Stroke to investigate neuromodulation and the role of neural parameters on rhythmic motor pattern generation, in particular those critical for life – e.g., breathing, mastication, and locomotion.

Role: Co-I

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Leeuwenburgh, Christiaan	Professor Department of Aging and Geriatric Research Chief Division of Biology of Aging
eRA COMMONS USER NAME cleeuwen	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
University of Florida, Gainesville	BS	1986-1988	Applied Physiology
University of Florida, Gainesville	MS	1988-1990	Applied Physiology
University of Illinois, Urbana-Champaign	PhD	1990-1995	Biochemistry and Aging
University of Wisconsin, Madison	Pre-Fellow	1993-1995	Biochemistry and Aging
Washington Univ. School of Medicine, St Louis	Post-Fellow	1995-1998	Geriatrics & Gerontology

A. Personal Statement

Christiaan Leeuwenburgh received his PhD from the University of Illinois, Urbana-Champagne in 1995 where his doctoral work focused on redox biology and the regulation of glutathione homeostasis during chronic glutathione deficiencies and/or supplementation. He completed his postdoctoral studies in Internal Medicine, Division of Geriatrics and Gerontology and Division of Atherosclerosis, Nutrition and Lipid Research at Washington University School of Medicine, Saint Louis with Drs. John Holloszy and Jay Heinecke. He became an Assistant Professor in 1998 at the University of Florida and the Director of the Biochemistry of Aging Laboratory. He was promoted to Associate Professor in 2002 and Professor in 2007. In 2005 he joined the newly created Institute on Aging at the University of Florida, where he became the Chief of the Division of Biology of Aging in the Department of Aging and Geriatric Research, College of Medicine. Dr. Leeuwenburgh has affiliate appointments with Anatomy and Cell Biology and Biochemistry and Molecular Biology and is a member of the graduate Interdisciplinary Program in Biomedical Sciences of the College of Medicine. Dr. Leeuwenburgh major research focus is to better understand the molecular mechanisms of mitochondrial dysfunction, autophagy, and programmed cell death (apoptosis) with age. The Division of Biology of Aging utilizes and collaborates with scientists who investigate, yeast, cell lines, transgenic mice, rodent models and humans. The division actively participates in several translational clinical research studies, with and without targeted interventions, investigating mitochondrial dysfunction, apoptosis, DNA repair and autophagy in muscle from older humans. He also directs a Metabolism and Translational Science Core and a Research Career Development Core within the NIA-funded Claude Pepper Older Americans' Independence Center. He has participated in various NIH study sections, both for basic and clinical research, NIH workshops focused on the biology of aging and geriatric research. He has published papers in The Journal of Biological Chemistry, American Journal of Physiology, PLoS One, Journal of Gerontology, FASEB Journal, Experimental Gerontology, Neurobiology of Aging, Rejuvenation Research, Aging Cell, Science, and Cell. He holds several editorial positions, which includes the Deputy Editor for Experimental Gerontology the oldest Gerontology Journal. He received the University of Florida Research Professor Faculty Award (2004-2006 and 2011-2013), Nathan Shock Award from the National Institute on Aging (2004), the Merck Geriatric Cardiology Research Award from the Society of Geriatric Cardiology (1999-2000) and the National Research Service Award of the NIH from the National Institute on Aging (1997-1998); a Young Investigator Award from the Oxygen Society (1996); and held an American Heart Association Pre-doctoral Fellowship (1993-1995) from the Illinois Affiliate. His work on assessment of mitochondrial function, bioenergetics, apoptosis, oxidative stress, and autophagy in aging has been increasingly recognized and appreciated by gerontologists worldwide.

B. Positions and Honors

Positions and Employment

1995–1998	Washington University School of Medicine, St. Louis, Department of Internal Medicine, Divisions of Geriatrics and Gerontology, and Atherosclerosis, Nutrition and Lipid Research Postdoctoral Fellow in Internal Medicine and Geriatrics and Gerontology; Research Associate in Medicine; Adjunct Instructor; Mentors: John O. Holloszy, MD and Jay W. Heinecke, MD
1998–2002	Assistant Professor, Director of the Biochemistry of Aging Laboratory, University of Florida
1998–	Faculty Associate of the Institute on Aging and Center for Gerontological Studies
2002–2005	Associate Professor and Director of the Biochemistry of Aging Laboratory, University of Florida
2005–2007	Associate Professor, College of Medicine, Department of Aging and Geriatric Research
2005–	Director, Genomics and Biomarkers Core of the University of Florida Institute on Aging, Joint and Affiliate Faculty, Departments of Anatomy and Cell Biology and Biochemistry and Molecular Biology
2005–2006	Chief, Division of Career Development, Mentoring and Education

2006– Chief, Division of Biology of Aging, Department of Aging and Geriatric Research
2007– Professor, College of Medicine, Department of Aging and Geriatric Research, Division of Biology of Aging

Other Experience and Professional Memberships

2003- Member, American Aging Association
2003- Member, Gerontological Society of America
1997- The American Physiological Society
1995-2008 Society for Free Radical Biology and Medicine
1995-2008 International Society for Free Radical Research
2008- Editor, Experimental Gerontology
2004-2013 NIH Peer Review Committees; Special Emphasis Panels.

Honors

2011-2013 University of Florida Research Foundation Professor
2010 Exemplary Teacher Award, College of Medicine
2004 Nathan W. Shock Lecture Award Winner, National Institute on Aging
(Nathan W. Shock was a former scientific director of the NIA and an NIH Scientist Emeritus)
2004–2005 University of Florida Research Foundation, Professor Award
2000-2002 American Heart Association, Young Investigator Award, FL
1999–2000 Merck Geriatric Cardiology Research Award, Society of Geriatric Cardiology
1997–1998 National Research Service Award, NRSA-NIH, National Institute of Aging
1996 Young Investigator Award, Oxygen Society, Intern. Soc. Free Rad. Res., Miami, FL
1993–1995 American Heart Association, Pre-doctoral Fellowship, Illinois Affiliate

C. Selected Peer-reviewed Publications (from 195) (1-15)

1. Joseph, A.M., Adhihetty, P.J., Wawrzyniak, N.R., Wohlgemuth, S.E., Picca, A., Kujoth, G.C., Prolla, T.A., and **Leeuwenburgh, C.** 2013. Dysregulation of mitochondrial quality control processes contribute to sarcopenia in a mouse model of premature aging. *PloS one* 8:e69327. **PMID: 23935986**
2. Dutta, D., Xu, J., Kim, J.S., Dunn, W.A., Jr., and **Leeuwenburgh, C**. 2013. Upregulated autophagy protects cardiomyocytes from oxidative stress-induced toxicity. *Autophagy* 9:328-344. **PMID: 23298947**
3. Coen, P.M., Jubrias, S.A., Distefano, G., Amati, F., Mackey, D.C., Glynn, N.W., Manini, T.M., Wohlgemuth, S.E., **Leeuwenburgh, C.**, Cummings, S.R., et al. 2013. Skeletal muscle mitochondrial energetics are associated with maximal aerobic capacity and walking speed in older adults. *The journals of gerontology. Series A, Biological sciences and medical sciences* 68:447-455. **PMID: 23051977**
4. Joseph, A.M., Adhihetty, P.J., Buford, T.W., Wohlgemuth, S.E., Lees, H.A., Nguyen, L.M., Aranda, J.M., Sandesara, B.D., Pahor, M., Manini, T.M., et al. 2012. The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals. *Aging cell* 11:801-809. **PMID: 22681576**
5. Wang, J.H., Ahn, I.S., Fischer, T.D., Byeon, J.I., Dunn, W.A., Jr., Behrns, K.E., **Leeuwenburgh, C.**, and Kim, J.S. 2011. Autophagy suppresses age-dependent ischemia and reperfusion injury in livers of mice. *Gastroenterology* 141:2188-2199 e2186. **PMID: 21854730**
6. Someya, S., Yu, W., Hallows, W.C., Xu, J., Vann, J.M., **Leeuwenburgh, C.**, Tanokura, M., Denu, J.M., and Prolla, T.A. 2010. Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction. *Cell* 143:802-812. **PMID: 21094524**
7. Seo, A.Y., Joseph, A.M., Dutta, D., Hwang, J.C., Aris, J.P., and **Leeuwenburgh, C.** 2010. New insights into the role of mitochondria in aging: mitochondrial dynamics and more. *Journal of cell science* 123:2533-2542. **PMID: 20940129**
8. Buford, T.W., Anton, S.D., Judge, A.R., Marzetti, E., Wohlgemuth, S.E., Carter, C.S., **Leeuwenburgh, C.**, Pahor, M., and Manini, T.M. 2010. Models of accelerated sarcopenia: critical pieces for solving the puzzle of age-related muscle atrophy. *Ageing research reviews* 9:369-383. **PMID: 20438881**
9. Someya, S., Xu, J., Kondo, K., Ding, D., Salvi, R.J., Yamasoba, T., Rabinovitch, P.S., Weindruch, R., **Leeuwenburgh, C.**, Tanokura, M., et al. 2009. Age-related hearing loss in C57BL/6J mice is mediated by Bak-dependent mitochondrial apoptosis. *Proceedings of the National Academy of Sciences of the United States of America* 106:19432-19437. **PMID: 19901338**
10. Bailey, L.J., Cluett, T.J., Reyes, A., Prolla, T.A., Poulton, J., **Leeuwenburgh, C.**, and Holt, I.J. 2009. Mice expressing an error-prone DNA polymerase in mitochondria display elevated replication pausing and chromosomal breakage at fragile sites of mitochondrial DNA. *Nucleic acids research* 37:2327-2335. **PMID: 19244310**
11. Malayappan, B., Garrett, T.J., Segal, M., and **Leeuwenburgh, C**. 2007. Urinary analysis of 8-oxoguanine, 8-oxoguanosine, fapy-guanine and 8-oxo-2'-deoxyguanosine by high-performance liquid chromatography-electrospray tandem mass spectrometry as a measure of oxidative stress. *Journal of chromatography*. A 1167:54-62. **PMID: 17765254**

12. Kujoth, G.C., Hiona, A., Pugh, T.D., Someya, S., Panzer, K., Wohlgemuth, S.E., Hofer, T., Seo, A.Y., Sullivan, R., Jobling, W.A., et al. 2005. Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. *Science* 309:481-484. **PMID: 16020738**
13. Obisesan, T.O., **Leeuwenburgh, C.**, Phillips, T., Ferrell, R.E., Phares, D.A., Prior, S.J., and Hagberg, J.M. 2004. C-reactive protein genotypes affect baseline, but not exercise training-induced changes, in C-reactive protein levels. *Arteriosclerosis, thrombosis, and vascular biology* 24:1874-1879. **PMID: 15271790**
14. **Leeuwenburgh, C.**, Rasmussen, J.E., Hsu, F.F., Mueller, D.M., Pennathur, S., and Heinecke, J.W. 1997. Mass spectrometric quantification of markers for protein oxidation by tyrosyl radical, copper, and hydroxyl radical in low density lipoprotein isolated from human atherosclerotic plaques. *The Journal of biological chemistry* 272:3520-3526. **PMID: 9013599**
15. **Leeuwenburgh, C.**, Hardy, M.M., Hazen, S.L., Wagner, P., Oh-ishi, S., Steinbrecher, U.P., and Heinecke, J.W. 1997. Reactive nitrogen intermediates promote low density lipoprotein oxidation in human atherosclerotic intima. *The Journal of biological chemistry* 272:1433-1436. **PMID: 8999808**

D. Research Support

NIH R01 DK090115 (Kim-Leeuwenburgh NIDDK) 4/1/2012-3/31/2017
Mitophagy: A novel target to improve liver function after ischemia/reperfusion injury
The goal is to develop therapeutic strategies to ameliorate the effects of ischemia/reperfusion injury in liver following resection and transplantation surgeries. This will ultimately improve liver function and expedite recovery periods.
Role: Co-PI

1 P30 AG028740-01 (Pahor) 4/1/2012-3/31/2017 NIH/NIA
Claude D. Pepper Older Americans Independence Center (OAIC)
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.
(Leeuwenburgh) Leader Genomics and Biomarkers Core: PI
(Leeuwenburgh) Leader Research Career Dev. Core: PI
(Leeuwenburgh) Leader Research Development Project #1: PI

1R01DC012552 (Someya) 7/1/2013-6/30/2018 National Institutes of Health
Mitochondrial thioredoxin, caloric restriction, and age-related hearing loss
The overall goal of our research proposal is to provide new basic knowledge of the mechanism underlying the efficacy of CR - the most reproducible intervention for increasing lifespan in mammals – to delay the development of AHL in mammals.
Role: Co-I

R01 AG042525 (Manini) 7/15/2013-6/30/2018 National Institutes of Health
MtDNA variant modifiers of cardiopulmonary responsiveness to physical activity
The proposed research will discover genes that explain the variability in cardiopulmonary response to long term physical activity—a widely accepted behavior known to influence many facets of health. Role: Co-I

1 R01 AT007564-01 (Anton) 4/01/2014-8/31/2017
REVIVE - Resveratrol to Enhance Vitality and Vigor in Elders
The proposed clinical trial will test whether daily supplementation with 1000mg of resveratrol will improve mitochondrial function and physical performance in generally healthy but moderately functioning older men and women. The central hypothesis is that resveratrol treatment will improve mitochondrial function by activating key genes involved in mitochondrial biogenesis and metabolism, and that these biological/cellular changes can enhance physical performance among both low to moderately-functioning older adults.
Role: Co-I

U01-AG022376 NIH/NIA (Pahor) 9/1/2009-11/30/2015
Physical Exercise to Prevent Disability – LIFE Study
We propose conducting a Phase 3, single-masked multicenter randomized controlled trial to compare a moderate-intensity physical activity program to a successful aging health education program in sedentary older persons who are at risk of disability.
Role: Co-I

KL2 TR000065 CTSI KL-2 program 4/1/2009-3/31/2014 Mentor
National Institutes of Health Clinical and Translational Science Awards Program
The CTSI KL2 Multidisciplinary Scholars Program is a research training and funding opportunity for junior faculty at UF to foster a career in clinical/translational research.

Osato Research Institute (Anton-Leeuwenburgh) 07/1/2013 – 12/31/2015
Efficacy of fermented papaya preparation (FPP) in improving health and physical function in older adults with mild functional limitations
This pilot study will evaluate the effects of supplementation with FPP (dosage = 9 grams per day) for one month on markers of systemic inflammation, physical performance, tissue oxygenation, fatigue, and health related quality of life, in generally healthy, older adults (age > 65 years) with elevated levels of systemic inflammation (C-reactive protein levels > 1.0) and moderate functional limitations (Short Physical Performance Battery Score < 10).
Role: Co-I

NIH 1P50 GM000052-01 (Moore) 9/1/2014-5/31/2015
Epidemiology of Chronic Critical Illness in Surgical ICU Patients after Sepsis
This project proposes to investigate and describe the epidemiology of CCI and PICS in sepsis patients, identify early biomarkers that can predict its incidence and outcome, explore mechanisms that drive this process, and examine potential interventions to prevent the development of PICS in septic CCI patients.
Role: PI - Core C – Bioanalytical Core
Co-I – Project 2 – MDSCS Drive the PICS
Co-PI - Project 4 – Diaphragm & Leg Strength Rehab

Completed Research Support
2RO1 AG 17994-06 NIH Leeuwenburgh (PI) 7/1/2006-6/30/2013
National Institute of Health/National Institute of Aging
Project Title: Molecular Mechanisms of Oxidative Stress in Aging Muscle
The major goals for this project are to study mitochondrial function, energy production and oxidative stress with age in cardiac and skeletal muscle.
Role: PI

NIA R01AG14979-10A1 (Foster) 6/1/2007–5/31/2012
Project Title: Mechanism for altered synaptic function during aging
The aim of this study is to investigate the molecular mechanisms of synaptic function during aging and potential interventions.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Dr. Andrew P. Maurer	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) DREWMAURER	

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)*	MM/YY	FIELD OF STUDY
University of Pittsburgh, Pittsburgh, PA, USA	B.S.	12/2004	Neuroscience
University of Arizona, Tucson, AZ, USA	Ph.D.	12/2008	Neuroscience
University of Arizona, Tucson, AZ, USA	Postdoctoral	06/2014	Neuroscience
University of Florida, Gainesville, FL, USA	Postdoctoral	06/2014	Neurobiology of Aging

A. Personal Statement

Throughout my scientific career, I have been focused on trying to understand the neurophysiological mechanisms underlying learning and memory. As a graduate student, I worked with Dr. Bruce McNaughton, acquiring skills in the acquisition and analysis of high-density single-unit electrophysiological recordings from awake-behaving rats. This technique enables over 100 neurons to be monitored simultaneously in multiple brain regions while rats perform behavioral tasks. Much of my research focus was on combining neuron spiking data with local-field potentials in order to determine how spike timing is altered as a consequence of both location and time (i.e., theta phase precession).

This research track was extended under the supervision of Dr. Carol A. Barnes, a leader in the field of the neurobiology of age-related cognitive decline. I continued to develop and implement high-level analyses to reveal novel computations of the CA1 subregion of the hippocampus. By using a population-vector correlation method, examining short-time scale hippocampal dynamics, I demonstrated that the hippocampus makes "predictions" regarding up-coming locations that are dependent on movement velocity. This study also revealed that the temporal sequences in which place fields are traversed are compressed into individual theta cycles in a manner that changes with velocity.

Currently, our research is focused on understanding the neuronal mechanisms by which information is propagated within the brain and how these processes are altered as a function of aging. By studying the ageassociated impact of neurogenesis decline, it will be possible to evaluate whether or not modulating the birth and migration of new neurons is a therapeutic intervention for episodic memory decline. Moreover, by recording from populations of neurons in the prefrontal cortex and using pharmacological intervention, we will test how inhibitory neuron function may underlie working memory decline in the elderly. Finally, by simultaneously monitoring blood flow and electrophysiology activity, we will have a novel approach that allows us to assay the neurovascular unit across the lifespan. We believe that this approach will open avenues to broader interventions that address both anatomical alterations in neural vasculature as well as physiological deficits.

B. Positions and Honors

Positions and Employment

2002-2004 Undergraduate Research Assistant in Dr. Bill Yates' Vestibular Research laboratory (U of Pitt)
2004-2008 Graduate Research Associate in Dr. Bruce McNaughton's Neural Systems, Memory and Aging Laboratory (U of Arizona)
2005-2006 Graduate Teaching Assistant for "Memory mechanisms & Neural Computation" (U of Arizona)
2009-2013 Postdoctoral Research Fellow in Evelyn F. McKnight Brain Institute with Dr. Carol Barnes (U of Arizona)
2013-2014 Postdoctoral Research Fellow with Dr. Jennifer Bizon (U of Florida)

Awards and Honors

2003 Graduated Cum Laude, University of Pittsburgh
2007 Society for Neuroscience Travel Award
2008 D.B. Marquis Behavioral Neuroscience Award
2011-2014 Ruth L. Kirschstein National Research Service Award

C. Selected Peer-reviewed Publications

Most relevant to the current application

1. **Maurer AP**, Lester A, Burke S, Ferng J, Barnes CA(In Press) Back to the Future: Preserved Hippocampal Network Activity During Reverse Ambulation. In Press. *J Neurosci*.
2. Topper NC, Burke SN, **Maurer AP** (2014) Multiple frequency audio signal communication as a mechanism for neurophysiology and video data synchronization. *J Neurosci Methods* 238C:35-42.
3. **Maurer AP**, Burke SN, Lipa P, Skaggs WE, Barnes CA (2012) Greater running speeds result in altered hippocampal phase sequence dynamics. *Hippocampus* 22:737-747.
4. **Maurer AP**, McNaughton BL (2007) Network and intrinsic cellular mechanisms underlying theta phase precession of hippocampal neurons. *Trends Neurosci* 30:325-333.
5. **Maurer AP**, Cowen SL, Burke SN, Barnes CA, McNaughton BL (2006a) Organization of hippocampal cell assemblies based on theta phase precession. *Hippocampus* 16:785-794.
6. **Maurer AP**, Cowen SL, Burke SN, Barnes CA, McNaughton BL (2006b) Phase precession in hippocampal interneurons showing strong functional coupling to individual pyramidal cells. *J Neurosci* 26:13485-13492.
7. **Maurer AP**, Vanrhoads SR, Sutherland GR, Lipa P, McNaughton BL (2005) Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus. *Hippocampus* 15:841-852.
8. 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* 122:535-548.
9. Burke SN, **Maurer AP**, Nematollahi S, Uprety AR, Wallace JL, Barnes CA (2011) The influence of objects on place field expression and size in distal hippocampal CA1. *Hippocampus* 21:783-801.
10. Burke SN, **Maurer AP**, Nematollahi S, Uprety A, Wallace JL, Barnes CA (2014) Advanced age dissociates dual functions of the perirhinal cortex. *J Neurosci* 34:467-480.
11. Burke SN, **Maurer AP**, Hartzell AL, Nematollahi S, Uprety A, Wallace JL, Barnes CA (2012) Representation of three-dimensional objects by the rat perirhinal cortex. *Hippocampus* 22:2032-2044.
12. Wilkinson KA, **Maurer AP**, Sadacca BF, Yates BJ (2004) Responses of feline medial medullary reticular formation neurons with projections to the C5-C6 ventral horn to vestibular stimulation. *Brain Res* 1018:247-256.

D. Research Support

Past

Ruth L. Kirschstein National Research Service Award (F32), 7/01/2011 – 6/30/2014

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Leonid L. Moroz	**Distinguished Professor of Neuroscience, Genetic, Chemistry & Biology**
eRA COMMONS USER NAME (credential, e.g., agency login) **MorozL**	

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)*	MM/YY	FIELD OF STUDY
Institute of Developmental Biology, Moscow, USSR	Ph.D.	1989	Physiology, Develop. Biol.
University of Leeds, Leeds, UK	Postdoc.	1994	Physiology
Dept. Molecular Physiol., Univ. of Illinois, Urbana,IL	Researcher	1997	Neuroscience
Beckman Institute, Univ. of Illinois, Urbana, IL	Researcher	1998	Bioanalytical Chemistry
Dept. Neuroscience & Brain Institute, Univ. of Florida, Gainesville, FL and Whitney Laboratory for Marine Bioscience, Univ. of Florida, St. Augustine, FL	Professor	1998-present	Neuroscience, Zoology, Chemistry, Genomics & Nanotechnology

A. Personal Statement

This proposal focuses on systematic determination and validation of new classes of molecular probes for realtime imaging of various biomolecules in single cells, characterized neural populations including well-defined memory forming circuits. To do so, we will develop and implement the innovative chemistry, single-cell genomic approaches and physiological measurements using tools of nanotechnology and single molecule measurements. Specifically, we plan to integrate imaging with genomic profiling to underestand the logic of gene regulation as neurons learn and remember. This data will be used to identify genes involved in memory mechanisms and reconstructing signal transduction pathways to generate a nearly complete computational portrait of a neuron. I have a broad background in comparative, integrative, cellular and molecular physiology and neuroscience, having spent more than 20 years working with various groups of experimental models in biology and medicine with specific training and expertise in key research areas for this application. As PI or co-Investigator on several previous University- and NIH funded grants, I laid the groundwork for this proposed research by developing single cell cDNA libraries for genomic, methylome and transcriptome profiling in Aplysia relevant to studies of the genomic bases of neuronal identity, plasticity, development and toxicology. In addition, I successfully administered NIH and NSF projects including, together with Drs. Tan, Ju and Kandel, a large multi-institutional collaborative project, The NIH Center of Excellence in Genomic Sciences. I also collaborated with researchers at Columbia University, UCLA, UIUC, European Centers, and Institutions, and produced several peer-reviewed publications from each project. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget. I have a demonstrated record of successful and productive research projects in an area of high relevance for this application, and my experiences have prepared me to lead the project.

B. Positions and Honors

Positions and Employment

1993-1994 Postdoctoral Researcher, Department of Physiology, University of Leeds, Leeds, UK.
1994-1997 Postdoctoral Researcher, Dept. Molecular and Integrative Physiology, University of Illinois, IL.
1997-1998 Research Specialist in Life Sciences, Beckman Institute, Dept. Chemistry, Urbana, IL.
1998 -2003 Assistant Professor of Neuroscience, Dept. Neuroscience University of Florida, Gainesville, FL.
2003 -2006 Associate Professor of Neuroscience, Dept. Neuroscience University of Florida, Gainesville, FL.
2006 - Professor of Neuroscience, Chemistry & Biology; Depts. Neuroscience, Chemistry, Biology; Brain Institute, Genetic Institute & The Whitney Laboratory, University of Florida, FL, USA
2011 - Professor of Genetic, Genetic Institute, University of Florida, Gainesville, FL
2013- Distinguished Professor, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

1993- present Member, Society for Neuroscience
1998- present Member, Society for Integrative and Comparative Biology
2000- present NSF, NIH, ad hoc reviewer
2011 – Editorial Board, J. Neurogenetics

Honors

1989 European Training Program in Brain and Behavioral Research (ETP) Award
1992 European Training Program in Brain and Behavioral Research (ETP) Research Award
1993-1994 Royal Society Postdoctoral Fellow Award, UK
1995-2000 Howard Hughes Medical Institute: International Scholar
2000 NSF medal for research in Antarctica
2002 Packard Interdisciplinary Science Award
2005 NIH Science Award (Nitrite Research)
2005 McKnight Brain Research Foundation Award
2007 Faculty Achievement Recognition Honoree & Award
2012 McKnight Brain Research Foundation Award

C. Selected Peer-Reviewed Publications (from 126 peer reviewed publications)

1. **Moroz LL** et al. (2014). The Ctenophore Genome and Evolutionary Origins of Neural Systems, *Nature*, 510, 109-114, doi: 10.1038/nature13400.
2. **Moroz L.L.**, Kohn A.B. (2013). Singe-Neuron Transcriptome and Methylome Sequencing for Epigenomic Analysis of Aging. *Methods in Molecular Biology*, 1048: 323-352
3. Puthanveettil SV et al., (2013). The Synaptic Transcriptome of Aplysia: Isolation and characterization of RNAs actively transported by kinesin complex from the cell body to synapses. *Proc.Natl.Acad. Sci*. USA, 110(18):7464-7469
4. Kohn A.B., Moroz, T.P., Barnes, J.P., Netherton, M., **Moroz, L.L.** (2013) Single-Cell Semiconductor Sequencing. *Methods in Molecular Biology*, 1048: 247-284
5. Ptitsyn A and **Moroz L.L.** (2012). Algorithm for gain and loss of gene analysis in distantly related genomes. *BMC Bioinformatics*. V. 15:S5. doi: 10.1186/1471-2105-13-S15-S5.
6. Yalan Z., et al. (2012). Regulation of neuronal excitability by interaction of Fragile X Mental Retardation Protein with Slack potassium channels. *J. Neuroscience* 32(44):15318 –15327
7. **Moroz LL**. Aplysia: A quick quide. (2011). *Current Biology*, 21(2):R60-61.
8. Philippe H, et al. (2011). Acoelomorph flatworms are deuterostomes related to Xenoturbella. *Nature* 470:255-258
9. Kocot et al.(2011). Phylogenomics reveals deep molluscan relationships. *Nature*, 477(7365):452-456
10. **Moroz, L.L.** Kohn, A. (2010). Do different neurons age differently? Direct genome-wide analysis of aging in identified cholinergic neurons. *Frontiers in Neuroscience*, 6(2), 1-18.
11. **Moroz, L.L.** (2009). On the independent origin of complex brains and neurons. *Brain, Behavior and Evolution*, v.74(3): 177-190.
12. Lee YS, et al. (2008). Transcriptome analysis and identification of regulators for long-term plasticity in Aplysia kurodai. Proc Natl *Acad Sci USA*;105(47):18602-18607.
13. Gillette, R., Huang, R., Hatcher, N., **Moroz, L.L.** (2000). Cost-benefit analysis potential in feeding behavior of a predatory snail by integration of hunger, taste and pain. *Proc.Natl Acad Sci*. USA: 97, 3585-3590.
14. **Moroz, L.L.** et al. (2006) Neuronal transcriptome of Aplysia: Neuronal compartments and circuitry. *Cell*;127:1453-1467.
15. Bourlat, S.J., et al. (2006). Deuterostome phylogeny reveals monophyletic chordates and the new phylum Xenoturbellida. *Nature*, 444, 85-88.

D. Research Support

Ongoing Research Support

NIH/NIGM Genomic Bases of Behavioral Learning (Moroz)
1R01GM097502-02 07/01/2011- 05/31/2015

NIH/NINDS (Moroz) "Genomic Approaches to Deciphering Memory Circuits"
1R01MH097062-01A1 09/01/2012 - 08/31/2017

NSF (Moroz) Quest for the Earliest Transmitters: Signal Molecules in Ctenophores 03/01/2012 - 28/02/2016

NASA (Moroz, Halanych). Genomics and Phylogeny of Basal Metazoa 04/01/2013 - 01/31/2018

There is no overlap of these grants with the current proposal

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Dr. Brandi K. Ormerod	Associate Professor
eRA COMMONS USER NAME (credential, e.g., agency login) BORMEROD	

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)*	MM/YY	FIELD OF STUDY
Queen's University, Kingston, ON, Canada	B.Sc.	1998	Biopsychology
University of British Columbia, BC, Canada	Ph.D.	2003	Neuroscience
Stanford University, Stanford, CA, USA	Postdoctoral	2006	Stem Cell Sciences

A. Personal Statement

My research program broadly focuses upon understanding how endogenous neurogenesis impacts hippocampus-dependent learning and memory across lifespan and how endogenous progenitor cells could be mobilized to treat CNS injury and disease, with emphasis upon how neuroinflammation impacts endogenous progenitor cell behavior. Our central approach combines neuroanatomical, biochemical and pharmacological techniques with behavioral variables to investigate how inflammation is translated into neuroinflammation and how neuroinflammation impacts memory in young, middle-aged and aged rats, potentially through its effects on adult hippocampal neurogenesis. We are particularly interested in how individual changes in rates of neurogenesis may impact spatial ability across lifespan. A key element of our approach involves the consideration of individual differences in cognitive aging, which can be leveraged to identify and to better understand the relevant mechanisms underlying both impaired and successful cognitive aging. Our ultimate goal is to develop strategies that rejuvenate impaired cognitive aging and promote successful cognitive aging. I have published extensively in areas relevant to this proposal that include gender differences in adult neurogenesis and cognition, how adult neurogenesis changes across lifespan and the quantification of inflammatory/neuroinflammatory analytes and how they impact adult neurogenesis and cognition across lifespan. I have expertise in all of the techniques that will be employed in the proposed work including the confocal and stereological quantification of neurogenesis and activated microglia, multiplex analyses of analyte concentrations and behavioral testing across cognitive domains. I have an excellent track record in graduate student training (with 7 PhD students and 10 Master's students graduated) and am currently training 2 PhD students and 1 Master's student and possess the skill set required to lead this project.

B. Positions and Honors

Positions and Employment

Since 2013 – Associate Professor, Biomedical Engineering Dept, University of Florida
- Developed and taught: Professional Development (BME6936) and Physiology (BME5401)
- Taught: BME Seminar (BME1008)

Since 11/2011 – Joint Faculty, Neuroscience Dept, University of Florida

Since 11/2006 - Assistant Professor, Biomedical Engineering Dept, University of Florida
- Developed and taught: Introduction to BME (EML4930), Cell Engineering Laboratory (BME3323L), Foundations of Neural Engineering (BME6936), Stem Cell Engineering (BME6936)
- Taught: Problem Based Learning (BME8654).

2003-2006 Postdoctoral Stem Cell Researcher, Dr. Theo Palmer' Stem Cell Lab, Stanford University

1998-2003 Teaching assistant/laboratory instructor for 5 different graduate and undergrad courses at UBC

1998-2003 Graduate Research Assistant in Dr. Liisa Galea's Behavioral Neuroendocrinology Lab (UBC)

1997-1998 Undergraduate Research Assistant in Dr. Weisman's Avian Bioaccoustics Laboratory (Queen's)

1997-1998 Undergraduate Teaching Assistant for 4th yr Behavioral Pharmacology (Queen's University)

1996-1998 Undergraduate Research Assistant in Dr. Beninger's Behavioral Pharm Laboratory (Queen's)

Awards/Honors

2007 UF College of Engineering Faculty Track Graduate Student Mentor

2003-2006 Chair of the Stanford Brain Food Bimonthly Seminar Series

2004 Natural Sci and Eng Research Council of Canada Post Doc Fellowship (Stanford; $40,000)

2004	NIH CHOC Human Embryonic Stem Cell Course (Burnham Inst; Scholarship Bursary; $1,500)
2003	Michael J. Fox Foundation Postdoctoral Fellowship (US$78,000)
2003	Society for Neuroscience Chapters Travel Award (US$735)
2003	UBC Brain Research Centre "3D Microscopy of Living Cells Course" scholarship (US$2,250)
2002	Invited to introduce UBC president Dr. Martha Piper at the first Nobel Awardee Michael Smith Honorary "Women at the Frontiers of EXXcellence" Conference opening ceremony
2001	Natural Sciences and Engineering Research Council of Canada Scholarship B (UBC; $38,400)
2001	Killam Predoctoral Fellowship (UBC; CDN$44,000 - $24,000 top-up accepted)
2001	Killam Predoctoral Fellowship Travel Award (UBC; CDN$1,500)
2001	Alzheimers Society of Canada Predoctoral Fellowship (UBC; CDN$44,000 – declined)
1998	Faculty of Graduate Studies Travel Award (UBC; CDN$400)
1999	Natural Sciences and Engineering Research Council of Canada Scholarship A (UBC; $34,600)

Committees and Service

Since 2013	Member of the Executive Board of the University of Florida's Association of Academic Women
Since 2013	Program Committee – UF Association of Academic Women
Since 2013	Member of the University of Florida Institutional Biosafety Committee
Since 2013	Reviewer for the NSF Faculty Early Career Development (CAREER) Panel
Since 2013	Reviewer for the New York State Stem Cell Science (NYSTEM) Grant Competition Panel
2013	UF BME Dept Laboratory Coordinator Search Committee
2010/11	UF BME Dept Lecturer Search Committee
2011	UF BME Health and Safety Committee
Since 2010	Reviewer for the US-Israel Binational Science Foundation
Since 2010	Reviewer - Korean Agency for Science, Technology & Research (A*Star)
2010	UF BME Dept Awards Committee
2010	UF BME Dept New Building Committee
2009	UF BME Dept New Faculty Search Committee
2009	UF BME Dept Chair Search Committee
2009	UF Neuroscience Department New Faculty Search Committee
2008/9	New Equipment Coordinator for New UF Biomedical Sciences Building (shopped, generated quotes, sole sourced, received and arranged assembly and training for > $1.2 million worth of equipment singlehandedly).
2009	UF BME Dept New Faculty Search Committee
2009	Reviewer NSF - Integrative Organismal Systems Section
2007	The Federation of Cloning and Aging webpage content editor
2007	Reviewer for U Washington Alzheimers Disease Research Center Grants
Since 2007	Member Maryland-Funded TEDCO Stem Cell Grant Competition Review Panel
2006-2013	UF BME Department Blood Borne Pathogens Training Officer
2006–2009	Biomedical Engineering Department Academic Committee

C. Selected Peer-reviewed Publications (from 31 peer reviewed publications; 46 published abstracts, 36 invited talks and 40 other scientific presentations)

1. Asokan A, Ball AR, Laird CD, Hermer L, **Ormerod BK**. Desvenlafaxine may accelerate neuronal maturation in the dentate gyri of adult male rats. *PlosOne*. 10.1371/journal.pone.0098530. **PMID 24896246**.
2. Qia X, Shana Z, Jia Y, Guerra V, Alexander JC, **Ormerod BK**, Bruijnzeel AW (2014) Sustained AAV-mediated overexpression of CRF in the central amygdala diminishes the depressive-like state associated with nicotine withdrawal in rats. *Translational Psychiatry*, 4:4385.
3. Hajihashemi MZ, Zhang T, **Ormerod BK**, Jiang H (2014). Non-invasive detection of seizure activity using timeseries analysis of light scattering images in a rat model of generalized seizure. *J Neuroscience Methods*, 227:18-28.
4. Speisman, RB, Kumar A, Rani A, Pastoriza JM, Severance JE, Foster TC and **Ormerod BK** (2013). Environmental enrichment restores neurogenesis and rapid acquisition in aged rats. *Neurobiol Aging*. 34:263-274. **PMID: 22795793; PMCID: 3480541**.
5. Speisman RB, Kumar A, Rani A, Foster TC and **Ormerod BK** (2013). Daily exercise improves memory, stimulates hippocampal neurogenesis and modulates immune and neuroimmune cytokines in aging rats. *Brain, Behavior and Immunity*, 28:25-43. **PMID: 23078985; PMCID: 3545095**.
6. **Ormerod BK**, Hanft SJ, Asokan A, Haditsch U, Lee SW and Palmer TD (2013). PPARγ activation prevents impairments in spatial memory and neurogenesis following transient illness. *Brain, Behav Immun*, 29:28-38. **PMID: 23108061; PMCID: 3570721**.

7. Ogle,WO, Speisman, RB, and **Ormerod BK** (2013). Potential of treating age-related depression and cognitive decline with nutraceutical approaches: A mini-review. *Gerontology*, 59:23-31. **PMID: 22947921**; doi: 10.1159/000342208
8. Bañuelos, C, LaSarge, CL, McQuail J, Hartman JJ, Gilbert RJ, **Ormerod BK**, Bizon JL (2013). Age-related changes in rostral basal forebrain cholinergic and GABAergic projection neurons: relationship with spatial impairment. *Neurobiology of Aging*, 34:845-862. **PMID: 22817834; PMCID: 3632262**.
9. Maden, M., Manwell L.A., **Ormerod B.K.** (2013). Proliferation zones in the axolotl brain and regeneration in the telencephalon. *Neural Development*, 8:1-15. **PMID: 23327114; PMCID: 3554517**.
10. Lee SW, Haditsch U, Monje ML, Cord BJ, Guzman R, Kim S, Boettcher C, Priller J, **Ormerod BK** and Palmer TD (2013). Absence of CCL2 is sufficient to restore hippocampal neurogenesis following cranial irradiation. *Brain, Behavior and Immunity*, 30:33-44. **PMID: 23041279; PMCID: 3556199**.
11. Stephens CL, Toda H., Palmer TD, DeMarse TB and **Ormerod BK** (2012). Adult neural progenitor cells reactivate superbursting in mature neural networks. *Experimental Neurology*, 234:20-30. **PMID: 22198136**; doi: 10.1016/j.expneurol.2011.12.009.
12. Bruijnzeel AW, Bauzo RM, Munikoti V, Rodrick GB, Yamada H, Fornal CA, **Ormerod BK**, Jacobs BL (2011). Tobacco smoke diminishes neurogenesis and promotes gliogenesis in the dentate gyrus of adolescent rats. *Brain Res*, 1413:32-42. **PMID: 21840504**; doi: 10.1016/j.brainres.2011.07.041.
13. Chen Z, Phillips LK, Gould E, Campisi J, Lee SW, **Ormerod BK**, Zwierzchoniewska M, Martinez OM, Palmer TD. (2011). MHC mismatch inhibits neurogenesis and neuron maturation in stem cell allografts. *PLoS One*. 6(3):e14787. **PMID: 21479168; PMCID: 3068158**.
14. Seifert AW, **Ormerod BK***, Cohn MJ* (2010). Sonic hedgehog regulates cell cycle kinetics during morphogenesis. *Nature Communications*. 1:1-9. *Corresponding Authors. **PMID: 20975695; PMCID: 2964453**.
15. **Ormerod BK.**, Palmer TD and Caldwell MA (2008). Neurodegeneration and Cell Replacement. *Philosophical Transactions of the Royal Society: Biological Sciences*, 363; 153-170. **PMID: 17331894; PMCID: 2605492**.
16. Buckwalter MS, Yamane M, Coleman BS, **Ormerod BK**, Chin JT, Palmer T, Wyss-Coray T (2006). Chronically increased transforming growth factor-beta1 strongly inhibits hippocampal neurogenesis in aged mice. *Am J Pathol*. 169:154-64. **PMID: 16816369; PMCID: 1698757**.

D. Research Support for the Past 3 Years

Current

McKnight Brain Research Foundation Age-related Memory Loss Panel 6/30/2013-12/31/2014

Causes of and relationships between olfactory/hippocampal neurogenesis and age-related cognitive decline

The major goal of this award is to quantify neurogenesis in samples already collected from young and aged male rats trained and tested in version of the water maze distinct from the one in the current proposal.

Role: PI (10% effort).

DoD PR121769 Carney, King, Ormerod (Multiple PI) 9/01/2014 – 8/31/2017

Advancement of Somatostatin Gene Delivery for Disease Modification and Cognitive Sparing in Epilepsy

The major goal of this award is to investigate whether somatostatin expression increased through delivery with a viral vector minimizes seizure behavior through its effects on neuroinflammation and/or neurogenesis.

Role: Multiple PI (30% effort).

Completed Support

NIH R37 AG036800-04 - Foster (PI) 9/30/2010 – 8/31/2014

Signaling cascades and memory deficits during aging

The major goal of this MERIT award is to identify inflammatory and neuroinflammatory biomarkers that predict age-related changes in NMDAr signaling and hippocampus-dependent behavior in male rats. Dr. Ormerod's role on this award is to quantify circulating and central cytokines and chemokines across lifespan in male rats and relate them to measures of behavior in a rapid water maze task. No Overlap.

Role: Co-I (30% effort).

NSF – DGE-0802270 Rachel Speisman (student) 5/31/2010-5/31/2013

Using biomarkers to predict successful versus unsuccessful aging in rats.

The major goal of this award was to support the PhD student to identify biomarkers of age-related cognitive decline in male rats.

Role: Sponsor/Mentor

McKnight Brain Institute Age-related memory loss panel Award 6/1/2010 – 5/31/2012

Biomarkers of age-related cognitive decline

The major goal of this award is to identify immunomodulatory/neuroimmunomodulatory markers of age-related cognitive decline in rats.

Role: PI

NSERC/SSHERC/CIHR Canada Tri-Council Michael Smith Foreign Study Supplements Program
Laurie Manwell (Student) 05/1/2011 – 08/1/2011
Axolotl neurogenesis following brain injury
The major goal of this award was to support the PhD student to conduct her project at a foreign institution.
Role: Sponsor/Mentor

Ruth K. Broad Biomedical Research Foundation Extramural Award 6/1/2008 – 5/31/2010
Neural stem cells and inflammation: Implications for Alzheimers disease
The major goal of this award is to understand how inflammation is transduced into neuroinflammation and to identify candidate inflammatory molecules that impact neural progenitor/stem cell behavior in young male mice.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Porges, Eric C.	Postdoctoral Fellow
eRA COMMONS USER NAME (credential, e.g., agency login) EPORGES	

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)*	MM/YY	FIELD OF STUDY
Hampshire College, Amherst, MA	B.A.	2004	Cognitive Science
University of Chicago, Chicago, IL	M.A.	2012	Integrative Neuroscience
University of Chicago, Chicago, IL	PhD.	2013	Integrative Neuroscience
University of Florida, Gainesville, FL	Postdoctoral Fellow	2013	Neuroscience

A. Personal Statement

The proposed study will examine the impact of alcohol use on HIV-associated brain dysfunction. By combining measurement of GABA concentration with functional MRI modalities, the proposed study will help achieve a better understanding of how functional cortical brain abnormality and neurocognitive impairment are linked to concentrations of GABA. GABA is the principal inhibitory neurotransmitter, and well known to be impacted by alcohol consumption. However, imaging of CNS GABA in the context of HIV-alcohol interactions and cognition is a new approach, proposed here for the first time (to my knowledge).

I recently completed my doctoral training at the University of Chicago, in the field of Integrative Neuroscience, under the mentorship of Dr. Jean Decety. My dissertation focused on individual differences in central and peripheral response to social stressors, with a specific emphasis on functions of the autonomic nervous system in modulating these responses. My research has employed many methods, with intensive training infunctional neuroimaging, characterization of autonomic nervous system responses, as well as methods for measuring behavior and affective states and experiences.

Currently I am a Postdoctoral Fellow at the Cognitive Aging and Memory Program and Clinical Translational Research Program (CAM-CTRP), in the Institute on Aging, at the University of Florida. My primary mentor is Dr. Ron Cohen. Under Dr. Cohen's mentorship I am currently working on the role of the central and autonomic nervous systems as mediators of cognitive function, especially in the context of social and non-social stressors. My current and proposed research extends my previous research questions to additional clinical populations, including individuals experiencing TBI (work in progress at the VA) and HIV (which I propose here). My role in the proposed project involved theoretical contributions, the design of experimental equipment and paradigms, and I will take primary responsibility for the analysis and interpretation of data collected.

I currently have a first author manuscript on individual differences in physiological responses to social stressors under review. Two additional manuscripts for which I am a co-author are in the later stages of review and expected to be accepted within the next few weeks. An additional fully completed manuscript will be submitted for publication in September. I also have a number of manuscripts for which data analysis is complete that are in preparation for submission. I anticipate first authorship on at least two of these.

B. Positions and Honors

Positions and Employment

2014 – Present Editorial Board Review Editor, Frontiers in Psychology, Emotion Science
2014 - Present Postdoctoral Fellow, Cognitive Aging and Memory Program, Clinical Translational Research Program (CAM-CTRP), Institute on Aging, University of Florida
2012 Annual meeting of the Society for Psychophysiological Research, 2012. Student Poster Award
2012 Psychology graduate student organization Travel award

2011 Psychology graduate student organization Research award
2010 – 2012 Norman Henry Anderson Travel award funded presentations at Society for Neuroscience, Cognitive Neuroscience, Association for Psychological Science and Society for Psychophysiological Research
2010 University of Chicago Summer Grants for Research
2009 University of Chicago Summer Grants for Research

C. Selected Peer-reviewed Publications

Most relevant to the current application

1. Clark, D.J., Rose, D.K., Ring, S. A., **Porges, E. C.** (2014). Utilization of central nervous system resources for preparation and performance of complex walking tasks in older adults. *Frontiers in Aging Neuroscience*, 6:217. DOI=10.3389/fnagi.2014.00217
2. *Smith, K. E., ***Porges, E. C.**, Norman, G. J., Connelly, J. J., & Decety, J. (2014). Oxytocin receptor (OXTR) gene variation predicts empathic concern and autonomic arousal while perceiving harm to others. *Social Neuroscience*, 9: 1. **PMCID: PMC3923324** (*contributed equally to this manuscript).
3. Williamson, J.B., **Porges, E.C.** Lamb, D.G. Heilman, K.M. & Porges, S.W. (2013). A possible mechanism for PTSD symptoms in patients with traumatic brain injury: The role of central autonomic network disruption. *Frontiers of Neuroengineering*, 6:13. **PMCID: PMC3867662**
4. **Porges, E. C.**, & Decety, J. (2013). Violence as a source of pleasure or displeasure is associated with specific functional connectivity with the nucleus accumbens. *Frontiers in Human Neuroscience*, 7: 447. **PMCID: PMC3741555**
5. Carter, C.S., & **Porges, E. C** (2011). Parenthood, stress, and the brain. *Biological Psychiatry*, 70, 804-805. **PMID: 21986092**
6. Decety, J., & **Porges, E. C.** (2011). Imagining being the agent of actions that carry different moral consequences: an fMRI study. *Neuropsychologia*, 49, 2994-3001. **PMID: 21762712**
7. Lamm, C., **Porges, E. C.**, Cacioppo, J. T., & Decety, J. (2008). Perspective taking is associated with specific facial responses during empathy for pain. *Brain Research*, 1227, 153-161. **PMID: 18619426**

D. Research Support

<u>Ongoing Research Support</u>

IOA-CAM 09/01/2013 – 08/31/2015
University of Florida, Institute on Aging postdoctoral fellowship funded by the Cognitive Aging and Memory Program and Clinical Translational Research Program.
Department of Veterans Affairs Co-I (Williamson, PI) 06/01/2014 – 12/01/2014 Brain Rehabilitation Research Center Pilot Innovation (VA RR&D grant)
External autonomic nervous system modulation for the treatment of PTSD.
Role: Co-I

1 LK2RX000707-01 CDA-2 (VA-K) Co-I (Williamson, PI) 04/01/2012 – 03/31/2017
White matter changes and mild TBI: Emotional and autonomic consequences.
Role: Co-I

<u>Previous Research Support</u>

09/01/08 - 07/01/13 University of Chicago, Integrative Neuroscience Program.
Five-year fellowship including tuition, stipend and benefits

09/1/11 - 6/1/12 University of Chicago Student research funds award

09/1/12 - 6/1/13 University of Chicago Student research funds award

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person.

NAME	POSITION TITLE
Catherine Price, PhD	Associate Professor, Department of Clinical & Health Psychology, Joint Appointment in Dept. of Anesthesiology
eRA COMMONS USER NAME ceprice	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Central Florida, Orlando, FL	BS	1995	Psychology
University of Central Florida, Orlando, FL	MS	1997	Clinical Psychology
Crozer-Chester Medical Center, Upland, PA	Externship	1998-1999	Geriatric Neuropsychology
Thomas Jefferson University, Phil., PA	Externship	1998-1999	Applied Neuropsychology
University of Pennsylvania, Phil., PA	Externship	1999-2001	Cognitive Neuroscience & Clinical Neuropsychology
University of Florida, Gainesville, FL	Internship	2001-2002	Clinical Neuropsychology
Drexel University, Philadelphia, PA	PhD	2002	Clinical Psychology
University of Florida, Gainesville, FL	PostDoc	2002-2004	Neuropsychology

A. Personal Statement

My primary research aims are: First, to understand the relative contribution of white matter versus subcortical gray matter structure integrity on the cognitive profiles of subcortical neurodegenerative diseases (e.g., small vessel vascular dementia, Parkinson's disease). Second, to apply this knowledge towards more collaborative and longitudinal research examining the predictive value of white and gray matter structure integrity on a) disease associated cognitive decline and b) vulnerability to accelerated cognitive change after elective medical interventions (i.e., DBS; major elective surgeries). I have peer reviewed published research articles examining cognitive and neuroanatomical components of cortical and subcortical dementias (e.g., papers published in Neurology, Stroke, Journal of the International Neuropsychological Society, Neuropsychology, and Neuropsychologia, Anesthesiology). I have expertise in the neuropsychological assessment of movement disorder, dementia, mild cognitive impairment, and post-operative cognitive dysfunction, as well as structural neuroimaging and reliable change analyses. I am currently directing two highly collaborative R01 investigations that address both of my career goals. One examines the role of subcortical and white matter integrity on the development of cognitive dysfunction after surgery (NINR). The other examines areas of white matter connectivity in Parkinson's disease cognitive phenotypes (NINDS). Both build directly on the experiences acquired from my NINDS K-23 award. In addition to these grants I serve as a clinician (neuropsychologist) and mentor to graduate students, undergraduate honor students, interns, and post-doctoral fellows (research and clinical).

B. Positions and Honors

Positions

2004-2005	Research Assistant Professor
10/05-2013	Assistant Professor, Dept of Clinical & Health Psychology, Joint in Dept. of Anesthesiology
07/2013-present	Associate Professor with Tenure, Dept. of Clinical & Health Psychology, Joint in Dept. of Anesthesiology

Honors

1995	University of Central Florida Psychology Undergraduate Student of the Year
1998	Philadelphia Neuropsychology Society President's Research Award
2003	P.E.O. Scholar Award (International women's educational organization
2006	University Scholar Mentor of the Year, University of Florida, Gainesville, Florida
2008	Mentor Award for University Scholar Program
2009	Invited Presenter: Postoperative Cognitive Dysfunction, International Neuropsychological Society BiAnnual Conference
2010, 2012, 2014	Mentor to recipients of the Florida Society of Neurology student research award
2010, 2013	NIH Loan Repayment Recipient
2011-2014	Associate Editor, Journal of the International Neuropsychological Society

2012 Research Mentor Award; Clinical and Health Psychology, University of Florida
2013 UF Provost's Assistant Professor of Excellence Award
2014 Awarded Paul Satz Term Professorship in Clinical Neuropsychology
2014 UF Research Foundation Professor Award

C. Selected Peer-reviewed Publications – five most relevant (*student; Price as mentor)

1. **Price, C.**, Pereira, D. B., Andre, R., Garvan, C.W., Nguyen, P., Herman, M., Seubert, C. (in press, October 2014). Prospective pilot investigation: Pre-surgical depressive symptom severity and anesthesia response in women undergoing surgery for gynecologic mass removal. *International Journal of Behavioral Medicine*.
2. *Schwab, N. A., Tanner, J. J., Nguyen, P., Schmalfuss, I.M., Okun, M., Bowers, D., **Price, C.C.** (in press, October 2014). Proof of principle: Transformation approach alters caudate nucleus volume and structure-function associations. *Brain Imaging and Behavior*.
3. **Price, C. C.**, Tanner, J. J., Schmalfuss, I., Garvan, C., Gearen, P., Dickey, D., Heilman, K., McDonagh, D., Libon, D. J., Leonard, T., Bowers, D., Monk, T. (2014). A pilot study evaluating pre-surgery neuroanatomical biomarkers for postoperative cognitive decline after total knee arthroplasty in older adults. *Anesthesiology*, 120(3), 601-13. **PMCID3930070**.
4. **Price, C. C.**, Mitchell, S. M., Brumback, B., Tanner, J. J., Schmalfuss, I., Lamar, M., Giovannetti, T., Heilman, K. M., Libon, D. J. (2012). MRI leukoaraiosis (LA) threshold and the phenotypic expression of dementia. *Neurology*, 79(8), 734-740. **PMCID4098873**.
5. **Price, C. C.**, Favilla, C., Tanner, J., Towler, S., Hass, C., Foote, K., Okun, M. (2011). Lateral ventricular volume poor predictor of DBS gait and motor outcome for idiopathic Parkinson's disease. *Parkinsonism and Related Disorders*, 17(5), 343-347. **PMCID3109211**.

D. Other relevant publications

1. Jones J.D., Jacobson C., Murphy M., **Price C.**, Okun M.S., Bowers D. (2014). Influence of hypertension on neurocognitive domains in nondemented Parkinson's disease patients. *Parkinsons Dis*. 2014, epub PubMed **PMID: 24587937**.
2. *Gullett, J.M., **Price, C. C.**, Nguyen, P., Okun, M.S., Bauer,R.M., Bowers,D. (2013). Reliability of three Benton Judgment of Line Orientation short forms in idiopathic Parkinson's disease. *The Clinical Neuropsychologist*, 27(7), 1167-1178. **PMCID3832287**.
3. Seidel, G.A., Giovannetti, T., **Price, C.C.**, Tanner, J., Mitchell, S., Eppig, J., & Libon, D.J. (2013). Neuroimaging correlates of everyday action in dementia. *Journal of Clinical and Experimental Neuropsychology*, 35(9), 993-1005. **PMCID3882061**
4. Jones, J.D., Malaty, I., **Price, C.C.**, Okun, M., Bowers, D. (2012). Health comorbidities and cognition in 1948 patients with idiopathic Parkinson's disease. *Parkinsonism Related Disorder*s, 18(10), 1073-1078. PMC Journal – In Process.
5. *Moum, S.J; **Price, C.C.**, Limotai, N., Oyama, G., Ward, H., Jacobson, C., Foote, K. D., Okun, M.S. (2012). Effects of STN and GPi deep brain stimulation on impulse control disorders and dopamine dysregulation syndrome. *PLoS*, 7(1), e29768. **PMCID3266249**.
6. **Price, C. C.**, Cunningham, H., Coronado, N., Freedland, A., Cosentino, S., Penney, D., Pennisi, A., Bowers, D., Okun, M., Libon, D. (2011). Clock drawing in the Montreal Cognitive Assessment: recommendations for dementia evaluation. *Dementia and Geriatric Cognitive Disorders*, 31(3), 179-187. **PMCID3065510**.
7. Zahodne, L.B., Bowers, D., **Price, C.C.**, Bauer, R.M., Nisenzon, A., Foote, K.D., & Okun, M.S. (2011). The case for testing memory with both stories and word lists prior to DBS surgery for Parkinson's disease. *The Clinical Neuropsychologist*, 25(3), 348-358. **PMID: 21491347**.
8. Nocera, J. R., **Price, C. C.**, Fernandez, H. H., Amano, S., Vallabhajosula, S., Okun, M. S., Hwynn, N., Hass, C. J. (2010). Tests of Dorsolateral Frontal Function Correlate with Objective Tests of Postural Stability in Early to Moderate Stage Parkinson's Disease. *Parkinsonism and Related Disorders*, 16, 590-594. **PMID20829093**.
9. **Price, C. C.**, Wood, M. F., Leonard, C. M., Towler, S., Ward, J., Montijo, H., Kellison, I., Bowers, D., Monk, T., Newcomer, J. C., Schmalfuss, I. (2010). Entorhinal cortex volume in older adults: reliability and validity considerations for three published measurement protocols. *Journal of the International Neuropsychological Society*, 16(5), 846-855. **PMCID3070302**.
9. **Price, C.**, Garrett, K. D., Jefferson, A. L., Cosentino, S., Tanner, J. T*.,Penney, D. L., Swenson, R., Giovannetti, T., Bettcher, B. M., Libon, D. J. (2009). Leukoaraiosis severity and list-learning in dementia. *The Clinical Neuropsychologist*, 23, 944-946. **PMC2866111**.
10. **Price, C.**, Garvan, C., Monk, T. (2008). Type and severity of cognitive impairment in older adults after non- cardiac surgery. *Anesthesiology*, 108 (1), 8-17. **PMCID2911011**.
11. **Price, C.**, Jefferson, A. J., Merino, J. G., Heilman, K., Libon, D. J. (2005). Towards an operational definition of the Research Criteria for Subcortical Vascular Dementia: Integrating neuroradiological and neuropsychological data. *Neurology*, 65(3), 376-82. **PMCID2746450**.

E. Research Support

<u>Ongoing Research Support</u>

NSF 12-543 Price (PI, UF site) 09/01/14 to 08/30/17

Title: Collaborative Research: Think-Inferring Cognitive State from Subtle Behaviors. This study will use smart technology to examine patterns of cognitive function relative to neuroanatomical connections.

R01 N5082386-02 Price (PI) 09/01/14 to 08/30/19
NIH NINDS
Title: White Matter Connectivity and PD Cognitive Phenotypes
The goal of this research project is to determine if cognitive phenotypes and cognitive trajectory can be partially explained by frontal and temporal circuit integrity.

Supplement to R01NS082385-01A1 Price (Mentor) 07/01/14-06/30/16
Title:Research Supplement to Promote Diversity in Health-Related Research (Admi Supplement) to White Matter Connectivity and PD Cognitive Phenotypes; Post-doctoral Fellow: Shellie-Anne Levy, Ph.D.

R01 NR014810-01 (PI, Price) Price (PI) 09/27/13 to 08/30/18
NIH NINR
Title: Neuroimaging Biomarkers for Post-Operative Cognitive Decline in Older Adults
This study will determine the extent that preoperative neuroimaging markers can predict type of post-operative cognitive decline after major orthopedic surgery in older adults.

Completed Research Support
K23NS060660_01 (PI/Trainee: Price) 09/31/07-09/30/13
White Matter and Cognition in PD
To learn methods associated with diffusion and tractography measurement and examine hypothesized patterns of white matter integrity relative to cognitive profiles in Parkinson's disease.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Kimberly T. Sibille	Assistant Professor
eRA COMMONS USER NAME ksibille	

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Auburn University, AL	B.S.Ed.	1987	Human Movement
University of South Florida	M.A.	1992	Counselor Education
Fielding Graduate University, CA American Psychological Association Accredited	M.A. Ph.D.	2006 2008	Psychology/Clinical
University of Florida	Fellowship	2010	Clinical/Translational Pain Research

A. Personal Statement

Chronic pain is a major public health issue with devastating consequences to individuals, communities, and the healthcare system (IOM, 2011). Further complicating matters, incidence is increasing with the growing population of the aging community while treatment progress lags due to a lack of biological indices for risk identification, clinical management, and evaluation of therapeutic interventions. My research interests and investigative pursuits encompass the interactive influences of biological, behavioral, psychological, and social factors specific to osteoarthritis and other chronic pain conditions with a focus on aging and resilience. My research efforts are benefited by over fifteen years of clinical experience with responsibilities that included program development/management in healthcare settings. Additionally, I have a strong background in teaching with a focus on graduate, medical, and professional education with experience working with post-doctoral residents in family medicine, dentistry, and pain research.

B. Positions and Honors

Positions and Employment

1992-1994 Adult Outpatient Therapist, Directions for Mental Health, Clearwater, FL
1994-1997 Supervisor, Outreach Services, Directions for Mental Health, Clearwater, FL
1997-2007 Consultant, Facilitator, Private Practitioner (2007-2013), Tampa Bay, FL
1997-1998 Counselor, Cancer Patient Support Services, Morton Plant Mease Healthcare, Clearwater FL
1998-2000 Manager, Cancer Patient Support Services, Morton Plant Mease Healthcare, Clearwater, FL
2000-2004 Behavioral Science Instructor, Bayfront Family Medicine Residency, St. Petersburg, FL
2001-2003 Continuing Education Presenter, St. Petersburg College, St. Petersburg, FL
2001-2007 Adjunct Instructor, Graduate Program/Professional Counseling, Argosy University, Tampa, FL
2003-2006 Doctoral Trainee, Brain Injury Unit, Bayfront Medical Center, St. Petersburg, FL
2005-2006 Doctoral Trainee, Post-Traumatic Stress Disorder Clinic, Tampa VAMC, Tampa, FL
2007-2008 Psychology Intern, North Florida/South Georgia Veteran's Health System, Gainesville, FL
2008-2010 Postdoctoral Fellow, Comprehensive Center for Pain Research, University of Florida, FL
2008-2011 Psychology Resident/Trainee, N Florida/S Georgia Veteran's Health System, Gainesville, FL
2010-2014 Research Assistant Professor, College of Dentistry, University of Florida, Gainesville, FL
2014-Present Assistant Professor, College of Medicine, University of Florida, Gainesville, FL

Honors

2008 NIH T-32 Fellowship, Comprehensive Center for Pain Research, University of Florida
2009 Outstanding Research Poster, Fielding Graduate University
2010 American Pain Society, Young Investigator Travel Award

2010 International Association for the Study of Pain, 13th World Congress on Pain, Travel Award
2010 Nominee, Council of Graduate Schools/University Microfilms International Dissertation Award
2010 American Pain Society Future Leaders in Pain Research Grant
2011-2013 University of Florida, Clinical and Translational Science Institute KL2 Scholar
2011-2013 University of Florida, Claude D. Pepper Junior Scholar
2011-2015 National Institutes of Health Loan Repayment Award

Other Experience and Professional Memberships

1998-1999 Suncoast Mental Health Counselors Association, President
1998-1999 Florida Mental Health Counselors Association, Regional Representative
2002-2005 St. Petersburg College Nursing/Allied Health Advisory Committee
2005-2007 Board of Directors, Family Service Centers, Inc.
2005-2007 Faculty Personnel Committee, Student Representative, Fielding Graduate University
2006-2010 Association for the Behavioral Sciences and Medical Education
2009-2011 Scientific & Professional Liaison Council, Society of Behavioral Medicine
2002-2014 Florida Behavioral Medicine Research Consortium
2003-2014 Florida Psychological Association
2008-2014 American Pain Society
2010-2014 International Association for the Study of Pain

C. Selected Peer-Reviewed Publications

1. Cruz-Almeida Y, **Sibille KT**, King C, Goodin B, Glover T, Riley III J, Sotolongo A, Herbert M, Schmidt J, Fessler B, Redden D, Staud R, Bradley L, Fillingim RB (2014). Racial and ethnic differences in older adults with knee osteoarthritis. *Arthritis & Rheumatology*, 66(7):1800-10. **PMID: 24729357, PMCID: PMC4077911**
2. Riley III JL, Cruz-Almeida Y, Glover TL, King CD, Goodin BR, **Sibille KT**, Bartley EJ, Herbert, MS, Sotolongo A, Fessler BJ, Redden DT, Staud R, Bradley LA, Fillingim RB (2013). Age and race effects on pain sensitivity and modulation among middle-aged and older adults. *Journal of Pain*, 15(3):272-82. **PMCID: PMC4005289**
3. King C, **Sibille KT**, Goodin BR, Cruz-Almeida Y, Glover TL, Bartley E, Riley JL, Herbert MS, Sotolongo A, Schmidt J, Fessler BJ, Redden DT, Staud R, Bradley LA, Fillingim RB (2013). Experimental pain sensitivity differs as a function of clinical pain severity in symptomatic knee osteoarthritis. *Osteoarthritis and Cartilage* 21(9), 1243-1252. **PMCID: PMC3831366**
4. Cruz-Almeida Y, King C, Goodin B, **Sibille KT**, Glover T, Riley III J, Sotolongo A, Herbert M, Schmidt J, Fessler B, Redden D, Staud R, Bradley L, Fillingim RB (2013). Psychological profiles and pain characteristics of older adults with knee osteoarthritis. *Arthritis Care & Research*, 65(11): 1786-94. **PMCID: PMC3922880**
5. **Sibille KT**, Riley III JL, McEwen B (2012). Authors build an important foundation for further research. Letter to the Editor: Role of allostatic load in sociodemographic patterns of pain prevalence in the U.S. population. *Journal of Pain*, 13(12), 1269-70. **PMCID: PMC4116687**
6. Goodin BR, Glover TL, Sotolongo A, King CD, **Sibille KT**, Herbert MS, Cruz-Almeida Y, Sanden SH, Staud R, Redden DT, Bradley LA, Fillingim RB (2012). The association of greater dispositional optimism with less endogenous pain facilitation is indirectly transmitted through lower levels of pain catastrophizing. *Journal of Pain*,14(2):126-35. **PMCID: PMC3592576**
7. Glover TL, Goodin BR, Horgas AL, Kindler LL, King CD, Sibille KT, Peloquin CA, Riley III JR, Staud R, Bradley LA, Fillingim RB (2012). Vitamin D, Race, and Experimental Pain Sensitivity in Older Adults with Knee Osteoarthritis. *Arthritis & Rheumatism*, 64(12), 3926-35. **PMCID: PMC3510313**
8. Goodin, B.R., Pham, Q.T., Glover, T.L., Sotolongo, A., King, C.D., **Sibille, K.T.**, Herbert, M.S., Cruz-Almeida, Y., Sanden, S.H., Staud, R., Redden, D.T., Bradley, L.A., & Fillingim, R.B. (2013). Perceived racial discrimination, but not mistrust of medical researchers, predicts the heat pain tolerance of African Americans with symptomatic knee osteoarthritis. *Health Psychology*,32(11):1117-26. **PMCID: PMC3943939**
9. **Sibille, K.T.**, Janusek, L., Mathews, H.L., & Fillingim, R.B. (2012). Telomeres and epigenetics: Potential relevance to chronic pain. *PAIN*, 153(9): 1789-93. **PMCID: PMC3631537**
10. **Sibille, K.T.**, Kindler, L., Glover, T., Staud, R., Riley III, J. L., & Fillingim, R.B. (2012). Affect balance style, experimental pain sensitivity, and pain-related responses. *Clinical Journal of Pain*, 28(5), 410-7. **PMCID: PMC3349000**
11. Goodin, B.R., Kronfli, T., King, C.D., Glover, T.L., **Sibille, K.T.**, & Fillingim, R.B. (2012). Testing the relation between dispositional optimism and conditioned pain modulation: Does ethnicity matter? *Journal of Behavioral Medicine*, 36(2):165-74. **PMCID: PMC3605222**
12. **Sibille, K.T.**, Langaee, T., Burkley, B., Gong, Y., Glover, T.L., King, C., Riley III, J.L., Leeuwenburgh, C., Staud, R., Bradley, L.A., Fillingim, R.B. (2012). Chronic pain, perceived stress, and cellular aging: an exploratory study. *Molecular Pain*, 8, 12. **PMCID: PMC3298803**

13. **Sibille, K.T.**, Kindler, L., Glover, T., Gonzalez, R., Staud, R., Riley, J. III, Fillingim, R. (2011). Individual differences in morphine and butorphanol analgesia: A laboratory pain study. *Pain Medicine*, 12(7), 1076-85. **PMCID: PMC3155877**
14. Kindler, L., **Sibille, K.**, Glover, T., Staud, R., Riley, III, J., & Fillingim, R. (2011). Drug response profiles to experimental pain are opioid and pain modality specific. *Journal of Pain*, 12(3), 340-51. **PMCID: PMC3052955**
15. **Sibille, K.**, Greene, A., & Bush, J. (2010). Preparing physicians for the 21st century: Targeting communication skills and the promotion of health behavior change. *Annals of Behavioral Science and Medical Education*, 16(1), 7-13. **PMCID: PMC3242004**

D. Research Support

Ongoing Research Support

American Pain Society and the Sharon S. Keller Chronic Pain Research Grant Sibille (PI) 06/14-05/16
Optimizing Chronic Pain Treatment with Enhanced Neuroplastic Responsiveness
The overall aims of the study are to identify strategies to optimize the neurobiological environment to respond to clinical treatment interventions and override the maladaptive neuroplastic changes associated with chronic pain in individuals with osteoarthritis.

NIH/NIAMS 1K23AR062099 Sibille (PI) 04/13-03/17
Biological Markers of System Burden in Symptomatic Knee OA: A Prospective Study
The objectives of the study are to prospectively evaluate associations of pain and functional limitations with a developing measure of system burden in ethnically diverse older adults with and without knee OA and explore the role of various biopsychosocial factors that may be protective or increase vulnerability for pain and functional decline.

International Association for the Study of Pain/Funded by Scan/Design Foundation by Inger & Jens Bruun
Sibille (PI) 06/12-06/15
Assessing the impact of Chronic Pain on Biological Measures of System Burden and Cellular Aging
Funding supports collaborative efforts between investigators from Norway and the United States. The project involves investigating the effects of chronic pain on biological functioning (system burden), and exploring associations with pain sensitivity, functioning, and disease progression (chronic pain severity).

Completed Research Support

American Pain Society Future Leaders in Pain Research Grant Program Sibille (PI) 01/11-09/13
Effects of Chronic Pain and Psychosocial Stress on Telomere Length/Telomerase Activity
To better understand the interaction between biological processes, chronic pain, and biopsychosocial variables among ethnically diverse older adults with and without symptomatic knee osteoarthritis; and 2) to determine the potential clinical and predictive utility of telomere biomarkers.

NIH/NCRR CTSA University of Florida UL1RR029890 and KL2 TR000065 Sibille (PI) 12/11-03/13
Biological Markers of System Burden in Symptomatic OA To better understand the interaction between biological processes, chronic pain, and biopsychosocial variables among ethnically diverse older adults with and without symptomatic knee osteoarthritis; and 2) to determine associations between baseline telomere measures and psychological and functional measures at 24 months.

2 P30 AG028740-06 Pahor (PI) 12/11–03/13
Claude D. Pepper Older Americans Independence Center - Pepper Junior Scholar
The mission of the University of Florida Older Americans Independence Center (OAIC) is to assess the risk factors of physical disability in older adults, develop and test effective prevention therapies, and train new investigators in research on aging and disability, while developing their leadership qualities.

NIH/NIA 3 R01 AG0333906 07S1 Fillingim (PI) 9/10-08/12
Ethnic Differences in Pain Responses/OppNet Competitive Revision
Evaluate the biological interface of behavioral and social variables in ethnically diverse older adults with and without chronic OA-related pain, determine the utility of telomere length and telomerase activity as tools in assessing system overload resulting from chronic pain and/or other biopsychosocial variables, and to identify vulnerability and resilience factors.
Role: Co-PI on ARRA OppNet Project

UF CTSI Pilot and Collaborative Research Projects – Major Initiatives Fillingim (PI) 12/09-06/12
Effects of OA-Related Pain on Telomere Length and Telomerase Activity
Obtain preliminary data on biomarkers of cellular aging and explore associations with experimental and chronic pain among ethnically diverse adults with and without knee osteoarthritis.
Role: Co-Investigator

00091387 HRSA Catalanotto (PI) 01/11-08/11
Predoctoral Training in General, Pediatric, and Public Health Dentistry and Dental Hygiene
Investigate experiences in seeking and receiving medical and dental care, and incorporate models in communication and diversity training of health care providers.

NIH T32 NS045551 Yezierski (PI) 10/08-09/10
Integrative and Translational Training in Pain Research
To prepare future pain researchers in an understanding of the biological and psychosocial complexity of pain and develop the skills and abilities to implement multidisciplinary, integrative, translational approaches.
Role: Postdoctoral Fellow

Ranganatha Sitaram, PhD

BIOGRAPHICAL SKETCH

Dr. Ranganatha Sitaram

Webpage: http://www.bme.ufl.edu/labs/sitaram/

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Gainesville
Florida, USA.

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ranganatha.sitaram@bme.ufl.edu,
tharale@gmail.com

Primary Faculty, J. Crayton Pruitt Family Department of Biomedical Engineering
University of Florida
Biomedical Sciences Building JG-56 P.O. Box 116131 Gainesville, FL, USA.

Affiliate Faculty, Department of Psychology, Center for Cognitive Aging
University of Florida, Gainesville, USA.

Visiting Professorships:
1. Institute of Medical Psychology & Behavioral Neurobiology University of Tuebingen, Germany.
2. Sri Chitra Tirunal Institute of Medical

EDUCATION

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY, AWARD
Mysore University, India	B.E.	1988	Mechanical Engg. ***High Distinction***
PSG College of Engineering, India	M.E.	1992	Engineering Design, ***High Distinction***
University of Tuebingen, Germany	Ph.D.	2008	Neuroscience, ***Summa Cum Laude***

A. Personal Statement

My research focus is in the fields of Neuroimaging and Brain-Machine Interfaces, which lie at the intersection of neuroscience, imaging and computational intelligence. My work is based on the pivotal question: can modulation of brain activity in selected regions and networks lead to specific changes in sensation, perception, cognition and action, and if so what are they and how can they be used in the clinical treatment of neurological and psychiatric disorders? My investigations are based on the fundamental neuropsychological paradigms of learning, namely, operant conditioning, classical conditioning and associative learning, to induce changes in the brain and behavior; combining it with innovative developments in functional brain imaging with real-time fMRI, fNIRS and EEG, physiological measurement technology, and computational algorithms.

Prior to my current position (from July 2012) at the University of Florida, I was a faculty member at the Institute of Medical Psychology and Behavioral Neurobiology (2009-2012) in the University of Tubingen. During 2000-2004 I served as Lead Scientist and Chief Technology Officer at the Institute of InfoComm Research in Singapore in a variety of computational and engineering fields, including artificial intelligence and robotics, communications and control, and software engineering. My cumulative experience as an independent investigator is about 14 years, the first half of which was spent in federal funded R&D labs, and the second half in academia as a faculty member. My formative years as a research scientist were spent at the Kent Ridge Digital Labs in Singapore (1992-2000).

B. Positions and Honors

(* indicates position as independent investigator)

Positions

1991-1992: Senior Research Fellow, PSG College of Technology, Coimbatore.
1992-1996: Research Scientist, Kent Ridge Digital Labs, Singapore.
1996-1999: Project Leader, Kent Ridge Digital Labs, Singapore.
1999-2000: Group Leader*, Kent Ridge Digital Labs, Singapore.
2000-2004: Lead Scientist*, Neuroinformatics Lab, Institute for Infocomm Research (I2R), Singapore.

2002-2004: Chief Technical Officer*, SmartEdge spinoff, I2R, Singapore.
2004-2008: Senior Research Scientist, Institute of Medical Psychology & Behavioural Neurobiology Eberhard-Karls-University.
2009-2012: Faculty Member*, Institute of Medical Psychology & Behavioural Neurobiology Eberhard-Karls-University.
2012-present: Visiting Professor*, Sri Chitra Institute of Medical Sciences and Technology, Trivandrum, India.

Honors

2002 - Infocomm Development Authority (IDA) award of 1 million Singapore dollars for the development of a suite of products and services based on intelligent wireless technology called SmartEdge built in Sitaram's laboratory.
2009-2012 - Indian President's Award of Visiting Professor of Neuroscience and Neuroimaging in the Department of Neurology, Sri Chitra Tirunal University of Medical Sciences and Technology, Trivandrum, India.

C. Relevant Publications: Google citations=1815, h-index=20, and i10-index=27.

(* indicates equal contribution by the authors, Bold font indicates corresponding, senior author)

Original Articles

1. **Sitaram R**, Caria A, Veit R, Gaber T, Ruiz S, Birbaumer N. Volitional control of the anterior insula in criminal psychopaths using real-time fMRI neurofeedback: A pilot study *Frontiers in Behavioral Neuroscience* 8, 344, October 2014.
2. van der Heiden L, Liberati G, **Sitaram R**, Kim S, Jaśkowski P, Raffone A, Olivetti Belardinelli M, Birbaumer N, Veit R. Insula and inferior frontal triangularis activations distinguish between conditioned brain responses using emotional sounds for basic BCI communication. *Front Behav Neurosci*. 2014 Jul 21;8:247. doi: 10.3389/fnbeh.2014.00247. eCollection 2014. PubMed **PMID: 25100958; PubMed Central PMCID: PMC4104703**.
3. Kotchoubey B, Bütof S, **Sitaram R**. Flagrant Misconduct of Reviewers and Editor: A Case Study. *Sci Eng Ethics*. 2014 Aug 26. [Epub ahead of print] PubMed **PMID: 25156788**.
4. Ruiz S, Buyukturkoglu K, Rana M, Birbaumer N, **Sitaram R**. Real-time fMRI brain computer interfaces: self-regulation of single brain regions to networks. *Biol Psycho*l. 2014 Jan;95:4-20. doi: 10.1016/j.biopsycho.2013.04.010. Epub 2013 May 1. Review. PubMed **PMID: 23643926**.
5. Rea M, Rana M, Lugato N, Terekhin P, Gizzi L, Broetz D, Fallgatter A, Birbaumer N &, **Sitaram R**, Caria A. Lower Limb Movement Preparation in Chronic Stroke: A Pilot Study Toward an fNIRS-BCI for Gait Rehabilitation. *Neurorehabil Neural Repair*. 2014 Jan 30. PubMed **PMID: 24482298**. (Impact Factor, IF: 4.88)
6. Lawrence EJ, Su L, Barker GJ, Medford N, Dalton J, Williams SC, Birbaumer N, Veit R, **Sitaram R**, Bodurka J, Brammer M, Giampietro V, David AS. Self-regulation of the anterior insula: Reinforcement learning using real-time fMRI neurofeedback. *Neuroimage*. 2013 Nov 11;88C:113-124. doi: 10.1016/j.neuroimage.2013.10.069. [Epub ahead of print] PubMed **PMID: 24231399**. (Impact Factor, IF: 7.06)
7. Rana, M., Gupta, N., Lee, S., Birbaumer, N., **Sitaram R**. A tool box for real-time subjectindependent and subject-dependent classification of brain states from fMRI signals. *Front. Neurosci*., 17 October 2013 | doi: 10.3389/fnins.2013.00170. (Impact " Factor, IF: 5.07)
8. Halder S, Varkuti B, Bogdan M, Kuebler A, Rosenstiel W, **Sitaram R**, Birbaumer N. Prediction of brain-computer interface aptitude from individual brain structure. *Front Hum Neurosci*. 2013;7:105. doi: 10.3389/fnhum.2013.00105. Epub 2013 Apr 2. PubMed **PMID: 23565083**; PubMed Central **PMCID: PMC3613602**. (Impact Factor, IF: 5.07)
9. Ruiz S, Birbaumer N, **Sitaram R**. Abnormal Neural Connectivity in Schizophrenia and fMRI-Brain-Computer Interface as a Potential Therapeutic Approach. *Front Psychiatry*. 2013;4:17. doi: 10.3389/fpsyt.2013.00017. Epub 2013 Mar 22. PubMed **PMID: 23525496**; PubMed Central **PMCID: PMC3605516**. (Impact Factor, IF: 5.07)
10. Sulzer J, **Sitaram R**, Blefari ML, Kollias S, Birbaumer N, Stephan KE, Luft A, Gassert R. Neurofeedback-mediated self-regulation of the dopaminergic midbrain. Neuroimage. 2013 Mar 1;75C:176-184. doi: 10.1016/j.neuroimage.2013.02.041. [Epub ahead of print] PubMed PMID: 23466940. (Impact Factor, IF: 7.06)
11. Liberati G, Dalboni da Rocha JL, van der Heiden L, Raffone A, Birbaumer N, Olivetti Belardinelli M, **Sitaram R**. Toward a Brain-Computer Interface for Alzheimer's Disease Patients by Combining Classical Conditioning and Brain State Classification. *J Alzheimers Dis*. 2012 Mar 26. [Epub ahead of print]. (Impact Factor, IF: 4.39)
12. Varkuti, B., Yaozhang, P., Kok Soon, Phua., Veit, R., Guan, C., **Sitaram, R**. Predicting individual Fugl-Meyer Score Gains over a 12-week Period from Functional Connectivity Changes based on repeated rs-fMRI Measurements in a subcortical Stroke Sample receiving Motor-Imagery based robot- assisted EEG-BCI Training. *Journal of Neurorehabilitation and Neural Repair* (2012, online publication). (Impact Factor, IF: 4.88)
13. Várkuti B, Cavusoglu M, Kullik A, Schiffler B, Veit R, Yilmaz Ö, Rosenstiel W, Braun C, Uludag K, Birbaumer N, **Sitaram R**. Quantifying the link between anatomical connectivity, gray matter volume and regional cerebral blood flow: an integrative MRI study. *PLoS One*. 2011 Apr 15;6(4):e14801. doi:10.1371/journal.pone.0014801. PubMed **PMID: 21525993**; PubMed Central **PMCID: PMC3078126**. (Impact Factor, IF: 3.73)

14. Matthew D. Sacchet, Jürgen Mellinger, **Ranganatha Sitaram**, Christoph Braun, Niels Birbaumer and Eberhard Fetz. Volitional control of neuromagnetic coherence. *Front. Neurosci*., 26 December 2012 | doi: 10.3389/fnins.2012.00189. (Impact Factor, IF: 5.07)
15. Schurholz M, Rana M, Robinson N, Ramos-Murguialday A, Cho W, Rohm M, Rupp R, Birbaumer N, **Sitaram R**. Differences in hemodynamic activations between motor imagery and upper limb FES with NIRS. *Conf Proc IEEE Eng Med Biol Soc*. 2012 Aug;2012:4728-31. PubMed **PMID: 23366984**. (Impact Factor, IF: 7.69)
16. Caria, A*., **Sitaram, R.***, Veit, R., Begliomini, C., Birbaumer, N. Volitional control of anterior insula activity modulates the response to aversive stimuli. A real-time fMRI study.Biological Psychiatry. *Biol Psychiatry*. 2010 Sep 1;68(5):425-32. Epub 2010 Jun 8. (Impact Factor, IF: 9.77
17. **Sitaram, R.**, Veit, R., Stevens, B., Caria, A., Birbaumer, N., Hummel, F. Acquired control of ventral premotor cortex: An exploratory real-time fMRI and TMS study. *Journal of Neurorehabilitation and Neural Repair. Neurorehabil Neural Repair*. 2012 Mar-Apr;26(3):256-65. Epub 2011 Sep 8. (Impact Factor, IF: 4.88)
18. Ruiz, S., Lee, S., Soekader, S., Caria, A., Veit, R., Kircher, T., Birbaumer, N., **Sitaram, R**. Learned self-regulation of anterior insula in schizophrenia: effects on emotion recognition and neural connectivity. *Hum Brain Mapp*. 2011 Oct 22. doi: 10.1002/hbm.21427. [Epub ahead of print]. (Impact Factor, IF: 7.03)
19. Veit R, Singh V, **Sitaram R**, Caria A, Rauss K, Birbaumer N. Using real-time fMRI to learn voluntary regulation of the anterior insula in the presence of threat-related stimuli. *Soc Cogn Affect Neurosci*. 2011 Oct 7. [Epub ahead of print]. (Impact Factor, IF: 6.78)
20. Halder, S., Furdea, A., Varkuti, B., **Sitaram, R.**, Bogdan, M., Rosenstiel, W., Birbaume, N., Kubler, A. Auditory standard oddball and visual P300 brain-computer interface performance. *International Journal of Bioelectromagnetism Vol. 13*, 2011. (Impact Factor, IF: 3.10)
21. Rota G, Handjaras G, **Sitaram R**, Birbaumer N, Dogil G. Reorganisation of functional and effective connectivity during fMRI-BCI modulation of prosody processing. *Brain Lang*. 2010 Sep 30. [Epub ahead of print]. (Impact Factor, IF: 3.84)
22. **Sitaram R***, Lee S*, Ruiz S, Rana M, Veit R, Birbaumer N. Real-time support vector classification and feedback of multiple emotional brain states. *Neuroimage*. 2010 Aug 6. 2011 May 15;56(2):753-65. Epub 2010 Aug 6. (Impact Factor, IF: 7.06)
23. Lee, S., Halder, S., Kübler, A., Birbaumer, N., **Sitaram R**. Effective functional mapping of fMRI data with support-vector machines. *Hum Brain Mapp*. 2010(a) Jan 28. [Epub ahead of print]. (Impact Factor, IF: 7.03)
24. Lee, S.,* Ruiz, S., Caria, A., Birbaumer, N., **Sitaram, R***. Cerebral reorganization induced by real-time fMRI feedback training of the insular cortex: a multivariate investigation. *Neuroreh and Neural Rep* (2010). (Impact Factor, IF: 4.88)
25. Rota, G., **Sitaram, R.**, Veit, R., Erb, M., Weiskopf, N., Dogil, G., Birbaumer, N., 2008. Selfregulation of regional cortical activity using real-time fMRI: The right inferior frontal gyrus and linguistic processing. *Hum Brain Mapp*. 30(5):1605-14. (Impact Factor, IF: 7.03)
26. Caria, A., Veit, R., **Sitaram, R.**, Lotze, M., Weiskopf, N., Grodd, W., Birbaumer, N.,2007. Regulation of anterior insular cortex activity using real-time fMRI. *Neuroimage* 35, 1238-1246. (Impact Factor, IF: 7.06)
27. **Sitaram, R.**, Zhang, H., Guan, C., Thulasidas, M., Hoshi, Y., Ishikawa, A., Shimizu, K., Birbaumer, N., 2007. Temporal classification of multichannel near-infrared spectroscopy signals of motor imagery for developing a brain-computer interface. Neuroimage 34, 1416-1427. (Impact Factor, IF: 7.03)

Conference Papers

1. Korhan Buyukturkoglu, Mohit Rana, Sergio Ruiz, Steven A. Hackley, Surjo R. Soekadar, Niels Birbaumer, **Ranganatha Sitaram**. Volitional Regulation of the Supplementary Motor Area with fMRI-BCI neurofeedback in Parkinson's Disease: A Pilot Study. 6th Annual International IEEE EMBS Conference on Neural Engineering, San Diego, California, USA; 11/2013.
2. **Sitaram, R.**, Guan, C., Thulasidas, M., Jian Kang, W. Comparison of artifact removal methods on their effect on motor task and imagery classification in a brain-computer interface. Paper published in the proceedings of the 2nd International Conference on Advances in Medical Signal and Information Processing (MEDSIP), September 2004, Malta.
3. Xu Wenjie, Guan Cuntai, Chng Eng Siong, **Sitaram R.**, Manoj Thulasidas, Wu Jiankang. High Accuracy Classification of EEG Signal. Paper published in the proceedings of the International Conference of Pattern Recognition (ICPR), August, 2004.
4. Thulasidas, M., Guan, C., **Sitaram R.**, Jian Kang, W., Zhu, X., Xu, W. Effect of Ocular Artifact Removal in Brain Computer Interface Accuracy. Published in the proceedings of the 26th Annual Inter Conf IEEE Engineering in Medicine and Biology Society (EMBS), Sept, 2004.
5. Guan Cuntai, Zhu Xiaoyuan, **Ranganatha Sitaram**, Manoj Thulasidas, Wu Jiankang, "Dynamic Feature for robust classification of EEG Signal", submitted to 2nd International Conference on Advances in Medical Signal and Information Processing (MEDSIP), 5-8, September 2004, Malta.

Reviews

1. Birbaumer N, Ruiz S, **Sitaram R**. Learned regulation of brain metabolism. Trends Cogn Sci. 2013 May 7. doi:pii: S1364-6613(13)00082-X. 10.1016/j.tics.2013.04.009. [Epub ahead of print] PubMed PMID: 23664452. (Impact Factor, IF: 16.85)

2. Ruiz S, Buyukturkoglu K, Rana M, Birbaumer N, **Sitaram R**. Real-time fMRI brain computer interfaces: Self-regulation of single brain regions to networks. *Biol Psychol*. 2013 May 1. doi:pii: S0301-0511(13)00113-0. 10.1016/j.biopsycho.2013.04.010. [Epub ahead of print] PubMed **PMID: 23643926**. (Impact Factor, IF: 4.34)
3. Sulzer J, Haller S, Scharnowski F, Weiskopf N, Birbaumer N, Blefari ML, Bruehl AB, Cohen LG, Decharms RC, Gassert R, Goebel R, Herwig U, Laconte S, Linden D, Luft A, Seifritz E, **Sitaram R**. Real-time fMRI neurofeedback: Progress and challenges. *Neuroimage*. 2013 Aug 1;76:386-99. doi: 10.1016/j.neuroimage.2013.03.033. Epub 2013 Mar 27. PubMed **PMID: 23541800**. (Impact Factor, IF: 7.06)
4. Caria A, **Sitaram R**, Birbaumer N. Real-Time fMRI: A Tool for Local Brain Regulation. Neuroscientist. *Neuroscientist*. 2012 Oct;18(5):487-501. Epub 2011 Jun 7. (Impact Factor, IF: 6.42).
5. **Sitaram, R.**, Caria, A., Birbaumer, N., 2009. Hemodynamic brain-computer interfaces for communication and rehabilitation. *Neural Netw*. 22(9):1320-8. Epub 2009 May 24. (Impact Factor, IF: 2.51)
6. **Sitaram, R.**, Weiskopf, N., Caria, A., Veit, R., Erb, M., Birbaumer, N., 2008. fMRI brain-computer interfaces: A tutorial on methods and applications. *IEEE Signal Processing Magazine, Special Issue on BCI*. (2008). (Impact Factor, IF: 7.69)
7. **Sitaram, R.**, Caria, A., Veit, R., Gaber, T., Giuseppina, R., Kubler, A., Birbaumer, N., 2007. fMRI Brain-Computer Interface: A Tool for Neuroscientific Research and Treatment. *Computational Intelligence and Neuroscience 2007*, Article ID 25487, 10 pages, 2007. doi:10.1155/2007/25487. (Impact Factor, IF: 3.2)
8. Weiskopf, N., **Sitaram, R.**, Josephs, O., Veit, R., Scharnowski, F., Goebel, R., Birbaumer, N., Deichmann, R., Mathiak, K., 2007. Real-time functional magnetic resonance imaging: methods and applications. *Magn Reson Imaging*. (Impact Factor, IF: 3.08)
9. Sreedharan S, **Sitaram R**, Paul JS, Kesavadas C. Brain-computer interfaces for neurorehabilitation. *Crit Rev Biomed Eng*. 2013;41(3):269-79. Review. PubMed **PMID: 24579648**. (Impact Factor, IF: 5.97).

Book Chapters

1. Ruiz S, Birbaumer N, **Sitaram, R**. Volitional Control of Neural Connectivity. Brain-Computer Interface Research, 63-74, 2014.
2. Ruiz, S., Birbaumer, N., **Sitaram, R**. Brain-Computer Interface Research, C. Guger, B. Allison, and E.C. Leuthardt (eds.), Biosystems & Biorobotics 6, 63. DOI: 10.1007/978-3-642-54707-2_7, © Springer-Verlag Berlin Heidelberg 2014.
3. **Sitaram, R**. Lee, S., Birbaumer, N. Book Chapter: "BCIs that use metabolic signals" in the Book: Brain-Computer Interfaces: Principles and Practice Oxford University Press (2012). Editors, Jonathan R. Wolpaw and Elizabeth Winter Wolpaw. Pages: 301-316.
4. Daly, J., **Sitaram, R**. Book Chapter: "Other Medical Uses of BCI Technology" in the Book: Brain-Computer Interfaces: Principles and Practice Oxford University Press (2012). Editors, Jonathan R. Wolpaw and Elizabeth Winter Wolpaw. Pages: 351-362.
5. **Sitaram, R.**, Ruiz, S., Lee, S., Birbaumer, N. Chapter Title: Real-time decoding and feedback of brain states'. Book Title: Neuromodulation and Neurofeedback. Elsevier. Eds. Coben and Evans. (2010).
6. Neuroimaging Meditation. Erb, M., **Sitaram, R**. Edited by Tan Trich Thong. Meditation in the Light of Science. Published by Sunyata Meditation Association. California Perri 2010.
7. **Sitaram, R.**, Caria A., Gabet T., Kübler, A., Birbaumer, N., 2006. Biomedizinische Technik, Graz. Functional Magnetic Resonance based BCI.
8. **Sitaram, R.**, Hoshi, Y., Cuntai, G. (Eds.), 2005. Near Infrared Spectroscopy based Brain Computer Interface. Proceedings of the SPIE.

Monographs/Books

1. **Sitaram, R**. Hemodynamic Brain-Computer Interfaces: Techniques and Applications. VDM Verlag Dr. Mueller. Dudweiler Landstr. 99, 66123 Saarbrueken, Germany, 2010. p-135.

D. Patents

1. A System, Method and Language for Programming Behaviour in Synthetic Creatures. **Ranganatha Sitaram**, Annapoorna Nayak Pongal. International Patent Application Number: PCT/SG01/00143 Date of Grant of Patent: 30/Jun/2005.
2. Method and Apparatus for Developing and Distributing Interactive Advertisements. **Ranganatha Sitaram**, Ramanath Padmanabhan. International Patent Application Number: PCT/SG01/00143 Date of Grant of Patent: 27/Jan/2006.
3. Portable Reward Checkout, Reward Management and Reward Redemption System. Ramanath Padmanabhan, **Ranganatha Sitaram**. International Patent Application Number: PCT/SG01/00143 Date of Grant of Patent: 28/Jan/2006.
4. Improved Method of Co-ordinating a Group of Toys. **Ranganatha Sitaram**, Chan Sek Yue Pat, Arcot Desai Narasimhalu. Patent Application Number: SG 90113 Date of Grant of Patent: 31/Jan/2004.
5. Smart Interactive Billboard Device. Bao Xiaoming, **Ranganatha Sitaram**, Ramanath Padmanabhan. International Patent Application Number: PCT/SG01/00115.
6. A System for Interactive Information Display on a Billboard Inventors. **Ranganatha Sitaram**, Ramanath Padmanabhan. Patent Application Number: 200301560-9.

7. Portable Reward Checkout, Reward Management and Reward Redemption System. Ramanath Padmanabhan, **Ranganatha Sitaram.** International Patent Application Number: PCT/SG01/00143 Date of Grant of Patent: 28/Jan/2006.
8. Realtime spatiotemporal classification of functional states of the brain from neuroimaging signals. **Ranganatha Sitaram**, Niels Birbaumer. Applied in 2009.

E. Software Toolboxes Developed and Distributed

1. MANAS: FMRI toolbox for offline pattern classification of brain states (**Sitaram** et al 2012, Rana, **Sitaram** et al 2013, Lee, **Sitaram** et al 2010)
2. tMANAS: FMRI toolbox for real-time pattern classification and feedback of brain states (Rana, **Sitaram** et al 2013).
3. PRADEEP: FNIRS toolbox for offline and real-time pattern classification and feedback of brain states (Robinson, **Sitaram** submitted).
4. TEJAS: EEG toolbox for offline and real-time pattern classification and feedback of brain states (Schmidt, **Sitaram** in preparation).
5. ANVITA: DTI toolbox for pattern analysis of brain structural connectivity and network (Varkuti, **Sitaram** et al 2011).

F. Research support

Minor Grants (< 2 year duration, funding < USD 100, 000)

Start Date	Title	Funding agency	Investigators	Funding Amount to Sitaram
04/2014	Enhancing Positive Affect: Learned control of the Brain's Appetitive Circuit Using Real-Time FMRI Neurofeedback	McKnight Brain Institute, University of Florida	Ranganatha Sitaram (PI), Peter Lang (CoI)	USD 25,000
08/2013	Simultaneous fMRI and EEG recording for the study of brain functioning in a BCI system	Vicerrectoría de Investigación, Pontificia Universidad Catolica de Chile	Sergio Ruiz (PI), Ranganatha Sitaram (CoI)	student exchange and travel
06/2013	Brain computer interfaces for the enhancement of brain networks and emotion processing. Applications in depression and schizophrenia	Ministry of Education, Government of Chile	Sergio Ruiz (PI), Ranganatha Sitaram (CoI)	student exchange and travel
12/2012	Neural Basis of Brain Self-regulation using Real-time fMRI, fNIRS and Electrophysiology in Primates.	Centre for Integrative Neuroscience (CIN), Tuebingen	Ranganatha Sitaram (PI), Niels Birbaumer	USD 65,000
02/2012	Self-Regulation of Broca's Area using Real time fMRI in Post Stroke Aphasia patients	Department of Biotechnology (DBT, India)	Kesavadas Chandrasekh aran (PI), Ranganatha Sitaram (CoI)	USD 25,000
09/2011	Neurobiological Marker for Population Differences: a Neuroeconomic Investigation with Anxiety & Depression Patients contrasted with Normal Population	Department of Biotechnology (DBT), India	Kesavadas Chandrasekh aran (PI), Ranganatha Sitaram (CoI)	USD 25,000
07/2011	Self-regulation of Anterior Insula in Patients of Obsessive Compulsive Disorder.	Centre for Integrative Neuroscience (CIN), Tuebingen, Germany.	Ranganatha Sitaram (PI), Niels Birbaumer CoI)	USD 65,000

Major Grants (> 2 year duration, funding > USD 100,000)

Start Date	Title	Funding agency	Investigators	Funding Amount to Sitaram
03/2013	Diffusion Tensor Imaging compared to standard clinical measures of concussion in female and male collegiate athletes: a longitudinal survey across the college years	Toshiba Medical Systems	Tony Mancuso (PI), Ranganatha Sitaram	USD 150,000
12/2012	Neural Basis of Brain Self-regulation using Real-time fMRI, fNIRS and Electrophysiology in Primates.	Centre for Integrative Neuroscience (CIN), Tuebingen	Ranganatha Sitaram (PI), Niels Birbaumer	USD 65,000
12/2012	OPTOSIS: A Portable NIRS-BCI with Functional Electrical Stimulation for Stroke Rehabilitation (A Mutlicountry Collaboration between Germany, India, Spain and Turkey).	INDIGO: European Union and DBT India Grant Call	Ranganatha Sitaram (PI)	Euro 150,000
02/2012	Self-Regulation of Broca's Area using Real time fMRI in Post Stroke Aphasia patients	Department of Biotechnology (DBT, India)	Kesavadas Chandrasekharan (PI), Ranganatha Sitaram (CoI)	USD 25,000
09/2011	Neurobiological Marker for Population Differences: a Neuroeconomic Investigation with Anxiety & Depression Patients contrasted with Normal Population	Department of Biotechnology (DBT), India	Kesavadas Chandrasekharan (PI), Ranganatha Sitaram (CoI)	USD 25,000
07/2011	Self-regulation of Anterior Insula in Patients of Obsessive Compulsive Disorder.	Centre for Integrative Neuroscience (CIN), Tuebingen, Germany.	Ranganatha Sitaram (PI), Niels Birbaumer CoI)	USD 65,000
01/2011	Development of a Portable Functional Near Infrared Spectroscopy Brain-Computer Interface for Stroke Rehabilitation	Badenwuerttemberg State Ministry for Education and Research of Germany and Singapore	Ranganatha Sitaram (PI), Trevor Penny (CoI)	Euro 150,000
09/2010	Effective Connectivity Enhancement and Behavior in Schizophrenia: An fMRI Brain-Computer Interface Study	German Research Foundation (DFG)	Ranganatha Sitaram (PI), Niels Birbaumer CoI)	USD 275,000
04/2010	Volitional Regulation of Brain System for Craving using Real-time fMRI Brain-Computer Interface.	German Research Foundation (DFG)	Ranganatha Sitaram (PI), Niels Birbaumer CoI), Anil Batra (CoI)	USD 250,000
08/2008	Development of Real-time Support Vector Classification in an fMRI-BCI: Applications to Stroke and Lie Detection.	German Research Foundation (DFG)	Ranganatha Sitaram (PI), Niels Birbaumer CoI), Anil Batra (CoI)	USD 250,000

06/2002	Smart Wireless Meter and Smart Billboard Technologies using SmartEdge Machine-to-Machine Technology	Infocomm Development Authority of Singapore	Ranganatha Sitaram (PI),Ramanath Padmanabhan (CoI)	SGD 250,000

G. PhD Supervision and Mentoring

Year	Title	PhD/MSc
2008	Combining Structural and Functional Connectivity Measures from fMRI Signals	MSc
2010	Application of multivariate methods to an fMRI Brain-Computer Interface, by Mr. Sangkyun Lee	PhD
2010	Volitional Regulation of Anterior Insula to Threat Stimuli	MSc
2011	Real-time fMRI Brain-Computer Interface in Schizophrenia, by Mr. Sergio Ruiz	PhD
2012	Revealing the Webs: Insights from the Exploitation of Complementary Information from various Magnetic Resonance Imaging related Connectivity Methods, by Mr. Balint Varkuti	PhD
2012	Neural Conditioning for Perception of Subliminal Visual Stimuli using RtfMRI Feedback, by Sunjung Kim	PhD
2013	Real-time Brain State Classification of EEG Signals for Neuroscience Experiments by Mr. Andreas Schmidt	MSc
Ongoing - Expected 2014	Detecting brain structural connectivity abnormalities in Alzheimer patients from Diffuse Tensor Imaging signals using Graph Theory and Pattern Classification, by Mr. Josue Dalboni Rocha	PhD
Ongoing - Expected 2014	Real-time Subject Independent Classification and Feedback of Brain States from fMRI Signals and Application to Rehabilitation of Nicotine Adiction	PhD
Ongoing - Expected 2015	Modulation of Functional Connectivity using MEG/EEG Neurofeedback, Mr. Diljit Singh Kajal	PhD
Ongoing - Expected 2016	Neural Mechanisms of BOLD Self-regulation of Prefrontal Cortex using Combined fNIRS and Electrophysiology in Primates, by Ali Zaidi	PhD
Ongoing - Expected 2016	Combined rt-fMRI and Electrophysiology in Primates, by Srinidhi Chandrashekar	PhD
Ongoing - Expected 2017	Computational Modeling of Neural Activity from BOLD Signals from Combined BOLD and Electrophysiological Acquisitions in Primates, by Paulo Rogerio	PhD
Ongoing - Expected 2017	Computational Modeling of BCI Learning from Combined BOLD and Electrophysiological Acquisitions in Primates, by Andreas Schmidt	PhD

H. Current focus in Research

Neural Conditioning for Perception of Subliminal Visual Stimuli using RtfMRI Feedback
Real-time Brain State Classification of EEG Signals for Neuroscience Experiments
Detecting brain structural connectivity abnormalities in Alzheimer patients from Diffuse Tensor Imaging signals using Graph Theory and Pattern Classification
Real-time Subject Independent Classification and Feedback of Brain States from fMRI Signals and Application to Rehabilitation of Nicotine Addiction
Modulation of Functional Connectivity using MEG/EEG Neurofeedback
Neural Mechanisms of BOLD Self-regulation of Prefrontal Cortex using Combined fNIRS and Electrophysiology in Primates

Combined rt-fMRI and Electrophysiology in Primates
Computational Modeling of Neural Activity from BOLD Signals from Combined BOLD and Electrophysiological Acquisitions in Primates
Computational Modeling of BCI Learning from Combined BOLD and Electrophysiological Acquisitions in Primates

I. Current Focus in Graduate and Undergraduate Teaching

Primary Courses

Cognitive Neuroscience, Medical Psychology, Neuroimaging Methods and Neural Engineering.

Secondary Courses

Matlab Programming, fMRI and fNIRS Analyses, Multivariate Pattern Classification and Functional Connectivity Analysis.

J. Committee Work

1. PhD defense committee member for the thesis of Mr. Raphael Zimmerman, ETH Zurich (thesis: Functional Near Infrared Spectroscopy BCI for Stroke Rehabilitation)
2. Graduate Affairs Committee, University of Florida
3. Research Committee, University of Florida, University of Florida
4. Seminar Series Organization Committee, University of Florida
5. Research Day Organization Committee, University of Florida

K. Journal Editoral Board and Reviews

1. Frontier in Neurorehabilitation (editorial board).
2. Neuroimage,
3. Human Brain Mapping,
4. Journal of Neuroscience,
5. Cerebral Cortex,
6. Journal Neurorehabilitation and Neural Repair,
7. Journal of Neural Engineering,
8. Cognitive Neuroscience,
9. IEEE Signal Processing,
10. Biological Psychology,
11. Magnetic Resonance Imaging.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME John B Williamson	POSITION TITLE Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) wjohnb	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
The Florida State University, FL	B.A.	1996	Psychology
Virginia Tech, Blacksburg, VA	M.S.	1999	Clinical Psychology
Virginia Tech, Blacksburg, VA	Ph.D.	2004	Clinical Psychology
University of Chicago	Internship	2004	Neuropsychology
University of Illinois at Chicago	Clinical Fellowship	2004-2006	Neuropsychology
University of Illinois at Chicago	Research Fellowship	2006-2008	Neuroscience

A. Personal Statement

My background is in neuropsychology, psychophysiology and neuroscience. I currently have active grant support for work on the mechanisms of post traumatic stress disorder after traumatic brain injury, spatial perception after stroke, and vagal nerve stimulation treatment of emotional dysregulation and sleep disorders. Through my work with the CAM at the Institute of Aging, we have a pending R01 project to further collaborations on the mechanism of cognitive deficit due to heart failure and a method for improvement (a cardiac stimulator device that enhances cardiac output). My interest is in the understanding of mechanism of cognitive dysregulation particularly with respect to recruitment of prefrontal resources for emotional cognitive and executive control tasks in diseases that affect the brain.

B. Positions and Honors

Positions and Employment

Clinical Fellow Dept. of Neurology, University of Illinois, 2004-2006
Research Fellow Depts. of Neurology and Psychiatry, University of Illinois, 2006 – 2008
Research Health Scientist Dept. of Veteran Affairs, Gainesville, FL 2008 – present
Research Assistant Professor Dept. of Neurology, University of Florida, 2008-2012
Assistant Professor Dept. of Neurology, University of Florida, 2012 – present
Assistant Professor Dept. of Aging and Geriatric Research, University of Florida 2013 - present
Cognitive Aging and Memory Clinical Translational Research Program Scholar, UF 2013 - present

Other Experience and Professional Membership

2002- Member, International Neuropsychological Society
2008- Member, Florida Society of Neurology
2013- Member, American Academy of Clinical Neuropsychology
Ad Hoc Reviewer, Biological Psychology
Ad Hoc Reviewer, Journal of the International Neuropsychological Society
Ad Hoc Reviewer, Neurology, Clinical Practice
Ad Hoc Reviewer, Psychiatry Research
Ad Hoc Reviewer, Neuroradiology
Ad Hoc Reviewer, Laterality: Asymmetries of Body, Brain and Cognition
Ad Hoc Reviewer, Brain and Cognition
Ad Hoc Reviewer, Neuropsychologia
Ad Hoc Reviewer, Journal of Clinical and Experimental Neuropsychology

Ad Hoc Reviewer, Plos One
Ad Hoc Reviewer, Movement Disorders
Ad Hoc Reviewer, Human Psychopharmacology: Clinical and Experimental

Academic and Professional Honors

1992-1996	Florida Academic Scholars Award (full academic scholarship)
1996	Phi Beta Kappa
2000	16th Annual Symposium of Virginia Tech Graduate Research Award – 1st place
2013-present	CAM-CTRP Scholar, Cognitive Aging and Memory Clinical Translational Research Program, University of Florida, Gainesville, FL

C. Selected peer-reviewed publications (from ~40)

Most Relevant to the current application

1. **Williamson JB**, Haque S, Harciarek M, Burtis DB, Lamb D, Zilli E, Heilman KM. The influence of stimulus proximity on judgments of spatial location in patients with chronic unilateral right and left hemisphere stroke. *Journal of Clinical and Experimental Neuropsychology 2014* (in press)
2. Burtis DB, Heilman KM, Mo J, Wang C, Lewis GF, Davilla MI, Ding M, Porges SW, **Williamson JB**. The effects of constrained left and right monocular viewing on the autonomic nervous system. *Biological Psychology 2014* (in press).
3. **Williamson JB**, Lewis GF, Nyenhuis DL, Stebbins GT, Murphy C, Handelman M, Harden E, Heilman KM, Gorelick PB, Porges SW. The effects of cerebral white matter changes on cardiovascular responses to cognitive and physical activity in a stroke population. *Psychophysiology 2012*, 49:1618-1628. PMCID pending
4. **Williamson JB**, Nyenhuis DL, Stebbins GT, Gorelick, PB. Regional differences in apparent white matter integrity, cognition and mood in patients with ischemic stroke. *Journal of Clinical and Experimental Neuropsychology*, 2010, 32, 673-681.
5. **Williamson JB**, Nyenhuis DL, Pedelty L, Byrd S, Jhaveri M, Wang C, deToledo-Morrell L, Sripathirathan K, Gorelick P. Baseline differences between Vascular Cognitive Impairment No Dementia reverters and nonreverters. *Journal of Neurology, Neurosurgery, & Psychiatry* 2008; 79:1208-14.

Additional recent publications of importance to the field

1. **Williamson JB**, Heilman KM, Porges Eric C, Lamb Damon G, Porges SW. A possible mechanism for PTSD symptoms in patients with traumatic brain injury: central autonomic network disruption. *Frontiers in Neuroengineering 2013* doi: 10.3389/fneg.2013/00013. **PMCID: PMC3867662**
2. Behforuzi H., Burtis DB, **Williamson JB**, Stamps JJ, Heilman KM. Impaired initial vowel versus consonant letter-word fluency in dementia of the Alzheimer type. *Cognitive Neuroscience 2013* (epub, ahead of print) 10.1080/17588929 2013.854200
3. Burtis DB, **Williamson JB**, Mishra M, Heilman KM. The blindside: Impact of monocular occlusion on spatial attention. *Journal of Clinical and Experimental Neuropsychology 2013*, 35:291-297. **PMCID: PMC3602898**
4. Kabasakalian A, Kesyan T, **Williamson JB**, Skidmore FM, Falchook AD, Harciarek M, Heilman KM. Hypometric allocentric and egocentric distance estimates in people with parkinson's disease. *Cognitive and Behavioral Neurology 2013*, 26:133-139.
5. Claunch J, Falchook A, **Williamson JB**, Fischler I, Jones E, Baum J, Heilman KM. Famous faces but not remembered spaces influence vertical line bisections. *Journal of Clinical and Experimental Neuropsychology 2012*, 34:919-924.
6. Susveri K, Falchook A, **Williamson JB**, Heilman KM. Right up there: Hemispatial and hand asymmetries of altitudinal pseudoneglect. *Brain and Cognition 2012*, 79:216-220.
7. Harciarek M, **Williamson JB**, Haque S, Burtis D, Heilman KM. Ipsilateral neglect from a subcortical lesion: The effects of spatial position, distractors, and repeated trials. *Cognitive and Behavioral Neurology 2012*, 25, 42-49.
8. Harciarek M, **Williamson John B**, et al. Risk factors for selective cognitive decline in dialyzed patients with end stage renal disease: evidence from verbal fluency analysis. *Journal of the International Neuropsychological Society 2012*, 18, 162-167.
9. **Williamson JB**, Lewis GF, Grippo A, Lamb D, Harden E, Hadleman M, Lebow J, Carter CS, Porges SW. Autonomic predictors of recovery following surgery: A comparative Study. *Autonomic Neuroscience 2010*, 156, 60-66.
10. **Williamson JB**, Harrison DW. Functional cerebral asymmetry in hostility: A dual task approach with fluency and cardiovascular regulation. *Brain and Cognition 2003*; 52:167-174.

D. Research Support

Active

VAMC 1 LK2RX000707-01 CDA-2 (VA-K) Williamson (PI) 2012-2017
Veterans Affairs Career Development Award – 2
White matter changes and mild TBI: Emotional and autonomic consequences.
The goal of this funding is to extend knowledge of white matter damage contributions after TBI do the development of emotional dysregulation in veterans with PTSD
Role: PI

VAMC BRRC Pilot Award Williamson (PI) 2014
Brain Rehabilitation and Research Pilot Award
External, non-invasive vagal nerve stimulation for the treatment of post-traumatic stress disorder.
The goal of this funding is to provide pilot data for the effect of VNS on autonomic response to emotional stimuli in patients with TBI and PTSD
Role: PI

Alzheimer's Disease Initiative, State of Florida Heilman (PI) 2009-present
Memory Disorders
The goal of this funding serves both clinical and research purposes and is geared at enhancing quality of life for patients with neurodegenerative disease.
Role: Co-I

VAMC Merit Review Heilman (PI) 2012-2016
Vertical Neglect.
The goal of this funding is to examine the impact of unilateral stroke on dorsal and ventral streams in vertical attention.
Role: Co-I

McKnight Brain Institute: Development Grant Bauer (PI) 2012-2014
Traumatic Brain Injury
The goal of this funding was to develop a program center for TBI at the University of Florida
Role: Co-I

VAMC Career Development Award 1 Falchook (PI) 2013-2015
CDA-1 (VA F32)
Traumatic Brain Injury and motor disorders.
Role: Co-I

Completed Research Support

VAMC Merit Review Heilman (PI) 2008-2012
Approach-Avoidance Spatial Neglect
The goal of this funding was to examine the contribution of unilateral stroke to neglect.
Role: Co-I

1 F32 AG027648-01A1 Williamson (PI) 2006-2008
NIA funded individual training grant
White matter integrity and autonomic stress response
The goal of this study was to provide data on the effect of white matter disease on mobilization of autonomic resources to perform cognitive tasks.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Woods, Adam Joshua	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) AJWOODS	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Alabama at Birmingham	B.S.	05/03	Psychology
George Washington University	Ph.D.	05/10	Cognitive Neuroscience
University of Pennsylvania	Post-Doctoral	06/13	Cognitive Neuroscience

A. Personal Statement

Dr. Adam J. Woods is an Assistant Professor in the Department of Aging and Geriatric Research and the Assistant Director of the Cognitive Aging and Memory Clinical Translational Research Program in the Institute of Aging at the University of Florida. He also serves as the director of the CAM-CTRP Human Electrophysiology and Neuromodulation Research Core. His active program of research investigates precursors and neuroimaging-based biomarkers of cognitive frailty in older adults. His work uses non-invasive brain stimulation to slow and counteract decline in cognitive function in aging. He has a strong background with multi-disciplinary clinical neuroscience methodologies (MRI/fMRI, electrophysiology, non-invasive brain stimulation), extensive experience with aging-related disorders, and past research with neurological diseases. Dr. Woods currently serves as a mentor on one funded K99, two submitted K99's, and two F31's. As the founder and workshop director of the Neuromodec Transcranial Direct Current Stimulation Workshop, he has trained over 200 clinicians and researchers in the use of non-invasive brain stimulation in clinical and research. He will serve as mentor for medical students in the T35, providing state of the art experience in the clinical neuroscience of aging.

B. Positions and Honors

Positions and Employment

2010-13 Post-Doctoral Fellow, Department of Neurology, University of Pennsylvania, Philadelphia, PA
2013- Assistant Professor, Department of Aging and Geriatric Research, University of Florida, Gainesville, FL
2013- Cognitive Aging and Memory Clinical Translational Research Program, University of Florida, Gainesville, FL
2014- Clinical Translational Science Institute KL2 Scholar, University of Florida, Gainesville, FL

Other Experience and Professional Membership

2007-09 Ad Hoc Reviewer, Journal of Clinical and Experimental Neuropsychology
2004- Member, American Psychological Association
2005- Member, Vision Science Society
2007- Ad Hoc Reviewer, Neurocase
2008- Ad Hoc Reviewer, Journal of Experimental Psychology: Human Perception & Performance
2010- Member, Cognitive Neuroscience Society
2010- Member, Society for Neuroscience
2010- Ad Hoc Reviewer, PM&R
2011- Ad Hoc Reviewer, Yale Journal of Biology and Medicine
2012- Ad Hoc Reviewer, Journal of Cognitive Neuroscience
2012- Ad Hoc Reviewer, Psychonomic Bulletin & Review
2012- Ad Hoc Reviewer, Journal of Experiment Child Psychology
2012- Ad Hoc Reviewer, Frontiers in Perception Science
2012- Ad Hoc Reviewer, International Journal of Clinical Practice
2013- Ad Hoc Reviewer, PLoS ONE
2013- Ad Hoc Reviewer, Experimental Gerontology
2013- Ad Hoc Reviewer, Rehabilitation Psychology

2013- Ad Hoc Reviewer, Journal of Experimental Psychology: Learning, Memory, and Cognition
2014- UF CTSI KL2 Scholar
2014- Ad Hoc Reviewer, Neurobiology of Aging
2014- Ad Hoc Reviewer, Journal of Neuroscience Methods
2014- Ad Hoc Reviewer, Brain Stimulation
2014- Junior Fellow, World Academy of Art and Science

Academic and Professional Honors

2008 Research Enhancement Fund grant award for advanced dissertation research, GWU
2006-2009 National Science Foundation (NSF) Graduate Research Fellowship
2009-2010 Graduate Research Fellowship, GWU
2009-2010 Thelma Hunt Research Fellowship in Psychology, GWU
2010-2013 Post-Doctoral Fellowship, Intellectual and Developmental Disabilities Research Center, Children's Hospital of Philadelphia
2013-present CAM-CTRP Scholar, Cognitive Aging and Memory Clinical Translational Research Program, University of Florida, Gainesville, FL
2014 Junior Fellow of the World Academy of Arts and Sciences
2014-present Clinical Translational Science Institute KL2 Scholar

C. Selected Peer-Reviewed Publications (Total publications: 25, 11 first author)

Most relevant to the current application

1. **Woods, A.J.**, Hamilton, R.H., Kranjec, A., Bikson, M., Minhaus, P., Yu, J., Chatterjee, A. (2014). Space, time, and causality in the human brain. *NeuroImage*, 92, 285-297. PMID: 24561228 [in process], **PMCID: PMC4008651** [Available 2015/5/15]
2. Kessler, S., Minhas, P., **Woods, A.J.**, Rosen, A., Bikson, M. (2013). Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. *PLoS ONE*, 8(9): e76112. **PMCID: PMC3785412**
3. **Woods, A.J.**, Goksun, T., Chatterjee, A., Zelonis, S., Mehet, A., Smith, S. (2013). The development of organized visual search. **Acta Psychologica**. 143(2), 191-199. **PMCID: PMC3651801**
4. **Woods, A.J.**, Philbeck, J.W., & Wirtz, P. (2013). Hyper-arousal decreases human visual thresholds. *PLoS ONE*, 8(4): e61415. **PMCID: PMC3620239**
5. **Woods, A.J.**, Mennemeier, M., Garcia-Rill, E., Meythaler, J., Mark, V.W., Jewell, G.R., Murphy, H. (2006). Bias in magnitude estimation following left hemisphere injury. *Neuropsychologia*, 44(8), 1406-12. **PMID: 16434066**

Additional recent publications of importance to the field

1. Mark, V.W., **Woods, A.J.**, Ball, K.K., Roth, D.L., Mennemeier, M. (2004). Disorganized search on cancellation is not a consequence of neglect. *Neurology*, 63(1):78-84. **PMID: 15249614**
2. Mennemeier, M., Pierce, C., Dowler, R., Chatterjee, A., Anderson, B., Jewell, G., **Woods, A.J.**, Mark, V.W. (2005). Biases in attentional orientation and magnitude estimation explain crossover: neglect is a disorder of both. *Journal of Cognitive Neuroscience*, 17(8), 1194-1211. **PMID: 16197678**
3. Mark, V.W., **Woods, A.J.**, Mennemeier, M., Abbas, S., Taub, E. (2006). Cognitive assessment for CI therapy in the outpatient clinic. *Neurorehabilitation*, 21(2), 139-46. **PMID: 16917160**
4. **Woods, A.J.**, Mark, V.W. (2007). Convergent validity of executive organization measures on cancellation. *Journal of Clinical and Experimental Neuropsychology*, 29(7), 719-723. **PMID: 17896197**
5. Mennemeier, M., Triggs, W., Chelette, K.C., **Woods, A. J.**, Kimbrell, T., Dornhoffer, J. (2009). Sham transcranial magnetic stimulation using electrical stimulation of the scalp. *Brain Stimulation*, 2(3): 168-173. **PMCID: PMC2774907**
6. **Woods, A.J.**, Mark, V.W., Pitts, A., & Mennemeier, M. (2011). Pervasive cognitive impairment in acute rehabilitation patients "without" brain injury. *PM&R*, 3(5), 426-432. **PMCID: PMC3275913**
7. **Woods, A.J.**, Philbeck, J. W., Chelette, K., Skinner, R. D., Garcia-Rill, E., & Mennemeier, M. (2011). Cold pressor stimulation diminishes P50 amplitude in normal subjects. *Acta Neurobiologiae Experimentalis*. 71(3), 348-358. **PMCID: PMC3262163**
8. **Woods, A.J.**, Mennemeier, M., Garcia-Rill, E., Huitt, T., Chelette, K. C., McCullough, G., Munn, T., Brown, G., Kiser, T. S. (2012). Improvement in arousal, visual neglect, and perception of stimulus intensity following cold pressor stimulation. *Neurocase*, 18(2), 115-122. **PMCID: PMC3266979**
9. **Woods, A.J.**, Lehet, M., Chatterjee, A. (2012). Context modulates the contribution of time and space in causal inference. *Frontiers in Psychology*, 3, 371. **PMCID: PMC3498891**
10. **Woods, A.J.**, Cohen, R.A., Pahor, M. (2013). Commentary: Cognitive frailty: frontiers and challenges. *Journal of Nutrition, Health, and Aging*, 17(9), 741-743. **PMID: 24154645**

D. Research Support

Ongoing Research Support

CTSI KL2 (Woods; PI) 03/15/14-03/15/16
Clinical Translational Science Institute KL2 Career Award
Neuromodulation of working memory function in older adults.
The goal of this funding is to provide investigators with further training in clinical translational science. The funded project will involve a randomized clinical trial pairing transcranial direct current stimulation with cognitive training to enhance working memory function in older adults.
Role: PI

NIH 1U54 EB020403 (Thompson, PI; Subcontract PI, Cohen) 09/29/14-09/30/18
ENIGMA Center for Worldwide Medicine, Imaging, and Genomics
The goal of this study is to utilize a worldwide research consortium to facilitate big data computing of medical, neuroimaging, and genome data to further our understanding of disease states in the human brain.
Role: Co-I

NIH 2 P30 AG028740-06 (Pahor; PI) 04/15/12-03/31/17
Claude D. Pepper Older Americans Independence Center (OAIC) Pilot Project:
A pilot study to evaluate the role of brain integrity on post-hospital sarcopenia (Pilot PI: Manini)
The goal of this funding is to provide pilot data on the role of brain white matter integrity in post-hospital physical decline.
Role: Co-PI

McKnight Brain Research Foundation (Cohen; PI) 10/15/13-10/15/16
McKnight Brain Research Foundation
CAM-CTRP Pilot Study Pilot Study: The ACTIVE Brain Study
The goal of this funding is to provide neuroimaging biomarkers of successful aging.
Role: Co-I

McKnight Brain Research Foundation (Woods; PI) 12/01/13-12/01/15
McKnight Brain Research Foundation
CAM-CTRP Pilot Study: Electrophysiological markers of aging
The goal of this funding is to identify biomarkers of aging using event-related electrophysiology in the human brain.
Role: PI

McKnight Brain Research Foundation (Woods; PI) 01/01/14-01/01/16
McKnight Brain Research Foundation
CAM-CTRP Pilot Study: Enhancing Cognition through Neuromodulation
The goal of this funding is to use transcranial direct current stimulation to improve functional neuroimaging biomarkers of cognitive and metabolic decline in healthy aging.
Role: PI

Cure Stroke Fund (Mennemeier; PI) 05/15/14-05/15/16
Jump-starting motor function after stroke using tDCS
The goal of this study will be to determine the efficacy of tDCS at facilitating motor recovery after stroke using transcranial direct current stimulation paired with GaitRite motor training.
Role: Consultant

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Wu, Samuel S.	Professor and Associate Chair Department of Biostatistics
eRA COMMONS USER NAME (credential, e.g., agency login) gatorwu	

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)*	MM/YY	FIELD OF STUDY
Peking University, Beijing, PR China	B.S.	08/1989	Probability & Statistics
Nankai University, Tianjin, PR China	M.A.	08/1992	Probability & Statistics
Cornell University, Ithaca, New York	M.S.	08/1997	Statistics
Cornell University, Ithaca, New York	Ph.D.	08/1998	Statistics

A. Personal Statement

As a statistician, my work has focused primarily on clinical trials. I have published numerous journal articles at the cutting edge of trial design, particularly in the area of adaptive designs (including Wu et al., 2010; Chang et al., 2011, Neal et al., 2011; Lu et al., 2013; Wu et al., 2014).

I have led the experimental design, data management and statistical analysis on many clinical trials: deep brain stimulation effects on mood & cognition in Parkinson's disease; scheduled and responsive brain stimulation for the treatment of Tourette syndrome; Prevention Of Low back pain in the Military (POLM); a six-year study of locomotor training programs for stroke patients which was the largest randomized controlled clinical trial of its kind funded by NINDS and NCMRR (Duncan et al., 2011); a study of Biopsychosocial Influence on Shoulder Pain (BISP); Functional Ambulation: Standard Treatment vs. Electrical Stimulation Therapy (FASTEST) trial in chronic post-stroke subjects with foot drop ; and a study to assess the safety and efficacy of the Bioness® StimRouter™ neuromodulation system in the treatment for patients with chronic pain of peripheral nerve origin. Also, I have participated in various neurological studies performed at the Center for Movement Disorders and Neurorestoration and the VA Brain Rehabilitation Research Center. Thus, my training and experience have given me extensive practical knowledge of the issues faced by clinical researchers.

In addition, I have strong experience to identify good treatment practices in tertiary clinical care centers through NPF's Quality Improvement Initiative. Furthermore, I already have a strong team who will assist me in data management and analysis. Dr. Pei has worked with me as a programmer and statistical research coordinator. Furthermore, collaborating with Dr. Chen from computer science, we invented some matrix-masking methods, which enable that nobody sees the actual data, but standard statistical analysis can still be performed with the same results for masked data as for the original data.

B. Positions and Honors

1992-1994	Software Engineer, Tianjin Computing Center, Tianjin, PR China
1994-1998	Research Assistant, Dept.t of Mathematics and Dept. of Social Statistics, Cornell University
1998-2001	Research Assistant Professor, Department of Statistics, University of Florida
2001-2005	Assistant Professor, Department of Statistics, University of Florida
2005-2008	Assistant Professor, Dept. of Epidemiology & Health Policy Research (EHPR), Univ. of Florida
2008-2010	Tenured Associate Professor, Dept. of EHPR, Univ. of Florida
2010-2012	Associate Professor and Interim Chair, Department of Biostatistics, University of Florida
2012-2014	Associate Professor and Associate Chair, Department of Biostatistics, University of Florida
2002-2014	Director of Biostatistics Core, Brain Rehabilitation Research Center, Department Of Veterans Affairs
2014-present	Professor and Associate Chair, Department of Biostatistics, University of Florida

Other Experience and Professional Membership

Member, American Statistical Association
Member, the Institute of Mathematical Statistics

C. Selected Peer-reviewed Publications (Selected from 135 peer-reviewed publications)

1. **Wu SS**, Tu Y, He Y. (2014). Testing for efficacy in adaptive clinical trials with enrichment. *Statistics in Medicine*. 33(16):2736-45. (**PMID: 24577792**)

2. Bega D, **Wu SS**, Pei Q, Schmidt, PN, Simuni T. (2014). Recognition and treatment of depressive symptoms in Parkinson's disease: the NPF dataset. *J Parkinsons Dis*. 165: 1-8. (**PMID: 25038641**)
3. George SZ, Parr J, Wallace MR, **Wu SS**, Borsa PA, Dai Y, Fillingim RB. (2014). Biopsychosocial influence on exercise-induced injury: genetic and psychological combinations are predictive of shoulder pain phenotypes. *J Pain*. 15(1):68 - 80. (**PMID: 24373571**)
4. O'Dell M, Dunning K., Kluding P, **Wu SS**, Feld J, Ginosian J, McBride K. (2014). Response and prediction of improvement in gait speed from functional electrical stimulation in persons with post stroke drop foot. *PM&R*. 6(7): 587-601. (**PMID:24412265**)
5. Lu X, Sun A, **Wu SS**. (2013). On estimating the mean of the selected normal population under the LINEX loss function in two-stage adaptive designs. *Journal of Statistical Planning and Inference*. 143: 1215 - 20.
6. Nadeau SE, **Wu SS**, Dobkin BH, Azen SP, Rose DK, Tilson JK, Cen SY, Duncan PW, for The LEAPS Investigative Team. (2013). Effects of task-specific and impairment based training compared with usual care on functional walking ability after inpatient stroke rehabilitation: LEAPS Trial. *Neurorehabilitation and Neural Repair*. 27(4): 370 - 380. (**PMID:23504552**)
7. Neal D, Casella G, Yang MCK, **Wu SS**. (2011). Interval estimation in two-stage, drop-the-losers clinical trials with flexible treatment selection. *Statistics in Medicine*. 30(23): 2804-14. (**PMID:21823142**)
8. Chang M, Jung SH, **Wu SS**. (2011). Two-stage designs with additional futility tests for phase II clinical trials with heterogeneous patient populations. *Sequential Analysis*. 30: 338-349.
9. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, **Wu SS**, Nadeau SE, Dobkin BH, Rose DK, Tilson JK, Cen S, Hayden SK for The LEAPS Investigative Team. (2011). Body-weight-supported treadmill rehabilitation after stroke. *New England Journal of Medicine*. 364(21):2026-2036.
10. **Wu SS**, Wang W, Yang MCK. (2010). Interval estimation for drop-the-loser designs. *Biometrika*. 97: 405-418.
11. **Wu SS**, Wang WZ. (2008). A note on step-up simultaneous tests in orthogonal saturated designs. *Journal of Statistical Planning and Inference*. 138: 3149-3156.
12. **Wu SS**, Wang WZ, Annis D. (2008). On identification of inferior treatments using the Newman-Keuls test. *Biometrical Journal*. 5: 861-869. (**PMID:18932144**)
13. **Wu SS**, Wang WZ. (2007). Step-up simultaneous tests for identifying active effects in orthogonal saturated designs. *Annals of Statistics*. 35(1): 449-463.
14. **Wu SS**, Yang MCK. (2007). Using pilot study information to increase efficiency in clinical trials. *Journal of Statistical Planning and Inference*. 137: 2172-2183.
15. **Wu SS**, Li HY, Casella G. (2006). Tests with optimal average power in multivariate analysis. *Statistical Sinica*. 16(1): 255-266.

D. Research Support

Ongoing Research Support

1R01DK099334 06/25/14 to 05/31/19

Obesity and type-2 diabetes: Bariatric surgery effects on brain function

This project is to determine the effect of bariatric surgery on brain function in adults with obesity and type-2 diabetes.
Role: Co-I

P30AG028740 04/01/13 to 03/31/17

The UF Claude D. Pepper Older Americans Independence Center (OAIC)

The mission of OAIC is to assess the risk factors of physical disability in older adults, develop and test effective prevention therapies, and train new investigators in research on aging and disability, while developing their leadership qualities.
Role: Director of Biostatistics Core

APTA KK-G000790 01/29/13 to 01/29/16

Creation of the Orthopaedic Physical Therapy Investigative Network (OPT-IN) for the Optimal Screening for Prediction of Referral and Outcome (OSPRO) Cohort Study.

The purpose of this research study is to develop a new questionnaire to direct physical therapy management of individuals seeking care for pain complaints at the back, neck, knee, or shoulder.
Role: Lead statistician and Co-I

NPF Wu (PI) 04/01/12 to 06/30/15

Biostatistical Research Support Services for National Parkinson Foundation

The purpose of the contract it to provide statistical support in design, analysis, and interpretation of studies titled "NPF's Quality Improvement Initiative," to identify good treatment practices in tertiary clinical care centers that specialize in Parkinson's disease care.
Role: PI

NIDRR 10/01/11 to 09/20/16
Restoring Lost Functions after Spinal Cord Injury: Combination Therapy with Dalfampridine and Locomotor Training in Persons with Chronic, Motor Incomplete Spinal Cord Injury
This project is to determine the efficacy, safety, and tolerability of combination therapy with dalfampridine and locomotor training in persons with chronic, motor incomplete spinal cord injury.
Role: Co-I

Dept of Veterans Affairs Wu (PI) 10/01/11 to 09/30/15
Biostatistical Research Support Services for VAMC Rehabilitation Studies
The object of the contracts is to provide statistical support in design, analysis, and interpretation of a series of rehabilitation studies at the Center of Innovation on Disability & Rehabilitation Research and at the Brain Rehabilitation Research Center.
Role: PI

Completed Research Support (in last 3 years)
TSU Contracts Wu (PI) 10/01/11 – 09/30/13
Texas State University
Contract between Texas State University - San Marcos and UF
Provide statistical support in development of TSU's Air Force Medical Support Agency SG9S grant proposal titled "Implications of Timing and Quality of Physical Therapy and Chiropractic Care on Low Back Pain Utilization and Costs in the Military Health System."
Role: PI

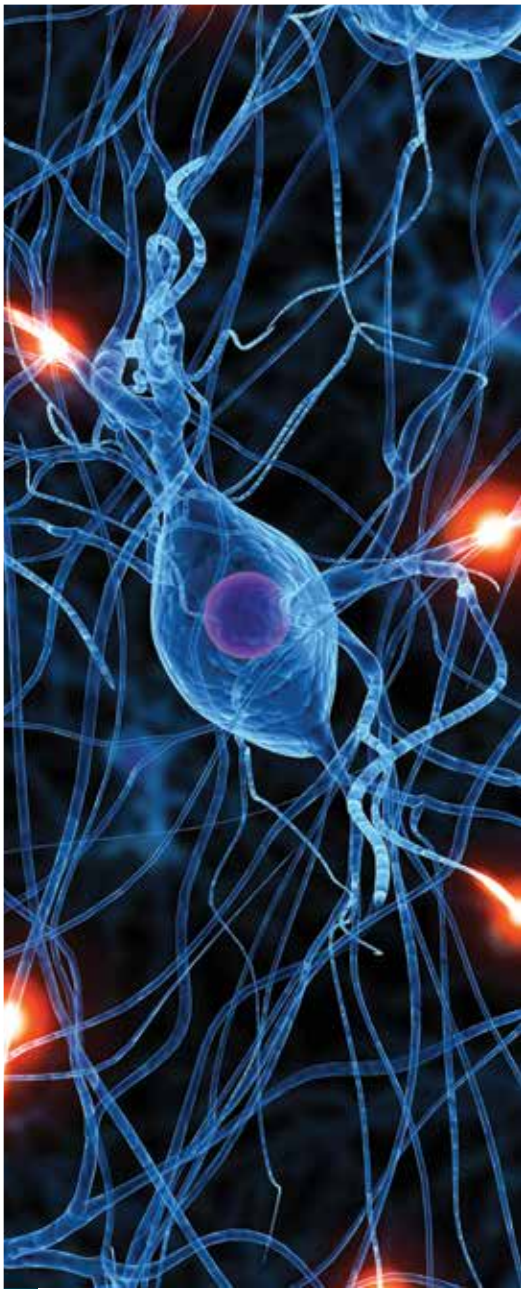
UF Award Wu (PI) 10/01/11 – 07/30/12
University of Florida
Faculty Enhancement Opportunity Award
The aim of the project is to develop new systematic and stochastic approaches that can efficiently extract radial velocity signals in the Multi-object APO Radial Velocity Exoplanet Large-area Survey (MARVELS) data and detect new planets.
Role: PI

R34 MH080764 Okun (PI) 09/17/09 - 05/31/11
NIH/NIMH
Scheduled and Responsive Brain Stimulation for the Treatment of Tourette Syndrome
This is a pilot study of the benefits and safety of a novel deep brain stimulation (DBS) device in adult subjects with severe and intractable Tourette Syndrome (TS).
Role: Co-I

1R01AR055899 George (PI) 07/01/08 – 04/30/13
NIH / NINDS
Biopsychosocial influence on shoulder pain
This study will develop a novel biopsychosocial model that considers the potentially interactive roles played by psychological and genetic risk factors in the development of chronic shoulder pain. Completion of the proposed studies will provide important information on how chronic musculoskeletal pain syndromes develop and could alter standard of care by allowing for early and accurate identification of individuals likely to develop chronic shoulder pain.
Role: Co-I

R01 NS050506 Duncan (PI) 07/01/05 - 06/30/12
NIH / NINDS&NCMRR
Locomotor Experience Applied Post-Stroke (LEAPS)
The goals of the LEAPS trial are to determine if a specialized locomotor training program that includes use of a body weight support system and a treadmill as a treatment modality can result in a functionally significant improvement in walking of individuals post-stroke compared to a control group and whether timing of therapy, severity of impairments, and the number of treatments make a difference.
Role: Lead statistician and Co-I

Selected Publications



Behavioral/Cognitive

Prefrontal Cortical GABAergic Dysfunction Contributes to Age-Related Working Memory Impairment

Cristina Bañuelos,[1] B. Sofia Beas,[1] Joseph A. McQuail,[1] Ryan J. Gilbert,[1] Charles J. Frazier,[4,1] Barry Setlow,[2,1] and Jennifer L. Bizon[1,2,3]

[1]Department of Neuroscience, [2]Department of Psychiatry, [3]McKnight Brain Institute, and [4]Department of Pharmacodynamics, University of Florida, Gainesville, Florida 32610

Working memory functions supported by the prefrontal cortex decline in normal aging. Disruption of corticolimbic GABAergic inhibitory circuits can impair working memory in young subjects; however, relatively little is known regarding how aging impacts prefrontal cortical GABAergic signaling and whether such changes contribute to cognitive deficits. The current study used a rat model to evaluate the effects of aging on expression of prefrontal GABAergic synaptic proteins in relation to working memory decline, and to test whether pharmacological manipulations of prefrontal GABAergic signaling can improve working memory abilities in aged subjects. Results indicate that in aged medial prefrontal cortex (mPFC), expression of the vesicular GABA transporter VGAT was unchanged; however, there was a significant increase in expression of the GABA synthesizing enzyme GAD67, and a significant decrease in the primary neuronal GABA transporter GAT-1 and in both subunits of the GABA(B) receptor (GABA(B)R). Expression of VGAT, GAD67, and GAT-1 was not associated with working memory ability. In contrast, among aged rats, GABA(B)R expression was significantly and negatively associated with working memory performance, such that lower GABA(B)R expression predicted better working memory. Subsequent experiments showed that systemic administration of a GABA(B)R antagonist, CGP55845, dose-dependently enhanced working memory in aged rats. This enhancing effect of systemic CGP55845 was reproduced by direct intra-mPFC administration. Together, these data suggest that age-related dysregulation of GABAergic signaling in prefrontal cortex may play a causal role in impaired working memory and that targeting GABA(B)Rs may provide therapeutic benefit for age-related impairments in executive functions.

Key words: **aging; CGP55845; executive function; GABA(B) receptor; inhibition; prefrontal cortex**

Introduction

With advancing age, many individuals will experience a significant decline of cognitive capacities supported by the prefrontal cortex (PFC), resulting in deficits across a wide range of adaptive behaviors that are essential for maintaining independence and quality of life (Robbins et al., 1998; Salthouse et al., 2003; Glisky, 2007; Bizon et al., 2012). One fundamental aspect of PFC function is working memory, which involves the ability to maintain a mental representation "in mind" of information that is no longer present in the environment, and to use this representational information to guide future action (Goldman-Rakic, 1996). Within the PFC, maintenance of information in mind following the removal of a sensory stimulus is associated with persistent excitation of pyramidal neurons, providing a possible neurophysiological basis for working memory (Goldman-Rakic, 1996; Wang et al., 2013). In addition, input from a diverse group of GABAergic interneurons onto somatodendritic compartments of pyramidal cells refines spatial and temporal specificity in this system (Goldman-Rakic, 1995; Zaitsev et al., 2009). Altered excitability of PFC pyramidal neurons is a central feature of cognitive disorders associated with a wide range of pathological conditions, such as Down syndrome and schizophrenia (Kleschevnikov et al., 2004; Gonzalez-Burgos and Lewis, 2008) and experimentally induced disruption of PFC GABAergic circuits can produce profound impairments in working memory (Kleschevnikov et al., 2004; Enomoto et al., 2011; Murray et al., 2011). A large body of work has implicated changes in PFC monoamine signaling in age-related working memory decline (Goldman-Rakic and Brown, 1981; Arnsten et al., 1994; Moore et al., 2005); however, less attention has been paid to whether disruptions in inhibitory synaptic substrates also contribute to such decline.

GABA(B) receptors (GABA(B)Rs) are G-protein-coupled receptors that are localized presynaptically on GABAergic and glutamatergic terminals where they regulate neurotransmitter release, as well as postsynaptically on dendritic spines and shafts where they contribute to tonic inhibition of pyramidal neurons (Gonzalez-Burgos, 2010; Pinard et al., 2010). Recently, McQuail et al. (2012) reported a marked and regionally specific reduction of GABA(B)R proteins in aged PFC. The impact on cognition of this age-related decline in PFC GABA(B)Rs is not yet known. Notably, however, other evidence from electrophysiological studies con-

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Author contributions: B.S. and J.L.B. designed research; C.B., B.S.B., and R.J.G. performed research; J.A.M., C.J.F., and B.S. contributed unpublished reagents/analytic tools; C.B., B.S., and J.L.B. analyzed data; C.B. and J.L.B. wrote the paper.

This work was supported by AG029421 and the McKnight Brain Research Foundation (J.L.B.), and a NSF Graduate Research Fellowship (B.S.B.).We thank Vicky Kelley and Bonnie McLaurin for technical assistance.

The authors declare no competing financial interests.

Correspondence should be addressed to Dr Jennifer L. Bizon, Department of Neuroscience, McKnight Brain Institute, University of Florida, Gainesville, FL 32610-0244. E-mail: bizonj@ufl.edu.

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ducted in both rodents and nonhuman primates indicates that PFC pyramidal neurons may be subject to increased inhibitory input in advanced aging (Luebke et al., 2004; Bories et al., 2013). The first goal of the current study was to investigate expression of GABA(B)Rs and other GABAergic signaling proteins in the young and aged medial prefrontal cortex (mPFC), the rodent homolog of the primate dorsolateral prefrontal cortex (Uylings et al., 2003), in relation to performance on a mPFC-dependent delayed response working memory task. The second goal of this study was to determine the effects of pharmacological manipulations of GABA(B)R signaling on working memory performance and, specifically, to determine whether modulation of GABAergic signaling in the mPFC can attenuate working memory deficits that accompany normal aging.

Materials and Methods

Subjects

Young (6-month-old) and aged (22-month-old) male Fischer 344 rats were obtained from the National Institute on Aging colony (Taconic Farms) and housed in the Association for Assessment and Accreditation of Laboratory Animal Care International accredited vivarium facility in the McKnight Brain Institute at University of Florida in accordance with the rules and regulations of the University of Florida Institutional Animal Care and Use Committee and NIH guidelines. The facility was maintained at a consistent 25°C with a 12 h light/dark cycle (lights on at 8:00 A.M.). Rats were maintained under specific pathogen-free conditions and had *ad libitum* access to food and water at all times except as noted below. A total of 59 rats (young, $n = 24$; aged, $n = 35$) were used in this study. Numbers of rats in each experiment were as follows: Experiment 1: young, $n = 6$ and aged, $n = 12$; Experiment 2: young, $n = 10$ and aged, $n = 13$; Experiment 3: young, $n = 8$ and aged, $n = 10$.

Experiment 1: GABA signaling protein expression and working memory abilities

The goal of Experiment 1 was to determine the expression of GABAergic signaling proteins in relation to age-related decline on a mPFC-dependent delayed response task that assesses working memory.

Delayed response task procedures

Apparatus. Testing in the delayed response task was conducted in eight identical standard rat behavioral test chambers (30.5 × 25.4 × 30.5 cm, Coulbourn Instruments) with metal front and back walls, transparent Plexiglas side walls, and a floor composed of steel rods (0.4 cm diameter) spaced 1.1 cm apart. Each test chamber was housed in a sound-attenuating cubicle, and was equipped with a recessed food pellet delivery trough located 2 cm above the floor in the center of the front wall. The trough was fitted with a photobeam to detect head entries and a 1.12 W lamp for illumination. Food rewards consisted of deliveries of a single 45 mg grain-based food pellet for each correct response (PJAI, Test Diet). Two retractable levers were located to the left and right of the food trough (11 cm above the floor). An additional 1.12 W house light was mounted near the top of the rear wall of the sound-attenuating cubicle. A computer interfaced with the behavioral test chambers and equipped with Graphic State 3.01 software (Coulbourn Instruments) was used to control experiments and collect data.

Shaping. Before the start of behavioral testing, rats were reduced to 85% of their free-feeding weights over the course of 5 d and maintained at this weight for the duration of behavioral testing. Rats progressed through three stages of shaping before the onset of the delayed response task, with a new stage beginning on the day immediately following completion of the previous stage. On the day before Shaping Stage 1, each rat was given five 45 mg food pellets in its home cage to reduce neophobia to the food reward used in the task. Shaping Stage 1 consisted of a 64 min session of magazine training, involving 38 deliveries of a single food pellet with an intertrial interval of 100 ± 40 s. Shaping Stage 2 consisted of lever press training, in which a single lever (left or right, counterbalanced across age groups) was extended and a press resulted in delivery of a single food pellet. After reaching a criterion of 50 lever presses in 30 min, rats were then trained on the opposite lever using the same procedures.

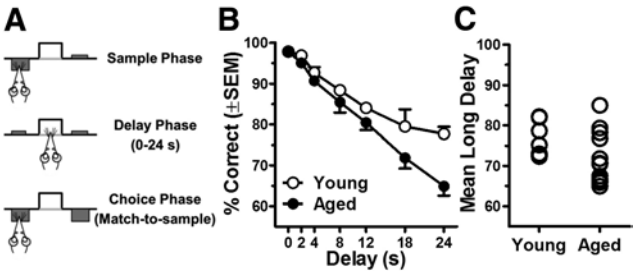

Figure 1. Working memory is impaired in aged Fischer 344 rats. ***A***, A schematic of the delayed response task used to assess working memory ability. There are three phases to this task. In the sample phase, rats are presented with either a left or right lever. After the rat presses the extended lever, the delay phase begins. In the delay phase, both levers are retracted for a variable time period ranging from 0 to 24 s, during which the rat must nosepoke into the food trough to initiate the choice phase. In the choice phase, both levers are presented and the rat must press the same lever presented in the sample phase to obtain a food reward. ***B***, Young ($n = 6$) and aged ($n = 12$) rats performance on the delayed response task. Aged rats displayed significantly less accurate performance relative to young and were disproportionately impaired at long delays. ***C***, Individual young and aged rats plotted by mean long delay (average of choice accuracy at 18–24 s) on the delayed response task. This measure was used as an index of individual working memory ability. Error bars represent ± SEM. See Results for statistical analysis.

During Shaping Stage 3, either the left or right lever (counterbalanced across trials in this Stage of testing) was extended and a press resulted in a single food pellet delivery. Rats were trained in Shaping Stage 3 until achieving 80 lever presses in a 30 min session.

Working memory assessment

The working memory assessment was based on Sloan et al. (2006), and was used previously to demonstrate age-related impairments in Fischer 344 rats (Beas et al., 2013). Each session was 40 min in duration, and the house light was illuminated throughout the entire session except during timeout periods (see below). Rats received only a single test session per day. A trial began with the extension of a single lever (the "sample" lever) into the chamber (Fig. 1). The left/right position of this lever was randomly selected within each pair of trials, and a lever press caused it to retract and started the delay period timer. During the delay, rats were required to nosepoke into the food trough to initiate the "choice" phase, and the first such nosepoke emitted after the delay timer expired caused both levers to extend. During this choice phase, a response on the same lever pressed during the sample phase (a correct response) resulted in both levers being retracted and delivery of a single food pellet. Entry into the food trough to collect the food pellet initiated a 5 s intertrial interval, after which the next trial was initiated. A response on the opposite lever from that chosen during the sample phase (an incorrect response) resulted in both levers being retracted and initiation of a 5 s "timeout" period during which the house light was extinguished, followed immediately by the start of the next trial.

During initial sessions in this task, there were no delays between the sample and choice phases, and a correction procedure was used such that the sample lever was repeated on the same side following an incorrect response to prevent development of side biases. Once rats reached a criterion of 80% correct choices across a session for two consecutive sessions, this correction procedure was discontinued and a set of seven delays was introduced. The presentation of delay durations was randomized within each block of seven trials, such that each delay was presented once within a block. Upon establishing >80% correct performance across two consecutive sessions in a Set, rats were progressed to the next Set (Set 1: 0, 1, 2, 3, 4, 5, 6 s; Set 2: 0, 2, 4, 8, 12, 16 s; Set 3: 0, 2, 4, 8, 12, 18, and 24 s). Rats were tested for five consecutive sessions on the delays in Set 3 to acquire baseline performance data.

Approximately 2 weeks after completion of behavioral testing and return to *ad libitum* food, rats were decapitated and brains were removed from the skull, cooled on ice, and sliced in 1 mm coronal sections using a rat brain matrix. Coronal sections were placed on an ice-cold plate, and the mPFC was dissected and stored at −80°C until use. At the rostrocau-

dal coordinates of Paxinos and Watson (AP: +3.7 through +2.2), the boundaries of the mPFC were delineated dorsally and medially by the emergence of the white matter tracts surrounding the striatum, and ventrally by the ventral tip of the corpus collosum. As cognitive task performance can elicit changes in protein expression (Davis et al., 1996; Wass et al., 2013), this 2 week post-training interval was selected to evaluate baseline rather than behaviorally stimulated protein levels. Western blot analysis performed on homogenates generated from these dissected tissue samples was used to evaluate the influence of age and cognitive performance on the following GABAergic signaling proteins: the GABA(B) receptor R1a, R1b, and R2 subunits, the primarily neuronal GABA transporter GAT-1, the GABA synthesizing enzyme GAD67, and the vesicular GABA transporter VGAT.

Western blotting procedures

Sample preparation. Frozen tissue was weighed, thawed, and homogenized in 10 volumes of an ice-cold buffer (50 mM 4-(2-Hydroxyethyl) piperazine-1-ethanesulfonic acid, *N*-(2-Hydroxyethyl)piperazine-*N*′-(2-ethanesulfonic acid) (HEPES), pH 7.4, 1 mM ethylenediaminetetraacetic acid and 1 mM ethylene glycol-bis(2-aminoethylether)-N,N,N′, N′-tetraacetic acid and protease inhibitors; Roche) using a glass-Teflon Dounce homogenizer. Homogenates were centrifuged at 14,000 rpm for 20 min at 4°C. The supernatant was collected and stored in aliquots for Western blotting assays of nonmembrane-bound proteins. The pellet was resuspended in 20 ml of the same buffer without protease inhibitors and incubated on ice for 30 min followed by centrifugation at 16,500 rpm for 15 min at 4°C. This pellet was resuspended in 10 volumes of 50 mM HEPES, pH 7.4, and aliquots were stored at −80°C until used for Western blotting assays. Protein concentration was determined using the Pierce BCA Kit according to the manufacturer's protocol.

Immunoblotting. Proteins were denatured and reduced in Laemmli sample buffer with 5% (v/v) β-mercaptoethanol (Fisher) and heated at 95°C for 5 min. Initial experiments focused on evaluating expression of PFC GABA(B)R1 and GABA(B)R2 subunits as well as GAT-1. Subsequently, and to the extent possible, expression of GAD67 and VGAT were assessed in this same cohort. The GABA(B)R1 and GABA(B)R2, GAT-1, and VGAT assays were conducted using the membrane preparation, whereas the GAD67 assay was conducted using the supernatant fraction collected as described above. Note that the supernatant was not available for all subjects and therefore only a subset of young and aged rats were included in the GAD67 study (young, $n = 6$; aged, $n = 7$). Similarly, for some animals, there was no remaining membrane homogenate available for use in the VGAT study, resulting in fewer animals included in this study (young, $n = 6$ young; aged, $n = 8$). In all Western blot experiments, 10 micrograms of protein per lane were electrophoretically separated on a 4–15% Tris-HCl gel at 200 V for 35 min then transferred to nitrocellulose membranes using a wet transfer apparatus for 90 min at 0.35A. Blots were washed 3 times with tris-buffered saline (TBS; pH 7.4) then blocked for 1 h in blocking buffer (Rockland). Blots were then incubated overnight at 4°C with antibodies (anti-GAD67, Millipore; anti-GAT-1, Millipore; anti-VGAT, Millipore; anti-GABA(B)R1, Cell Signaling Technology; anti-GABA(B)R2, Cell Signaling Technology) diluted 1:1000 in blocking buffer (Rockland) with 0.1% Tween 20 (Bio-Rad). Blots were then washed three times with 0.1 M TBS and incubated with the appropriate AlexaFluor 680-conjugated anti-IgG (Invitrogen) diluted 1:20,000 in TBS with 0.1% Tween 20 (Bio-Rad) for 1 h. Following three additional TBS washes, blots were scanned on an Odyssey imaging system (LI-COR Biosciences).

Statistical analyses

Raw data files generated from delayed response test sessions were exported from Graphic State software and compiled using a custom macro written for Microsoft Excel (Dr Jonathan Lifshitz, University of Kentucky). To assess working memory abilities, mean accuracy (percentage correct responses) at each delay across five test sessions performed at the final set of delays (Set 3) was calculated and age comparisons were conducted using two-factor repeated-measure ANOVA (age × delay). For Western blot analyses, integrated protein density was measured for each band and the individual values of both young and aged samples were normalized to the mean expression of young samples run on the same gel. Age comparisons of protein expression were conducted using independent *t* tests. Note that each blot was probed separately for glyceraldehyde 3-phosphate dehydrogenase (GAPDH) expression to confirm that age effects were not a result of nonspecific effects of loading or quantification of protein content. In no cases were age comparisons performed on GAPDH measures significant (GAPDH on R1a and R1b blot: $t_{(16)} = 0.34$, $p = 0.74$; GAPDH on GABA(B)R2 blot: $t_{(16)} = -0.98$, $p = 0.35$; GAPDH on GAT-1 blot: $t_{(16)} = 0.49$, $p = 0.63$; GAPDH on GAD67 blot: $t_{(11)} = -0.10$, $p = 0.34$). To directly test relationships between changes in protein expression and working memory abilities among aged rats, mean percentage accuracy averaged across the two longest delays (18 and 24 s) was calculated for each subject and this "mean long delay" performance measure was used as an index of working memory ability. Relationships between expression of each protein of interest and mean long delay performance were tested using Pearson's correlations. For this and all subsequent experiments, data are presented as the mean ± SEM. All statistical analyses were conducted using SPSS 21.0 and GraphPadPrism. For all statistical comparisons, values of $p < 0.05$ were considered significant.

Experiment 2: Systemic administration of the GABA(B) receptor antagonist CGP55845

This experiment was designed to test the hypothesis that blockade of GABA(B)Rs via systemic administration of the selective antagonist CGP55845 can improve working memory performance in aged rats.

Drug administration procedures

Rats were trained on the delayed response task as described above for Experiment 1. Pharmacological testing began on the day after establishing baseline performance measures (i.e., after completing 5 sessions of testing on the longest set, Set 3, of delays). Rats received intraperitoneal (1.0 ml/kg) injections of the selective GABA(B)R antagonist CGP55845 (0.01 or 0.1 mg/kg; Tocris Bioscience) or 0.9% saline vehicle 40 min before testing. The choice of this drug and dose regimen was based on several previous studies in which systemic administration of CGP55845 was shown to exert behavioral effects in rodents. Froestl et al. (1996), showed that CGP55845 reversed baclofen-induced hypothermia, supporting *in vivo* actions at GABA(B) receptors. Moreover, previous work from our lab and others has shown that intraperitoneal administration of CGP55845 can exert cognitive benefits in a mouse model of Down syndrome as well as in aged rats (Kleschevnikov et al., 2012, LaSarge et al., 2009). Drugs were administered in a randomized, counterbalanced order such that each rat was tested under each drug condition. A 48 h washout period was interposed between injections, during which delayed response testing was conducted in the absence of drug administration.

Data analyses

Analysis of baseline performance in the delayed response task was calculated as described above in Experiment 1. The effects of GABA(B)R antagonist administration were assessed using a three-factor repeated-measures ANOVA, with both drug dose and delay as repeated measures variables and age as a between-subjects variable. *Post hoc* comparisons within each age group were performed using two-factor repeated ANOVAs (drug dose × delay). When justified, additional two-factor ANOVAs were used to compare individual drug doses against vehicle conditions within each age group to determine those doses that significantly altered performance.

Experiment 3: Intracerebral microinjections of the GABA(B) receptor antagonist CGP55845

This experiment was designed to test the hypothesis that the mPFC is a critical site of action for the cognitively enhancing effects of the selective GABA(B)R antagonist CGP55845.

Cannulation surgery

Young and aged rats were anesthetized with isofluorane gas and fixed into a stereotaxic frame (Kopf Instruments) fitted with atraumatic earbars. The incisor bar was set at −3.3 mm relative to the interaural line to

provide a flat skull position. Bilateral guide cannulae, which consisted of a plastic body holding two 22-gauge stainless steel cannulae 1.4 mm apart (Plastics One), were implanted to target mPFC (AP: +1.7 relative to bregma, ML: ±0.7, DV: −3.8 relative to skull). Cannulae were secured to the skull with dental acrylic and stainless steel screws, and wire stylets were used to occlude the guide cannulae to prevent infection.

Intracerebral microinjections of the GABA(B) receptor antagonist CGP55845

Following a 2 week recovery period, rats were trained in the delayed response task until they completed five sessions at the longest set of delays as in Experiments 1 and 2. On the next day, rats received a dummy injection during which the stylets were removed from the guide cannulae and injectors (28 gauge needles which extended 1.0 mm beyond the end of the guide cannulae; Plastics One) were lowered into the mPFC. This dummy injection (in which no drug was injected) served to acclimate the rat to the handling necessary to administer the drug. In subsequent test sessions, rats received bilateral microinjections of the GABA(B)R antagonist CGP55845 (0.2, 0.6, and 2.0 μmol) or vehicle (artificial CSF, Harvard Apparatus) using a randomized, counterbalanced design such that each rat was tested in each drug condition. Microinjections (0.5 μl per hemisphere, given over the course of 60 s) were administered 5 min before the start of delayed response test sessions. Microinjections were delivered via 10 μl syringes connected to the injection needles by a length of PE-20 tubing. These parameters were chosen based on previous work showing that drug microinjections of this volume into mPFC produce reliable and specific effects on mPFC-dependent cognitive tasks including working memory, with minimal diffusion to the midline or ventricles (Taylor et al., 1999; Ragozzino, 2002; Stefani and Moghaddam, 2005; Allen et al., 2008; St Onge et al., 2011). The syringes were mounted on a syringe pump (Pump 11 Elite, Harvard Apparatus) and needles were left in place for 1 min after injections to allow for drug diffusion. A 48 h washout period was interposed between drug injection sessions, during which delayed response testing was conducted in the absence of drug. Performance on these nondrug washout days was monitored for residual effects of the microinjections.

Histological assessment of cannulae placement

Following completion of testing, rats were killed with 100 mg/kg sodium pentobarbital, then perfused with 0.1 M phosphate buffer solution (PBS) followed by 4% paraformaldehyde in 0.1 M PBS. Brains were removed and postfixed in 4% paraformaldehyde overnight and then cryoprotected in 20% sucrose in PBS. Brains were then flash frozen and sliced coronally at 50 micrometers on a cryostat (Leica Jung Frigocut 2800E). Every other tissue slice was thionin-stained and visualized using a microscope under conventional bright-field illumination. Cannula tip placements were verified and mapped onto standardized coronal sections of the rat brain (Paxinos and Watson, 2005).

Data analyses

Baseline working memory performance of young and aged rats in this cohort was assessed using a two-factor repeated-measure ANOVA (age × delay) as in Experiments 1 and 2. The effects of drug manipulations were assessed using three-factor repeated-measures ANOVA as in Experiment 2, with both drug dose and delay as repeated measures variables and age as a between-subjects variable. *Post hoc* comparisons within each age group were performed using two-factor repeated-measures ANOVAs (drug dose × delay). When justified, additional two-factor ANOVAs were used to compare individual drug doses against vehicle within each age group to determine those doses that significantly affected performance.

Results

Experiment 1: GABA signaling protein expression and working memory abilities

Working memory performance is impaired in aged F344 rats

To relate age-related changes in GABAergic signaling protein expression to mPFC-dependent cognitive abilities, young and aged rats were characterized on a delayed response task that assesses working memory (Fig. 1*A*, task schematic). Previous work has shown that performance on this task critically depends upon the mPFC and that aged rats are impaired relative to young cohorts (Sloan et al., 2006; Beas et al., 2013). Delayed response performance of young and aged rats is shown in Figure 1*B*. Consistent with previous findings, a two-factor repeated-measures ANOVA (age × delay) indicated that both young and aged rats showed reduced accuracy as delays increased (main effect of delay: $F_{(6,96)} = 65.69$, $p < 0.001$). Notably, however, aged rats performed significantly worse than young cohorts (main effect of age: $F_{(1,16)} = 7.07$, $p = 0.02$), and this impairment was disproportionately evident at long delays (interaction between delay and age: $F_{(6,96)} = 3.14$, $p = 0.01$). Given that the greatest magnitude age-related deficits occurred at the longest two delays tested (i.e., 18 and 24 s), performance at these delays was averaged for each subject and this value (mean long delay) was used as an index of individual working memory ability. Figure 1*C* shows the mean long delay performance for individual young and aged rats.

Age-related alterations in GABAergic signaling protein expression in aged mPFC

Figure 2*A* shows representative immunoreactive bands from young and aged mPFC samples when incubated with antibodies to GABA(B) receptor R1 or R2 subunits, GAT-1, GAD67, or VGAT. As GABA(B)Rs are obligate heterodimers and functional receptors require at least one GABA(B)R1 subunit with one GABA(B)R2 subunit (Jones et al., 1998; Kaupmann et al., 1998; White et al., 1998), mPFC expression of both R1 and R2 subunits was assessed. In addition, note that two distinct bands were detected for GABA(B)R1 (130 kDa and 95 kDa), corresponding to the two different isoforms of this subunit: GABA(B)R1a and GABA(B)R1b, respectively (Kaupmann et al., 1997). The GABA(B)R1a isoform contains a pair of short consensus repeats at the N-terminal that traffick GABA(B)R complexes containing this isoform to presynaptic terminals where these receptors modulate neurotransmitter release (Biermann et al., 2010). Conversely, GABA(B)R1b lacks this N-terminal extension and is primarily localized to dendrites where it mediates postsynaptic inhibition (Vigot et al., 2006). Given the distinct localization and function of these R1 isoforms, R1a and R1b were analyzed separately. In agreement with previous work from our laboratory (McQuail et al., 2012), expression of both R1 isoforms and of the R2 subunit were robustly and significantly reduced in aged compared with young mPFC (R1a: −29%, $t_{(16)} = 2.80$, $p = 0.01$; Fig. 2*B*; R1b: −42%, $t_{(16)} = 3.42$, $p = 0.003$; Figure 2*C*; and GABA(B)R2: −28%, $t_{(16)} = 2.67$, $p = 0.02$; Figure 2*D*). In addition, bivariate correlation analyses were performed on individual data from aged rats to compare the expression of each GABA(B)R isoform and subunit to individual performance on the delayed response task. As shown in Figure 2*B*, expression of the GABA(B)R1a isoform in aged rats was not significantly associated with mean long delay performance (R1a: $r = -0.48$, $p = 0.12$; Fig. 2*B*). In contrast to R1a, expression of both R1b and R2 in aged rats was significantly and negatively associated with mean long delay performance (R1b: $r = -0.66$, $p = 0.02$; Fig. 2*C*; R2: $r = -0.75$, $p = 0.01$; Fig. 2*D*), such that lower expression was associated with better performance on the working memory task. Bivariate correlation analyses were also performed separately on data from young rats and in no cases were significant relationships observed between individual GABA(B)R subunit expression and mean long delay performance (R1a: $r = -0.12$, $p = 0.82$; R1b: $r = 0.28$, $p = 0.60$; R2: $r = -0.03$, $p = 0.96$).

The primary neuronal GABA transporter, GAT-1 has been strongly implicated in GABA(B)R occupancy (Gonzalez-Burgos

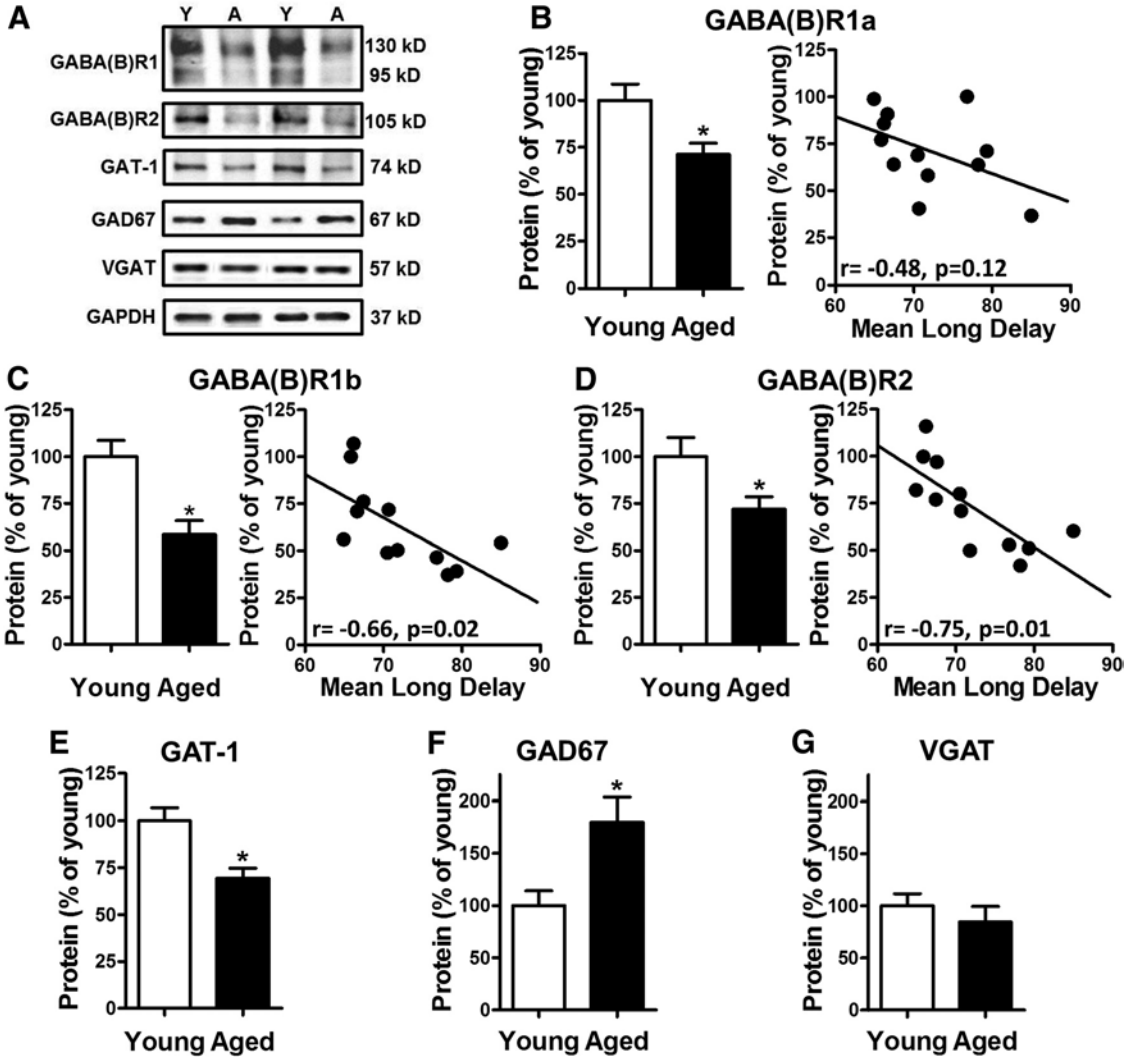

Figure 2. Age-related changes in GABAergic signaling protein expression and relationship with working memory ability. ***A***, Representative immunoreactive bands from young ($n = 6$) and aged ($n = 12$) mPFC homogenates following incubation with antibodies to the GABA(B)R subunits R1 and R2, the GABA transporter GAT-1, the GABA synthesizing enzyme GAD67, the vesicular GABA transporter VGAT and loading control GAPDH. ***B***, In the aged mPFC, GABA(B)R1a expression was significantly reduced compared with young; however, as shown in the scatter plot of individual aged rats, there was no significant relationship between GABA(B)R1a expression and delayed response performance. ***C***, Expression of GABA(B)R1b was significantly reduced in aged mPFC compared with young. The scatter plot of individual aged rats shows that, in contrast to GABA(B)R1a, GABA(B) R1b expression was significantly and inversely associated with delayed response performance such that lower expression was associated with better working memory ability. ***D***, GABA(B)R2 expression was also significantly reduced in aged mPFC compared with young. Like the R1b isoform, the scatter plot of protein expression of individual aged rats shows that GABA(B)R2 expression in the mPFC is significantly and inversely related to working memory performance such that those aged rats with the lowest levels of GABA(B)R2 exhibited better working memory. ***E***, Expression of GAT-1 was significantly decreased in aged mPFC compared with young. ***F***, In contrast to all other signaling proteins examined, expression of GAD67, was significantly elevated in aged mPFC compared with young. Neither GAT-1 nor GAD67 expression in mPFC was reliably related to working memory performance. ***G***, Notably, expression of VGAT did not differ between young and aged mPFC, suggesting that aging does not produce a robust loss of inhibitory terminals in this brain region. Error bars represent ± SEM. See Results for statistical analyses. Asterisks indicate significant differences ($p < 0.05$).

et al., 2009), and therefore expression of GAT-1 was also evaluated in the same membrane homogenates. Similar to GABA(B)R expression, GAT-1 was significantly reduced in aged compared with young mPFC (−31%, $t_{(16)} = 3.82$, $p = 0.002$; Fig. 2*E*). Notably, however, no significant relationship was observed between GAT-1 expression and mean long delay performance in aged rats (GAT-1: $r = -0.30$, $p = 0.34$). Likewise, there was no significant relationship between GAT-1 expression and working memory abilities among young rats (GAT-1: $r = -0.42$, $p = 0.15$).

Given the marked reduction of GABA(B)Rs and GAT-1 expression in aged mPFC described above, subsequent experiments were performed to provide additional information regarding how aging influences inhibitory synapses in this brain region. Specifically, expression of the GABA synthesizing enzyme, GAD67, and of the vesicular transporter for GABA, VGAT, was evaluated in the mPFC of young and aged rats. As shown in Figure 2*F*, GAD67 expression was robustly and significantly elevated in aged mPFC compared with young (GAD67: +80%, $t_{(11)} = -2.80$, $p = 0.02$). In contrast, VGAT expression in mPFC did not differ between young and aged rats (VGAT: $t_{(12)} = 1.03$, $p = 0.33$; Fig. 2*G*). As described in Materials and Methods, tissue from only a subset of the rats was available for GAD67 and VGAT immunoblots. Analysis of delayed response performance of the rats included in these assays revealed the same working memory impairment in aged rats compared with young that was observed in the larger cohort (In the behavioral cohort used to assess GAD67 expression, there was a main effect of delay: $F_{(6,66)} =$

68.31, $p < 0.001$; a main effect of age: $F_{(1,11)} = 7.27, p = 0.02$; and an interaction between delay and age: $F_{(6,66)} = 4.68, p = 0.001$. In the behavioral cohort used to assess VGAT expression, there was a main effect of delay: $F_{(6,72)} = 99.51, p < 0.001$; a main effect of age: and an $F_{(1,12)} = 7.08$, $p = 0.02$; and an interaction between delay and age: $F_{(6,66)} = 5.08$, $p < 0.001$). Notably, no significant relationships were observed between GAD67 or VGAT expression in mPFC and mean long delay performance in the working memory assessment among aged (VGAT-1: $r = -0.34$, $p = 0.40$; GAD67: $r = 0.22$, $p = 0.64$) or young (VGAT: $r = -0.30$, $p = 0.47$; GAD67: $r = -0.30$, $p = 0.56$) rats.

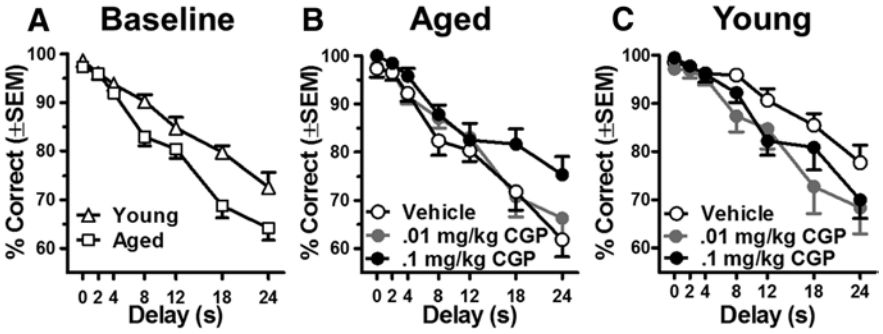

Figure 3. Systemic GABA(B) receptor antagonist administration significantly improves working memory performance in aged rats. ***A***, Baseline performance on the delayed response task of young ($n = 10$) and aged ($n = 13$) rats before drug administration. Aged rats displayed significantly less accurate performance relative to young and were disproportionately impaired at long delays. ***B***, Systemic injection of the selective GABA(B)R antagonist CGP55845 (shaded circles) significantly improved performance of aged rats in the delayed response task over vehicle conditions (open circles). Note that at the highest dose administered (black circles), accuracy of aged rats was restored to a level on a par with young baseline performance (open triangles in ***A***). ***C***, In contrast to drug effects observed in aged rats, systemic injection of CGP55845 (shaded circles) significantly impaired working memory performance in young rats compared with vehicle conditions (open circles). Error bars represent ± SEM. See Results for statistical analyses.

Experiment 2: Systemic administration of the selective GABA(B)R antagonist CGP55845 restores working memory performance in aged rats

Data from Experiment 1 show that expression of GABAergic signaling proteins is altered in aged mPFC in a manner that is consistent with increased inhibition of cortical pyramidal neurons (Luebke et al., 2004; Bories et al., 2013). Moreover, reduced expression of postsynaptic GABA(B)Rs (GABA(B)R1b and GABA(B)R2 subunits) is significantly associated with better performance on the delayed response task. Together, these data support the hypothesis that reducing GABA(B)R activity should improve working memory performance in aged rats. To test this hypothesis, performance of young and aged rats was evaluated in the delayed response task following systemic administration of the selective GABA(B)R antagonist CGP55845 or vehicle. Baseline performance before drug administration, shown in Figure 3*A*, was similar to that observed in Experiment 1. A two factor ANOVA (age × delay) indicated that both young and aged rats performed less accurately at longer delays (main effect of delay: $F_{(6,126)} = 110.72, p < 0.001$) and that aged rats performed significantly worse than young rats (main effect of Age: $F_{(1,21)} = 9.23, p = 0.006$; Fig. 3*A*), particularly at longer delays (interaction between delay and age: $F_{(6,126)} = 3.94, p = 0.04$).

With respect to the effects of GABA(B)R blockade, a three factor ANOVA (age × delay × drug dose) revealed main effects of delay ($F_{(6,252)} = 89.53$, $p < 0.001$) and drug dose ($F_{(2,42)} = 3.64$, $p = 0.04$), as well as a significant interaction between age and drug dose ($F_{(2,42)} = 7.42, p = 0.002$). No other main effects or interactions were statistically significant. To better understand the nature of the interaction between age and the effects of the GABA(B)R antagonist on delayed response performance, two factor ANOVAs (drug dose × delay) were performed separately in young and aged rats. Among aged rats, there were significant main effects of delay ($F_{(6,72)} = 98.46$, $p < 0.001$) and drug dose ($F_{(2,24)} = 7.81$, $p = 0.002$) but no interaction between these two variables. Given the main effect of drug dose, subsequent *post hoc* analyses were performed to individually compare the two doses of GABA(B)R antagonist to vehicle and to each other. These comparisons showed that in aged rats, 0.1 mg/kg ($F_{(1,12)} = 16.89$, $p = 0.001$), but not 0.01 mg/kg CGP55845 ($F_{(1,12)} = 0.93$, $p = 0.35$), significantly enhanced performance relative to the vehicle condition (Fig. 3*B*). The 0.1 mg/kg dose also significantly enhanced performance relative to the 0.01 mg/kg dose ($F_{(1,12)} = 6.76, p = 0.02$). In contrast to the enhancing effects of GABA(B)R antagonist administration in aged rats, systemic administration of CGP5545 impaired working memory performance in young rats. A two-factor ANOVA (drug dose × delay) revealed main effects of delay ($F_{(6,54)} = 41.48$, $p < 0.001$) and drug dose ($F_{(2,18)} = 3.93$, $p = 0.04$), but no interaction between these two variables. *Post hoc* comparisons showed that the 0.01 mg/kg ($F_{(1,9)} = 7.17$, $p = 0.025$) but not the 0.1 mg/kg dose ($F_{(1,9)} = 3.06$, $p = 0.11$) significantly impaired working memory performance of young rats compared with vehicle conditions. There was no significant difference in performance between the 0.1 mg/kg and the 0.01 mg/kg doses ($F_{(1,9)} = 1.25$, $p = 0.29$).

Experiment 3: Intra-mPFC infusions of the selective GABA(B) receptor antagonist CGP55845 restores working memory performance in aged rats

Data from Experiment 2 demonstrate that blocking GABA(B)Rs via systemic administration of CGP55845 significantly improves working memory performance in aged rats. To determine whether these effects were mediated by actions in mPFC, young and aged rats were implanted with guide cannulae targeting mPFC. Figure 4*A* shows the location of cannula placements for rats used in this study. Figure 4*B* shows predrug baseline performance of these young and aged rats before drug microinjections. A two-factor ANOVA (age × delay) indicated that both young and aged rats performed less accurately at longer delays (main effect of delay: $F_{(6,96)} = 76.84$, $p < 0.001$) and that aged rats performed significantly worse than young rats (main effect of age: $F_{(1,16)} = 7.66$, $p = 0.02$; Fig. 3*B*).

With respect to the effects of mPFC GABA(B)R blockade, a three factor ANOVA (age × delay × drug dose) revealed a main effect of delay ($F_{(6,96)} = 104.94, p < 0.001$) and significant interactions between age and delay ($F_{(6,96)} = 3.15$, $p = 0.007$) and age × drug dose ($F_{(3,48)} = 2.92, p = 0.04$). No other main effects or interactions were observed. To better understand the nature of the interaction between age and the effects of mPFC GABA(B)R blockade on delayed response performance, two-factor ANOVAs (drug dose × delay) were performed separately in young and aged rats. Among aged rats, there were main effects of drug dose ($F_{(3,27)} = 3.16$, $p = 0.04$) and delay ($F_{(6,54)} = 75.52$, $p < 0.001$) but no interaction between these variables. *Post hoc* ANOVAs comparing each dose with vehicle and each other indicated that the 0.6 μmol dose of CGP55845 ($F_{(1,9)} = 6.25, p = 0.03$), but not the 0.2 μmol ($F_{(1,9)} = 0.29, p = 0.61$) or 2.0 μmol ($F_{(1,9)} = 0.81$,

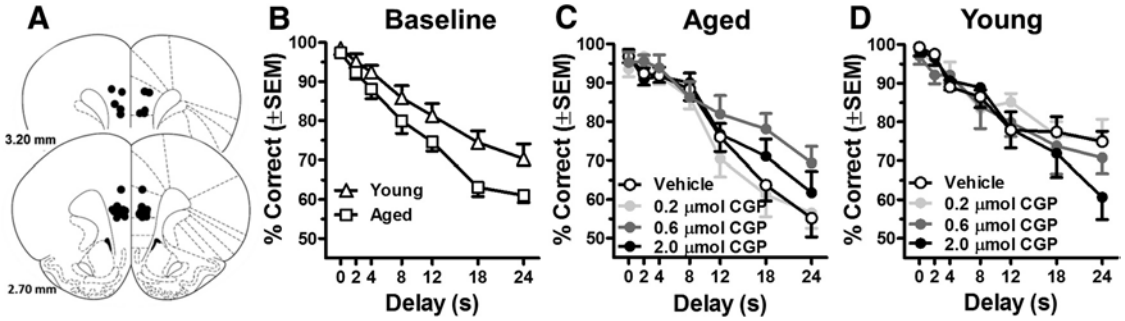

Figure 4. Intra-mPFC GABA(B) receptor antagonist administration improves working memory performance in aged rats. ***A***, shows bilateral cannula placements in mPFC for each rat included in this experiment (schematic illustrations modified from Paxinos and Watson, 2005). ***B***, Baseline delayed response task performance of young ($n = 8$) and aged ($n = 10$) rats before drug administration. Aged rats displayed significantly less accurate performance relative to young. ***C***, Direct mPFC administration of the selective GABA(B)R antagonist CGP55845 (shaded circles) significantly enhanced working memory performance in aged rats over vehicle conditions (open circles). Note that administration of the 0.6 μmol dose (dark gray circles), improved accuracy of aged rats to a level on par with young baseline performance (open triangles in ***B***). ***D***, In contrast to drug effects observed in aged rats, direct mPFC administration of CGP55845 (shaded circles) did not significantly affect working memory performance of young rats compared with vehicle conditions (open circles). Error bars represent ± SEM. See Results for statistical analyses.

$p = 0.37$) doses, significantly improved working memory performance relative to vehicle conditions (Fig. 3*C*). Furthermore, performance at the 0.6 μmol dose of CGP55845 was significantly better compared with the 0.2 μmol dose ($F_{(1,9)} = 6.83$, $p = 0.03$), whereas no other dose comparisons yielded significant differences in performance (0.2 μmol vs 2.0 μmol: $F_{(1,9)} = 4.07$, $p = 0.07$; 0.6 μmol vs 2.0 μmol: $F_{(1,9)} = 61.45$, $p = 0.26$). Performance on the nondrug days that intervened between drug microinjection days was also monitored to assess nonspecific effects on performance of repeated mPFC microinjections. A two-factor (day × delay) ANOVA performed on aged rats' data from these intervening days indicated the expected main effect of delay ($F_{(6,54)} = 58.52$, $p < 0.001$), but no main effect of day ($F_{(4,36)} = 1.44$, $p = 0.24$) nor a day × delay interaction ($F_{(24,216)} = 0.99$, $p = 0.48$), indicating that there were no adverse effects on performance of repeated mPFC microinjections.

In contrast to aged rats, a two factor (delay × drug dose) ANOVA performed on data from young rats revealed a main effect of delay ($F_{(6,42)} = 1.31$, $p = 0.18$) but no main effect or interaction involving drug dose.

Discussion

Working memory, or the ability to hold task-relevant information in mind, is a foundational aspect of cognition that is vulnerable to decline with normal aging. Persistent activity of PFC pyramidal neurons is a central feature of most neural models of working memory, and input to these neurons from diverse classes of GABAergic interneurons is considered essential for providing spatial and temporal specificity in the encoding and maintenance of to-be-remembered information (Goldman-Rakic, 1995; Arnsten, 2013). Data presented in the current study demonstrate that GABAergic signaling proteins in rat mPFC become dysregulated in normal aging, and suggest that these changes contribute to increased pyramidal neuronal inhibition and a reduced ability to maintain information in working memory stores. In direct support of this idea, we demonstrate that reducing inhibition via GABA(B)R antagonist administration both systemically and directly within mPFC can significantly enhance working memory performance in aged rats to a level on par with young adult cohorts.

Increased inhibition in aged prefrontal cortex

Electrophysiological recordings from PFC in both rodents and nonhuman primates indicate that inhibitory input onto PFC pyramidal neurons can increase with aging (Luebke et al., 2004; Bories et al., 2013). One previous study described a reduction in excitatory postsynaptic spontaneous currents (PSCs) coupled with an increase in inhibitory PSCs onto layer II/III pyramidal neurons in aged nonhuman primate PFC compared with young (Luebke et al., 2004). More recently, Bories et al. (2013) reported that miniature IPSPs onto mPFC pyramidal neurons were increased in aged rats that were impaired on a corner exploration behavioral task. The biochemical data presented in the current study provide further evidence for an age-related increase in the inhibition of mPFC pyramidal neurons. First, the increase in GAD67, the rate-limiting enzyme for GABA synthesis, suggests that there is elevated GABA production in aged mPFC. Second, the R1a isoform of the GABA(B)R, which is localized to presynaptic terminals and negatively regulates neurotransmitter release, was significantly reduced in aged PFC. Loss of the GABA(B)R on inhibitory terminals would be expected to attenuate autoinhibition of GABA release. Finally, GAT-1 expression was significantly reduced in aged mPFC. GAT-1 plays an integral role in clearing GABA from the synapse by translocating GABA through the neuronal membrane. Several studies have localized GAT-1 extrasynaptically on presynaptic terminals (Minelli et al., 1995; Conti et al., 2004), where it has been suggested to play an important role in preventing synaptic GABA spillover and maintaining GABA homeostasis. Electrophysiological data from studies in which GAT-1 is selectively blocked or genetically deleted clearly indicate that reduced GAT-1 expression results in an increase in extracellular GABA concentrations (Frahm et al., 2001; Jensen et al., 2003; Chiu et al., 2005; Gonzalez-Burgos et al., 2009). Together, this constellation of biochemical alterations would be expected to produce increased GABAergic inhibition of pyramidal cells in aged PFC.

Against the background of these changes, postsynaptic GABA(B)R subunit expression was robustly attenuated in aged PFC. This finding agrees with a previous study from our laboratory in which expression of both R1 and R2 subunits of the GABA(B)R was reduced in aged PFC (McQuail et al., 2012). Although rats were not characterized on a PFC-dependent behavioral task in that prior study, findings herein show that attenuated GABA(B)R expression is significantly and inversely related to mPFC-dependent working memory. Notably, this relationship was only observed with the GABA(B)R2 subunit and the postsynaptic GABA(B)R1b isoform of the R1 subunit, but not with the

presynaptic R1a isoform of the R1 subunit. Postsynaptic GABA(B) receptors are largely located extra-synaptically and are sensitive to alterations in tonic GABA and GABA spillover from active synapses (Kulik et al., 2003, 2006; Glykys and Mody, 2007). Indeed, previous work by Wang et al. (2010) has indicated that GABA(B) receptors mediate a small tonic inhibitory current in layer 2/3 mPFC pyramidal neurons in young rats. The data presented here support a model in which interneuron dysfunction in aging contributes to elevated GABA availability and increased GABA(B) mediated tonic activity in aging. In this context, the downregulation of GABA(B)Rs may reflect an effective compensatory mechanism for preserving optimal neuronal excitability and working memory abilities.

GABA(B) receptor antagonist administration improves working memory in aging

Consistent with the relationship between lower endogenous GABA(B)R expression and better working memory in aging, both systemic and intra-mPFC administration of a GABA(B)R antagonist (CGP55845) significantly improved working memory performance of aged rats. Indeed, with both routes of administration, doses of CGP55845 were identified which completely restored working memory performance in aged rats to a level on par with young performance. These cognitively enhancing effects are consistent with prior reports that have primarily focused on the efficacy of this class of GABA(B)R antagonists in improving hippocampal mediated cognition in young and aged rats (Mondadori et al., 1993; Froestl et al., 2004; Helm et al., 2005; Lasarge et al., 2009; Froestl, 2010; Kleschevnikov et al., 2012). Interestingly, systemic injections of the same doses of CGP55845 impaired young rat performance in the delayed response task. One interpretation of these differential effects in young and aged rats is that GABA(B)R blockade in young rats opposes GABAergic transmission that is optimal for working memory. Blocking GABA(B)R activity in young rats may shift the mPFC toward a hyperexcitable state which could ultimately be as deleterious to working memory as the excessive inhibition that may accompany advanced age. Indeed, in schizophrenia, interneuron dysfunction and PFC hyperexcitability are thought to contribute to impaired working memory, a hallmark feature of this disorder (Lewis et al., 2005; Yizhar et al., 2011). Alternatively, it is possible that the impairing effects of GABA(B)R blockade in young animals have a site of action that is distinct from the enhancing effects of this drug at advanced ages. Data to date support a model in which GABA(B) blockade in aged mPFC serves to attenuate the effects of postsynaptic and/or extrasynaptic GABA(B)Rs expressed by mPFC pyramidal neurons. However, GABA(B)Rs are also localized presynaptically where their blockade could contribute to excess GABA release and increased pyramidal neuron inhibition. It is interesting to speculate that in young animals, GABA(B)R antagonists might serve to disinhibit GABA terminals themselves, ultimately resulting in greater pyramidal neuron inhibition, an effect which could confer impaired working memory. It is notable that although a similar pattern of impaired performance in young rats was observed following both systemic and intra-mPFC administration of the GABA(B)R antagonist, the effects did not reach statistical significance when the drug was delivered intracerebrally. As such, it is important to consider the possibility that critical site of action for the impairing effects of GABA(B)R antagonists may be outside of the mPFC. Overall, a better understanding of the synaptic dynamics of GABA(B)R signaling in both the young and aged brain will be essential for clarifying the role of these receptors in normal cognition and in age-related cognitive disorders.

The current biochemical and pharmacological findings as well as several prior electrophysiological studies suggest that pyramidal neurons may be subject to greater inhibition in aged rats. However, it is also important to consider that numbers of both interneurons and inhibitory, i.e., symmetrical, synapses can decline with age (de Brabander et al., 1998; Wong et al., 2000; Jacobs et al., 2001; Poe et al., 2001; Uylings and de Brabander, 2002; Duan et al., 2003; Stranahan et al., 2012). In the current study, expression of VGAT, which is critical for packaging GABA into synaptic vesicles and thus should be present in all inhibitory terminals, was stable across ages. Although the VGAT data support a relative preservation of inhibitory terminals in this model, the failure of this measure to recapitulate the previous anatomical reports of reduced inhibitory synapse number may reflect insufficient sensitivity of the methodologies used here to detect inhibitory terminal loss in cortical microcircuits. Alternatively, it is certainly possible given the other dynamic changes in GABA signaling proteins reported here, that although overall synapse number is reduced, there is an upregulation of VGAT expression with age in remaining inhibitory synapses. Given the diversity of interneurons and evidence that interneuron subclasses can be differentially sensitive to changes with age (Potier et al., 1994; Shetty and Turner, 1998; Vela et al., 2003), it will be important in future work to determine whether the findings described here are a pervasive feature of aged PFC interneurons, or rather if these biochemical alterations reflect very robust but anatomically restricted effects in specific interneuron subclasses.

The present study provides evidence that GABAergic substrates in mPFC are dysregulated during normal aging. The pattern of changes in protein expression suggest that mPFC pyramidal neurons are subject to greater inhibition with advanced aging and that downregulation of GABA(B)R expression in these neurons reflects an effective compensatory mechanism for preserving working memory function. GABA(B)R expression was strongly and inversely related to working memory abilities such that lower expression was associated with better preservation of working memory function in aged rats, and GABA(B)R blockade effectively reversed age-related impairments in working memory. These findings highlight that altered excitatory-inhibitory dynamics within the aged PFC may contribute to working memory decline in aging, and that targeting GABA(B)Rs may provide therapeutic benefits for improving cognitive functions supported by this brain region.

References

Allen TA, Narayanan NS, Kholodar-Smith DB, Zhao Y, Laubach M, Brown TH (2008) Imaging the spread of reversible brain inactivations using fluorescent muscimol. J Neurosci Methods 171:30–38. CrossRef Medline

Arnsten AF (2013) The neurobiology of thought: the groundbreaking discoveries of Patricia Goldman-Rakic 1937–2003. Cereb Cortex 23:2269–2281. CrossRef Medline

Arnsten AF, Cai JX, Murphy BL, Goldman-Rakic PS (1994) Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. Psychopharmacology 116:143–151. CrossRef Medline

Beas BS, Setlow B, Bizon JL (2013) Distinct manifestations of executive dysfunction in aged rats. Neurobiol Aging 34:2164–2174. CrossRef Medline

Biermann B, Ivankova-Susankova K, Bradaia A, Abdel Aziz S, Besseyrias V, Kapfhammer JP, Missler M, Gassmann M, Bettler B (2010) The sushi domains of GABAB receptors function as axonal targeting signals. J Neurosci 30:1385–1394. CrossRef Medline

Bizon JL, Foster TC, Alexander GE, Glisky EL (2012) Characterizing cognitive aging of working memory and executive function in animal models. Front Aging Neurosci 4:19. CrossRef Medline

Bories C, Husson Z, Guitton MJ, De Koninck Y (2013) Differential balance of prefrontal synaptic activity in successful versus unsuccessful cognitive aging. J Neurosci 33:1344–1356. CrossRef Medline

Chiu CS, Brickley S, Jensen K, Southwell A, Mckinney S, Cull-Candy S, Mody I, Lester HA (2005) GABA transporter deficiency causes tremor, ataxia, nervousness, and increased GABA-induced tonic conductance in cerebellum. J Neurosci 25:3234–3245. CrossRef Medline

Conti F, Minelli A, Melone M (2004) GABA transporters in the mammalian cerebral cortex: localization, development and pathological implications. Brain Res Brain Res Rev 45:196–212. CrossRef Medline

Davis S, Rodger J, Hicks A, Mallet J, Laroche S (1996) Brain structure and task-specific increase in expression of the gene encoding syntaxin 1B during learning in the rat: a potential molecular marker for learning-induced synaptic plasticity in neural networks. Eur J Neurosci 8:2068–2074. CrossRef Medline

de Brabander JM, Kramers RJ, Uylings HB (1998) Layer-specific dendritic regression of pyramidal cells with ageing in the human prefrontal cortex. Eur J Neurosci 10:1261–1269. CrossRef Medline

Duan H, Wearne SL, Rocher AB, Macedo A, Morrison JH, Hof PR (2003) Age-related dendritic and spine changes in corticocortically projecting neurons in macaque monkeys. Cereb Cortex 13:950–961. CrossRef Medline

Enomoto T, Tse MT, Floresco SB (2011) Reducing prefrontal gamma-aminobutyric acid activity induces cognitive, behavioral, and dopaminergic abnormalities that resemble schizophrenia. Biol Psychiatry 69: 432–441. CrossRef Medline

Frahm C, Engel D, Draguhn A (2001) Efficacy of background GABA uptake in rat hippocampal slices. Neuroreport 12:1593–1596. CrossRef Medline

Froestl W (2010) Chemistry and pharmacology of GABAB receptor ligands. Adv Pharmacol 58:19–62. CrossRef Medline

Froestl W, Mickel SJ, Schmutz M, Bittiger H (1996) Potent, orally active GABAB receptor antagonists. Pharmacol Rev Commun 8:127–133.

Froestl W, Gallagher M, Jenkins H, Madrid A, Melcher T, Teichman S, Mondadori CG, Pearlman R (2004) SGS742: the first GABAB receptor antagonist in clinical trials. Biochem Pharmacol 68:1479–1487. CrossRef Medline

Glisky EL (2007) Changes in cognitive function in human aging. In: Brain aging: models, methods, and mechanisms (Riddle DR, ed). Boca Raton, FL: CRC.

Glykys J, Mody I (2007) The main source of ambient GABA responsible for tonic inhibition in the mouse hippocampus. J Physiol 582:1163–1178. CrossRef Medline

Goldman-Rakic PS (1995) Cellular basis of working memory. Neuron 14: 477–485. CrossRef Medline

Goldman-Rakic PS (1996) Regional and cellular fractionation of working memory. Proc Natl Acad Sci U S A 93:13473–13480. CrossRef Medline

Goldman-Rakic PS, Brown RM (1981) Regional changes of monoamines in cerebral cortex and subcortical structures of aging rhesus monkeys. Neuroscience 6:177–187. CrossRef Medline

Gonzalez-Burgos G (2010) GABA transporter GAT1: a crucial determinant of GABAB receptor activation in cortical circuits? Adv Pharmacol 58:175–204. CrossRef Medline

Gonzalez-Burgos G, Lewis DA (2008) GABA neurons and the mechanisms of network oscillations: implications for understanding cortical dysfunction in schizophrenia. Schizophr Bull 34:944–961. CrossRef Medline

Gonzalez-Burgos G, Rotaru DC, Zaitsev AV, Povysheva NV, Lewis DA (2009) GABA transporter GAT1 prevents spillover at proximal and distal GABA synapses onto primate prefrontal cortex neurons. J Neurophysiol 101:533–547. CrossRef Medline

Helm KA, Haberman RP, Dean SL, Hoyt EC, Melcher T, Lund PK, Gallagher M (2005) GABAB receptor antagonist SGS742 improves spatial memory and reduces protein binding to the cAMP response element (CRE) in the hippocampus. Neuropharmacology 48:956–964. CrossRef Medline

Jacobs B, Schall M, Prather M, Kapler E, Driscoll L, Baca S, Jacobs J, Ford K, Wainwright M, Treml M (2001) Regional dendritic and spine variation in human cerebral cortex: a quantitative golgi study. Cereb Cortex 11: 558–571. CrossRef Medline

Jensen K, Chiu CS, Sokolova I, Lester HA, Mody I (2003) GABA transporter-1 (GAT1)-deficient mice: differential tonic activation of GABAA versus GABAB receptors in the hippocampus. J Neurophysiol 90:2690–2701. CrossRef Medline

Jones KA, Borowsky B, Tamm JA, Craig DA, Durkin MM, Dai M, Yao WJ, Johnson M, Gunwaldsen C, Huang LY, Tang C, Shen Q, Salon JA, Morse K, Laz T, Smith KE, Nagarathnam D, Noble SA, Branchek TA, Gerald C (1998) GABA(B) receptors function as a heteromeric assembly of the subunits GABA(B)R1 and GABA(B)R2. Nature 396:674–679. CrossRef Medline

Kaupmann K, Huggel K, Heid J, Flor PJ, Bischoff S, Mickel SJ, McMaster G, Angst C, Bittiger H, Froestl W, Bettler B (1997) Expression cloning of GABA(B) receptors uncovers similarity to metabotropic glutamate receptors. Nature 386:239–246. CrossRef Medline

Kaupmann K, Malitschek B, Schuler V, Heid J, Froestl W, Beck P, Mosbacher J, Bischoff S, Kulik A, Shigemoto R, Karschin A, Bettler B (1998) GABA(B)-receptor subtypes assemble into functional heteromeric complexes. Nature 396:683–687. CrossRef Medline

Kleschevnikov AM, Belichenko PV, Villar AJ, Epstein CJ, Malenka RC, Mobley WC (2004) Hippocampal long-term potentiation suppressed by increased inhibition in the Ts65Dn mouse, a genetic model of Down syndrome. J Neurosci 24:8153–8160. CrossRef Medline

Kleschevnikov AM, Belichenko PV, Faizi M, Jacobs LF, Htun K, Shamloo M, Mobley WC (2012) Deficits in cognition and synaptic plasticity in a mouse model of Down syndrome ameliorated by GABAB receptor antagonists. J Neurosci 32:9217–9227. CrossRef Medline

Kulik A, Vida I, Luján R, Haas CA, López-Bendito G, Shigemoto R, Frotscher M (2003) Subcellular localization of metabotropic GABA(B) receptor subunits GABA(B1a/b) and GABA(B2) in the rat hippocampus. J Neurosci 23:11026–11035. Medline

Kulik A, Vida I, Fukazawa Y, Guetg N, Kasugai Y, Marker CL, Rigato F, Bettler B, Wickman K, Frotscher M, Shigemoto R (2006) Compartment-dependent colocalization of Kir3.2-containing K+ channels and GABAB receptors in hippocampal pyramidal cells. J Neurosci 26:4289–4297. CrossRef Medline

Lasarge CL, Bañuelos C, Mayse JD, Bizon JL (2009) Blockade of GABA(B) receptors completely reverses age-related learning impairment. Neuroscience 164:941–947. CrossRef Medline

Lewis DA, Hashimoto T, Volk DW (2005) Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 6:312–324. CrossRef Medline

Luebke JI, Chang YM, Moore TL, Rosene DL (2004) Normal aging results in decreased synaptic excitation and increased synaptic inhibition of layer 2/3 pyramidal cells in the monkey prefrontal cortex. Neuroscience 125: 277–288. CrossRef Medline

McQuail JA, Bañuelos C, LaSarge CL, Nicolle MM, Bizon JL (2012) GABA(B) receptor GTP-binding is decreased in the prefrontal cortex but not the hippocampus of aged rats. Neurobiol Aging 33:1124 e1–12. CrossRef Medline

Minelli A, Brecha NC, Karschin C, DeBiasi S, Conti F (1995) GAT-1, a high-affinity GABA plasma membrane transporter, is localized to neurons and astroglia in the cerebral cortex. J Neurosci 15:7734–7746. Medline

Mondadori C, Jaekel J, Preiswerk G (1993) CGP 36742: the first orally active GABAB blocker improves the cognitive performance of mice, rats, and rhesus monkeys. Behav Neural Biol 60:62–68. CrossRef Medline

Moore TL, Schettler SP, Killiany RJ, Herndon JG, Luebke JI, Moss MB, Rosene DL (2005) Cognitive impairment in aged rhesus monkeys associated with monoamine receptors in the prefrontal cortex. Behav Brain Res 160:208–221. CrossRef Medline

Murray AJ, Sauer JF, Riedel G, McClure C, Ansel L, Cheyne L, Bartos M, Wisden W, Wulff P (2011) Parvalbumin-positive CA1 interneurons are required for spatial working but not for reference memory. Nat Neurosci 14:297–299. CrossRef Medline

Paxinos G, Watson C (2005) The rat brain in stereotaxic coordinates, Ed 5. Boston: Elsevier.

Pinard A, Seddik R, Bettler B (2010) GABAB receptors: physiological functions and mechanisms of diversity. Adv Pharmacol 58:231–255. CrossRef Medline

Poe BH, Linville C, Brunso-Bechtold J (2001) Age-related decline of presumptive inhibitory synapses in the sensorimotor cortex as revealed by the physical dissector. J Comp Neurol 439:65–72. CrossRef Medline

Potier B, Krzywkowski P, Lamour Y, Dutar P (1994) Loss of calbindin-immunoreactivity in CA1 hippocampal stratum radiatum and stratum lacunosum-moleculare interneurons in the aged rat. Brain Res 661:181–188. CrossRef Medline

Ragozzino ME (2002) The effects of dopamine D(1) receptor blockade in

the prelimbic-infralimbic areas on behavioral flexibility. Learn Mem 9:18–28. CrossRef Medline

Robbins TW, James M, Owen AM, Sahakian BJ, Lawrence AD, McInnes L, Rabbitt PM (1998) A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. J Int Neuropsychol Soc 4:474–490. Medline

Salthouse TA, Atkinson TM, Berish DE (2003) Executive functioning as a potential mediator of age-related cognitive decline in normal adults. J Exp Psychol Gen 132:566–594. CrossRef Medline

Shetty AK, Turner DA (1998) Hippocampal interneurons expressing glutamic acid decarboxylase and calcium-binding proteins decrease with aging in Fischer 344 rats. J Comp Neurol 394:252–269. CrossRef Medline

Sloan HL, Good M, Dunnett SB (2006) Double dissociation between hippocampal and prefrontal lesions on an operant delayed matching task and a water maze reference memory task. Behav Brain Res 171:116–126. CrossRef Medline

Stefani MR, Moghaddam B (2005) Systemic and prefrontal cortical NMDA receptor blockade differentially affect discrimination learning and set-shift ability in rats. Behav Neurosci 119:420–428. CrossRef Medline

St Onge JR, Abhari H, Floresco SB (2011) Dissociable contributions by prefrontal D1 and D2 receptors to risk-based decision making. J Neurosci 31:8625–8633. CrossRef Medline

Stranahan AM, Jiam NT, Spiegel AM, Gallagher M (2012) Aging reduces total neuron number in the dorsal component of the rodent prefrontal cortex. J Comp Neurol 520:1318–1326. CrossRef Medline

Taylor JR, Birnbaum S, Ubriani R, Arnsten AF (1999) Activation of cAMP-dependent protein kinase A in prefrontal cortex impairs working memory performance. J Neurosci 19:RC23. Medline

Uylings HB, de Brabander JM (2002) Neuronal changes in normal human aging and Alzheimer's disease. Brain Cogn 49:268–276. CrossRef Medline

Uylings HB, Groenewegen HJ, Kolb B (2003) Do rats have a prefrontal cortex? Behav Brain Res 146:3–17. CrossRef Medline

Vela J, Gutierrez A, Vitorica J, Ruano D (2003) Rat hippocampal GABAergic molecular markers are differentially affected by ageing. J Neurochem 85:368–377. CrossRef Medline

Vigot R, Barbieri S, Bräuner-Osborne H, Turecek R, Shigemoto R, Zhang YP, Luján R, Jacobson LH, Biermann B, Fritschy JM, Vacher CM, Müller M, Sansig G, Guetg N, Cryan JF, Kaupmann K, Gassmann M, Oertner TG, Bettler B (2006) Differential compartmentalization and distinct functions of GABAB receptor variants. Neuron 50:589–601. CrossRef Medline

Wang M, Yang Y, Wang CJ, Gamo NJ, Jin LE, Mazer JA, Morrison JH, Wang XJ, Arnsten AF (2013) NMDA receptors subserve persistent neuronal firing during working memory in dorsolateral prefrontal cortex. Neuron 77:736–749. CrossRef Medline

Wang Y, Neubauer FB, Lüscher HR, Thurley K (2010) GABAB receptor-dependent modulation of network activity in the rat prefrontal cortex in vitro. Eur J Neurosci 31:1582–1594. CrossRef Medline

Wass C, Pizzo A, Sauce B, Kawasumi Y, Sturzoiu T, Ree F, Otto T, Matzel LD (2013) Dopamine D1 sensitivity in the prefrontal cortex predicts general cognitive abilities and is modulated by working memory training. Learn Mem 20:617–627. CrossRef Medline

White JH, Wise A, Main MJ, Green A, Fraser NJ, Disney GH, Barnes AA, Emson P, Foord SM, Marshall FH (1998) Heterodimerization is required for the formation of a functional GABA(B) receptor. Nature 396:679–682. CrossRef Medline

Wong TP, Marchese G, Casu MA, Ribeiro-da-Silva A, Cuello AC, De Koninck Y (2000) Loss of presynaptic and postsynaptic structures is accompanied by compensatory increase in action potential-dependent synaptic input to layer V neocortical pyramidal neurons in aged rats. J Neurosci 20:8596–8606. Medline

Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, Sohal VS, Goshen I, Finkelstein J, Paz JT, Stehfest K, Fudim R, Ramakrishnan C, Huguenard JR, Hegemann P, Deisseroth K (2011) Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature 477:171–178. CrossRef Medline

Zaitsev AV, Povysheva NV, Gonzalez-Burgos G, Rotaru D, Fish KN, Krimer LS, Lewis DA (2009) Interneuron diversity in layers 2–3 of monkey prefrontal cortex. Cereb Cortex 19:1597–1615. CrossRef Medline

Systems/Circuits

Advanced Age Dissociates Dual Functions of the Perirhinal Cortex

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The perirhinal cortex (PRC) is proposed to both represent high-order sensory information and maintain those representations across delays. These cognitive processes are required for recognition memory, which declines during normal aging. Whether or not advanced age affects the ability of PRC principal cells to support these dual roles, however, is not known. The current experiment recorded PRC neurons as young and aged rats traversed a track. When objects were placed on the track, a subset of the neurons became active at discrete locations adjacent to objects. Importantly, the aged rats had a lower proportion of neurons that were activated by objects. Once PRC activity patterns in the presence of objects were established, however, both age groups maintained these representations across delays up to 2 h. These data support the hypothesis that age-associated deficits in stimulus recognition arise from impairments in high-order stimulus representation rather than difficulty in sustaining stable activity patterns over time.

Introduction

The perirhinal cortex (PRC) processes, represents, and stores high-order sensory information that is critical for a wide range of behaviors (Murray and Wise, 2012). The PRC enables, for example, fear-conditioning to a stimulus (Kholodar-Smith et al., 2008) or a context (Bucci et al., 2000), and paired-associative learning (Higuchi and Miyashita, 1996). The PRC also supports an animal's ability to discriminate between novel and familiar stimuli (Málková et al., 2001; McTighe et al., 2010). A number of these cognitive functions are altered during normal aging, including observations that aged rats are more likely to incorrectly identify a novel stimulus as familiar (Burke et al., 2010) and show poorer consolidation of information in fear conditioning (Oler and Markus, 1998).

Although there is no loss of PRC neurons with age (Rapp et al., 2002), several biochemical and molecular alterations within the PRC of old animals have been identified that may contribute to cognitive deficits. First, protein composition is altered, including a reduction in the expression of the NR2A subunit of the NMDA receptor in aged compared with young rats (Liu et al., 2008). Moreover, old rats have reduced immunoreactivity for calbindin-D28k in PRC principal cells (Moyer et al., 2011), and overall glutamate levels are lower in the aged PRC (Liu et al., 2009). Finally, following object exploration, fewer PRC neurons in old rats transcribe the activity-dependent immediate-early gene *Arc* (Burke et al., 2012b), which encodes an effector protein critical for AMPA receptor trafficking (Chowdhury et al., 2006).

In freely behaving young rats, PRC principal neurons show firing rate increases at locations adjacent to objects (Burke et al., 2012a; Deshmukh et al., 2012). This activity remains consistent as objects become familiar and across delays (Burke et al., 2012a). It is probable that this object-specific activity is a critical physiological correlate of stimulus recognition. The age-associated decline in the proportion of PRC neurons that transcribe *Arc* predicts that old rat PRC cells may show reduced object-associated spiking. Because *Arc* expression has been shown to be decoupled from neuronal activity under some conditions in which rats show learning impairments (Fletcher et al., 2006), it is also possible that old PRC neuron firing remains normal despite the fact that fewer cells show *Arc* expression during this activity. Because *Arc* expression is critical for memory maintenance (Guzowski et al., 2000), such a decline could lead to deficits in stable activity patterns across delays.

The aim of the current experiment was to determine the extent to which age-associated declines in PRC-dependent behavior arise from deficits in stimulus representation, maintenance, or both. PRC neurons were recorded as young and aged rats traversed a circular track that was empty or contained objects for two epochs separated by a delay. If object-associated neuron firing is similar between age groups, then it can be assumed that old rats have a deficit in inducing *Arc* transcription that may result in unstable activity patterns across delays. On the other hand, if there are alterations in the pattern of PRC cell activity in response to objects, then it could be inferred that advanced age results in impaired PRC-dependent stimulus representation.

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Materials and Methods

Subjects and behavioral training. All behavioral procedures were in accordance with the National Institutes of Health guidelines for rodents and protocols approved by the University of Arizona Institutional Animal Care and Use Committee. Electrophysiological studies were conducted on six young (8–10 months old), and six aged (24–27 months old) Fisher-344 male rats. All rats participated in these experiments in pairs of one young rat and one aged rat such that a single old–young pair arrived in the colony in the same batch of animals, went through identical behavior procedures on the same days, and underwent surgical implantation within 24 h of each other. The rats were housed individually and maintained on a 12 h light/dark cycle. Before rats were implanted with the hyperdrive recording device, they were screened for spatial memory impairments and normal vision using the Morris swim task (Morris, 1984). All animals were tested over 4 d with six spatial trials on each day. Animals were then screened for visual ability with 2 d of cued visual trials (6 trials/d) in which the escape platform was above the surface of the water but the position of the platform changed between each trial. This procedure has been described in detail previously (Barnes et al., 1996). Rats' performance on the swim task was analyzed offline with either in-house software (WMAZE, M. Williams) or a commercial software application (ANY-maze). Because different release locations and differences in swimming velocity produce variability in the latency to reach the escape platform, a corrected integrated path length (CIPL) was calculated to ensure comparability of the rats' performance across different release locations (Gallagher et al., 1993). The CIPL value measures the cumulative distance over time from the escape platform corrected by an animal's swimming velocity, and is equivalent to the cumulative search error described by Gallagher and colleagues (1993). Therefore, regardless of the release location, if the rat mostly swims toward the escape platform, the CIPL value will be low. In contrast, the more time a rat spends swimming in directions away from the platform, the higher the CIPL value.

During electrophysiological recordings, the animals were food-deprived to ~85% of their *ad libitum* weight and trained to run on a circular track (~335 cm in circumference) in both the counterclockwise and clockwise directions for food reinforcement. The food reward was a mixture of rat food pellets made soft by soaking them in water, applesauce, and the diet supplement Ensure. All electrophysiological recordings took place during the dark phase of the rats' light/dark cycle. Food rewards were given in a small plastic food dish (4 × 4 cm) at two positions on the track. Both food dishes were located at the position on the track that marked the completion of one lap on opposite sides of a barrier; that is, where the rat was required to turn around and run in the opposite direction (Fig. 1*A*). During all electrophysiological recording sessions, rats were required to run at least 20 laps (10 in the counterclockwise direction and 10 in the clockwise direction) during two distinct episodes of behavior. Each track-running epoch was flanked by a rest period in which the rat was placed in a towel-lined pot located in a position that was central to the circumference of the track. Thus, the activity of PRC neurons was monitored during an initial rest session (before behavior), during the first epoch of track running, during a second rest session after Epoch 1 that was either 20 min or 2 h long, during a second epoch of track running, and then finally during a third rest period. Data from the rest periods were used to assess firing stability across the entire recording session.

All 12 rats participated in the same behavioral procedures. During the first procedure (Day 1), rats ran on an empty track (no objects–both epochs; Fig. 1*A*) for both epochs of behavior. A 20 min rest period occurred between Epoch 1 and Epoch 2. For the second procedure (Day 2), during Epoch 1, eight novel objects that varied in size, color, and texture were placed at eight different locations along the track. All the objects used in these experiments were at least 7 cm in each dimension, so as to be easily identified by the rats. The side of the track on which the objects were placed alternated between the left and the right side and the rat had to run past these objects to obtain the food reward. This also ensured that the rats had to briefly attend to the objects while traversing the track to avoid colliding with them. Following either a 20 min or a 2 h rest period, during Epoch 2, six of the same objects used in Epoch 1 remained in the same location on the track and two objects that were on the track during Epoch 1 were replaced with two novel objects (objects–both epochs condition; Fig. 1*B*). This manipulation was included to control for any differences that object novelty could have on firing rate before it was shown that changing the objects and their relative novelty have minimal effects on PRC neuron activity (Burke et al., 2012a). Each rat completed these behavioral procedures on consecutive days, and this process was repeated a minimum of two times and a maximum of six times. Eight novel objects were always used for Epoch 1 of the 20 min and 2 h delay conditions. Yoked old–young rats pairs that underwent electrophysiological recordings on the same days were always presented with identical objects in the same location. Different aged–young rat pairs were presented with distinct novel objects such that across yoked pairs of animals, objects sets were not the same. For one aged rat only, no single-unit data were collected for the objects–both epochs condition with a 2 h delay. Following the completion of these behavioral procedures, all rats traversed the track for two additional control conditions to measure the extent to which objects modulated PRC activity within the same population of principal cells. This included a no objects–objects condition (Fig. 1*C*) and an objects–no objects condition (Fig. 1*D*) that rats participated in on different days than the conditions described above. For both of these procedures, Epochs 1 and 2 were separated by a 20 min delay.

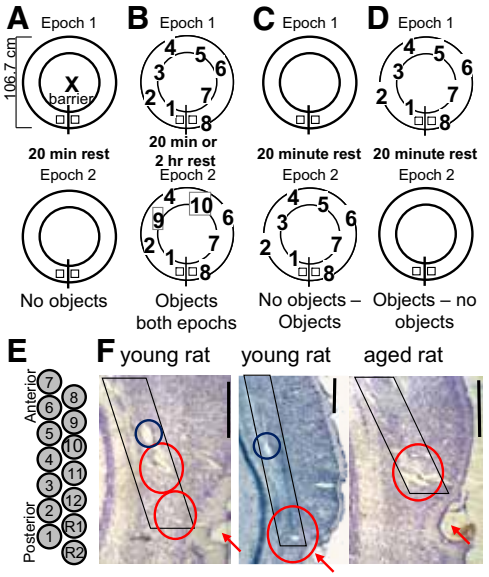

Figure 1. Behavioral procedures used during electrophysiological recordings. The track used for behavior during all electrophysiological recordings required rats to run 20 laps bidirectionally (10 counterclockwise, 10 clockwise) for a food reward. ***A***, Under the no objects condition the track was empty during both epochs of track running. Rewards were given in two food dishes located on opposite sides of a barrier (indicated by squares), at the position where the rat was required to turn around. The "X" indicates the location of the pot that the rat was placed in during rest episodes. ***B***, In the objects– both epochs condition, eight novel objects were placed at discrete locations around the track for the first epoch of behavior (top), and the rat had to run past the objects to obtain the food reward. During the second epoch of behavior (bottom), six of the eight objects used in Epoch 1 were placed on the track at the same location as in Epoch 1, while two of the eight objects were removed and substituted with two novel objects (in this case Objects 3 and 5 were replaced with Objects 9 and 10 as indicated by the gray boxes). ***C***, ***D***, All rats participated in two additional behavioral procedures: the no objects– objects (***C***) and the objects–no objects (***D***) conditions. ***E***, A schematic view of bottom of the tetrode guide cannulae showing an example of the configuration of the recording probes. The numbers indicate tetrode assignment, which was used for determining the recording location of each tetrode. ***F***, Coronal Nissl-stained sections of two young rat brains (left and middle), and one aged rat brain (right) showing representative tetrode tracks (black lines) and lesions (red circles) for perirhinal cortical recordings. In the young rats, the tetrodes recorded neurons in Layer V (left) and Layers II/III (left and right). In the aged rats, most perirhinal cortical neurons were recorded from Layer V. The red arrows indicate the location of the rhinal sulcus. Scale bars, ~1 mm. In some cases the tetrodes did not reach the PRC (blue circles) and cells recorded from these tetrodes were not used in the current analyses.

Table 1. Number and cell layer of PRC single units recorded from each young and aged rat over all conditions

		Number (cell layer)				
Rat	Age	No objects	20 min delay	2 h delay	No objects–no objects	Objects–no objects
8412	Young	7 (V)	8 (V)	11 (V)	9 (V)	2 (v)
8413	Aged	62 (V)	34 (V)	45 (V)	9 (V)	13 (V)
8509	Young	7 (V)	14 (V)	12 (V)	9 (V)	4 (V)
8507	Aged	20 (V)	17 (V)		7 (V)	6 (V)
8583	Young	93 (II/III)	94 (II/III)	83 (II/III)	50 (II/III)	53 (II/III)
8615	Aged	99 (V)	56 (V)	62 (V)	55 (V)	17 (V)
8661	Young	34 and 14 (II/III and V)	33 and 12 (II/III and V)	25 and 10 (II/III and V)	1 and 26 (II/III and V)	1 and 25 (II/III and V)
8662	Aged	99 (V)	41 (V)	59 (V)	33 (V)	63 (V)
8670	Young	60 and 68 (II/III and V)	48 and 58 (II/III and V)	21 and 27 (II/III and V)	11 and 15 (II/III and V)	28 and 29 (II/III and V)
8696	Aged	39 (V)	44 (V)	27 (V)	30 (V)	44 (V)
8883	Young	35 (V)	30 (V)	12 (V)	3 (V)	2 (V)
8865	Aged	7 and 31 (II/III and V)	4 and 44 (II/III and V)	2 and 35 (II/III and V)	16 (V)	3 and 26 (II/III and V)
Total		675	537	431	274	316

For all conditions in which objects were placed on the track, the objects were fixed in place using Velcro. Thus, rats could actively explore, rear, and climb on the objects without displacing them. Additionally, during all rest periods the objects were removed from the track so that the rat could not see them during the intervening delay period.

Surgical procedures. Surgery was conducted according to National Institutes of Health guidelines for rodents and protocols approved by the University of Arizona Institutional Animal Care and Use Committee. Before surgery, the rats were administered penicillin G (30,000 U, i.m., in each hindlimb) to combat infection. During surgical implantation, the rats were maintained under anesthesia with isoflurane administered at doses ranging from 0.5 to 2.5%.

All rats were implanted with a "hyperdrive" manipulator device that held an array of 14 separately moveable tetrode recording probes (Gothard et al., 1996). Each hyperdrive consisted of 14 drive screws coupled by a nut to a guide cannula. Twelve of these cannulae contained tetrodes (McNaughton et al., 1983b; Recce and O'Keefe, 1989), four-channel electrodes constructed by twisting together four strands of insulated 13 μm nichrome wire (H.P. Reid). Two additional tetrodes had their individual wires shorted together, and the shorted tetrode with the least cellular activity was used as an indifferent reference. A full turn of the screw advanced the tetrode 318 μm and all tetrodes were lowered between 4.0 and 6.0 mm ventral to the surface of brain. The 14 guide cannulae were arranged in two linear columns of seven each such that the configuration of tetrodes spanned ~2 mm from the anterior to posterior position (Fig. 1*E*). This permitted sampling of neurons from a greater extent of the PRC and enabled more precise matching of tetrode number to track and lesion location for histological verification or recording sites (see below).

The implant was cemented in place with dental acrylic anchored by small screws. Immediately after surgery, all tetrodes were lowered ~1 mm into the cortex, and rats were orally administered 26 mg of acetaminophen (Children's Tylenol Elixir or ibuprofen) for analgesia. Oral administration of acetaminophen was continued for 3–5 d after surgery. Additionally, all rats were given either 25 mg of ampicillin (Bicillin, Wyeth Laboratories) or a combination of 20 mg of sulfamethoxale and 0.4 mg of trimethoprin (Hi-Tech Pharmacal) on a 10 d on/10 d off regimen for the duration of the experiment.

In all rats, recordings were made from the middle to caudal PRC region (between 4.0 and 6.5 mm posterior, 6.0 mm lateral to bregma, and angled 14° toward the midline). Following experimental procedures, 20 μA of direct current was administered to each tetrode. One to 2 weeks following microlesioning, rats were given a fatal dose pentobarbital and perfused with 4% paraformaldehyde (Gage et al., 2012). Brains were extracted and soaked in a 30% sucrose solution for 1 week or until they sank. Tissue was then frozen with dry ice and the area under the cranial implant was coronally sliced at 40 μm with a cryostat. Sections were directly mounted to superfrost slides and dried overnight in a fume hood. Finally, tissue was Nissl-stained and tetrode location was verified. In most cases the tetrode tracks were not parallel to the plane of sectioning and tracks had to be followed over several adjacent slides. In these cases the section in which the lesion was the largest was considered the approximate location. Only the units recorded from tetrodes histologically verified to be in the PRC were used in the current analyses and neurons recorded from other brain regions (e.g., ventral CA1 or area TE of the inferotemporal cortex) were excluded. The majority of tetrodes were located in Area 36 of the PRC, but in two young and two aged rats four tetrodes reached Dorsal Area 35. Moreover, in the young rats neurons were recorded from both Layer V and Layers II/III, but for the aged rats only one rat had tetrodes in Layers II/III, and all of the other single-unit recordings were from neurons in Layer V. Figure 1*F* shows Nissl-stained coronal sections from different young and aged rat brains with representative tetrode recording tracks and lesions within the PRC. Neurons recorded from tetrodes that produced lesions outside of the PRC were not included in any of the current analyses. In most cases these tracks were in Area TE (Fig. 1*F*, blue circles).

Neurophysiology. After surgery, tetrodes were lowered into the PRC over several weeks. The neutral reference electrode was advanced with other tetrodes and when an area of cortex was reached that did not record any unit activity, it was not moved again. The four channels of each tetrode were attached to a 50-channel unity-gain head stage (Neuralynx). A multiwire cable connected the head stage to digitally programmable amplifiers (Neuralynx). The spike signals were amplified by a factor of 1000–5000, bandpass-filtered between 600 Hz and 6 kHz, and transmitted to the Cheetah data acquisition system (Neuralynx). Signals were digitized at 32 kHz, and events that reached a predetermined threshold were recorded for a duration of 1 ms. Spikes were sorted offline on the basis of the amplitude and principal components from the four tetrode channels by means of a semiautomatic clustering algorithm (KlustaKwik, K.D. Harris). The resulting classification was corrected and refined manually with custom-written software (MClust, A.D. Redish, University of Minnesota; updated by S.L. Cowen, University of Arizona, and D.R. Euston, University of Lethbridge), resulting in a spike-train time series for each of the well isolated cells. No attempt was made to match cells from one daily session to the next. Therefore, the numbers of recorded cells reported does not take into account possible recordings from the same cells on consecutive days and the actual number of unique recorded neurons could be lower than reported in Table 1. Note that all statistics were run on the basis of pooled data for individual rats, and not with total cells as the sample size. This conservative approach was used as a means to not create a bias from oversampling the same neuron.

Putative principal neurons in the deep and superficial layers of the PRC were identified by means of their waveform characteristics and autocorrelogram features (Barthó et al., 2004). Specifically, neocortical principal cells tend to have autocorrelograms with peaks at 3–6 ms followed by an exponential decay, which is indicative of "bursting" cells, or an autocorrelogram with an exponential rise from 1 to 10s of milliseconds. These cells are considered regular-spiking neurons. In contrast, the autocorrelograms of putative interneurons are not as fast decaying or slow rising as those of pyramidal neurons (Barthó et al., 2004).

Activity from putative principal neurons was used for analysis only if their respective waveform features showed clear separation from the

spikes of other cells and from noise. This was initially determined with qualitative ratings made by experimenters. Following this rating, the extent that clusters obtained from the waveforms of neurons included in the present analyses showed separation from other cells and from noise was quantified by calculating the L ratio and isolation distance of each cluster (Schmitzer-Torbert et al., 2005). The L ratio is the degree that a cluster separates from other spikes recorded on the same tetrode normalized by the total number of spikes for a given cluster. A lower L-ratio value is indicative of better separation (Schmitzer-Torbert et al., 2005). The average L ratio was 0.15 (±0.02 SEM) for the young rats and 0.11 (±0.02 SEM) for the aged rats, which was not significantly statistically different ($t_{(5)} = 1.22$, $p = 0.28$; paired samples). The isolation distance estimates how distant the cluster spikes are from the other spikes recorded on the same tetrode (Harris et al., 2001). Higher isolation distance therefore corresponds to better separation and a reduced probability of contamination from noise or spikes from other neurons. The mean isolation distance was 68.9 (±20.9 SEM) for the young rats and 55.7 (±5.1 SEM) for the aged rats, which was not significantly different ($t_{(5)} = 0.58$, $p = 0.59$; paired samples). These values indicate that cluster quality was not different between the young and aged rats and that all cells used in the current analyses showed intermediate to good separation (Schmitzer-Torbert et al., 2005).

Several diodes were mounted on the head stage to allow position tracking. The position of the diode array was detected by a TV camera placed directly above the experimental apparatus and recorded with a sampling frequency of 60 Hz. The sampling resolution was such that a pixel was ~0.3 cm. A portion of the principal data obtained from the young rats during the no objects–both epochs and objects–both epochs conditions has been published previously (Burke et al., 2012a).

Analyses and statistics. Spike-activity diagrams were constructed by plotting the circular trajectories of the animals on a linearized, one-dimensional scale, using a linear interpolation (Maurer et al., 2005). For each cell, the maximum firing rate, mean firing rate, and information content (spikes/bit) were calculated. Maximum and mean firing rates were obtained after normalizing spike activity by the occupancy of the animal, and information content was calculated from 161 bins of ~4.1 cm with the following formula: $\Sigma P_i(R_i/R)\log_2(R_i/R)$, where P_i was the probability of occupancy for a bin, R_i was the firing rate of the bin, and R was the mean firing rate of the cell (Skaggs et al., 1993). The area of the track within seven bins of a food dish (28.7 cm) was excluded for the calculation of information content, because when the rats were within this area of the track, their running speed was either zero or it was changing rapidly as the rat was stopping to obtain reward or accelerating after eating. Moreover, this area of the track contained a food dish, the reward and an object during conditions with objects. Therefore, activity at this location could presumably be related to the food dish, reward, the ripple activity known to occur during behavior when animals pause (O'Neill et al., 2006), and/or the object. Because it was difficult to dissociate the relative contribution of these factors, activity in this area of the track was excluded from analysis. It is notable, however, that when a velocity filter of 10 cm/s was applied to spikes, the firing rates at the food dish regions did not significantly vary between object and no object conditions and between other regions on the track (data not shown). This suggests that activity in these areas were related to stimulus properties rather to reward.

When the information content was calculated for all cells that showed activity on the maze (a mean firing rate >0.2 spikes/bin occupancy), there was not a significant difference in mean information content between Epochs 1 and 2 ($t_{(45)} = 0.10$, $p = 0.94$; paired-samples t test). Moreover, when all behavioral conditions were analyzed for the three rats (two young and one aged) that had tetrodes in both the deep and the superficial layers of the PRC, information content was not significantly different ($t_{(5)} = 1.51$, $p = 0.19$; paired-samples t test) between neurons in Layer V (0.61 bits/spike) and neurons in Layers II/III (0.53 bits/spike). Therefore, the data obtained from the different epochs of track running, and from the different cortical laminae were combined for additional analysis of the effects of behavioral condition and age.

Information content was used to examine the activity correlates of PRC neurons. Specifically, it was observed that many PRC neurons show increased firing rates at the location of objects (Burke et al., 2012a; Deshmukh et al., 2012). These patterns of activity were termed "object fields" (Burke et al., 2012a), and a PRC neuron was considered to have an object field if its information content was >0.5 bits/spike, and the occupancy-normalized mean firing rate within a bin exceeded the mean firing rate for ≥4 consecutive bins (Burke et al., 2012a). Using the criteria described above, the mean size of object fields was 26.9 cm in the young rats and 26.1 cm in the aged rats, and object field size did not vary significantly across age group and behavioral epoch ($F_{(3,15)} = 0.68$, $p > 0.58$; repeated measures). Moreover, the proportion of neurons with object fields was not significantly different between Epoch 1 and Epoch 2 for any of the behavioral conditions ($F_{(1,42)} = 0.04$, $p = 0.85$; repeated-measures ANOVA). Therefore, the data were collapsed across epoch for the age comparison.

The correlated activity patterns between epochs were quantified by dividing the track into 80 bins of ~4.1 cm, and the firing rate of an individual neuron was calculated for each bin. Laps that the rats ran in the counterclockwise direction were separated from laps where the running direction was clockwise. Therefore, the firing rate was determined for a total of 160 bins resulting in a 160 × 1 firing-rate vector. The Pearson's correlation coefficient between the Epoch 1 and the Epoch 2 firing-rate vectors was then calculated for all PRC neurons across the six different behavioral conditions in the two age groups.

To examine any possible age-related differences, the mean for all cells was calculated for every rat. This reduced the chances that the analysis would be skewed because more neurons were recorded from some rats than others or because recordings were taken from the same cells over multiple days. This conservative approach also safeguarded against a bias toward finding an age difference due to the high statistical power obtained by the large number of cells. Finally, because data were always obtained from yoked pairs of young–aged rats, repeated-measures or paired statistical analyses (Spatz, 2011) were used for significance testing and α was set to the 0.05 level. This analysis approach has been used previously for *in vivo* high-density electrophysiology studies comparing age groups (Insel et al., 2012; Schimanksi et al., 2013).

Results

Recognition behavior and spatial learning

The aged rats had impaired spatial learning compared with the young animals, but were equally able to use visual cues to guide behavior, as measured by the Morris swim task (Fig. 2). Rats have a natural tendency to explore objects, or other stimuli, that are novel (Ennaceur and Delacour, 1988). Therefore, decreased running velocity during track traversals can be used as an indication of novel object detection, as animals will stop to explore new objects, while faster speeds suggest stimulus recognition. To test this idea, the rats' velocities during the first two laps were compared with the last two laps for epochs in which the track contained no objects, novel objects (Epoch 1 for the objects–both epochs conditions), and familiar objects (Epoch 2 of objects–both epochs condition; Fig. 3*A*). When the mean running speed of the rats for the first two laps was compared with the velocity for last laps, statistical analysis revealed that the rats ran significantly slower during the first laps relative to the last laps ($F_{(1,20)} = 14.23$, $p < 0.001$; repeated measures). There was also a significant effect of behavioral condition on the difference in running velocity between the first and last laps ($F_{(3,60)} = 7.59$, $p < 0.01$; repeated-measures ANOVA), which did not significantly interact with age group ($F_{(1,20)} = 1.91$, $p = 0.18$; repeated measures). *Post hoc* analysis indicated that the difference in running speeds between the first laps and the last laps was greatest when there were novel objects on the track compared with the other conditions ($p <$ 0.005 for all comparisons, Tukey HSD). This indicates that both the young and aged animals showed the same pattern of reduced running speed when novel objects were on the track compared with when the track contained familiar objects or was empty. In

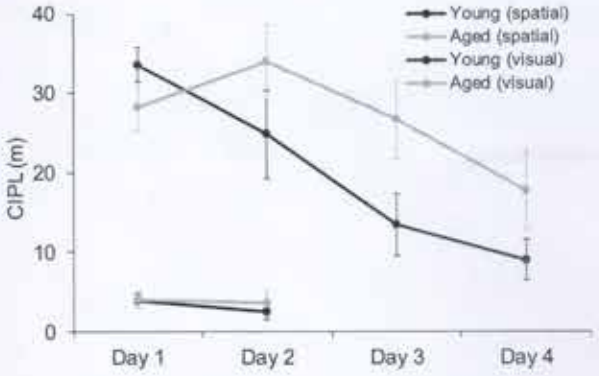

Figure 2. Performance on the Morris swim task. The results from the Morris swim task for the adult (black) and the aged (gray) rats. The *x*-axis is the day of testing and the *y*-axis is the mean CIPL score. Higher CIPL scores indicate longer path lengths to reach the escape platform. All rats completed 4 d of spatial trials (solid lines), in which the platform was hidden below the surface of the water, followed by 2 d of visually cued trials (dashed lines), in which the platform was visible but its location changed after every trial. During the spatial trials, the aged rats had significantly longer CIPL scores compared with the adult rats ($F_{(1,40)} = 6.12, p < 0.02$; ANOVA). *Post hoc* analysis revealed that this difference was due to the aged rats having significantly longer CIPL scores on Days 3 and 4 of spatial testing ($p < 0.05$ for all comparisons; Tukey HSD) while there was no significant difference in the path lengths between young and aged rats on Day 1 or Day 2 of spatial testing ($p > 0.2$ for both comparisons; Tukey HSD). The CIPL scores of all rats were significantly decreased when the platform was visible, and there was no significant effect of age on the CIPL values during either Day 1 or Day 2 of the visual swim task testing ($F_{(1,10)} = 0.07, p = 0.79$; repeated-measures ANOVA). Therefore, it is unlikely that any of the aged animals used in the current series of experiments had significant visual impairment relative to the young group. Error bars represent ±1 SEM.

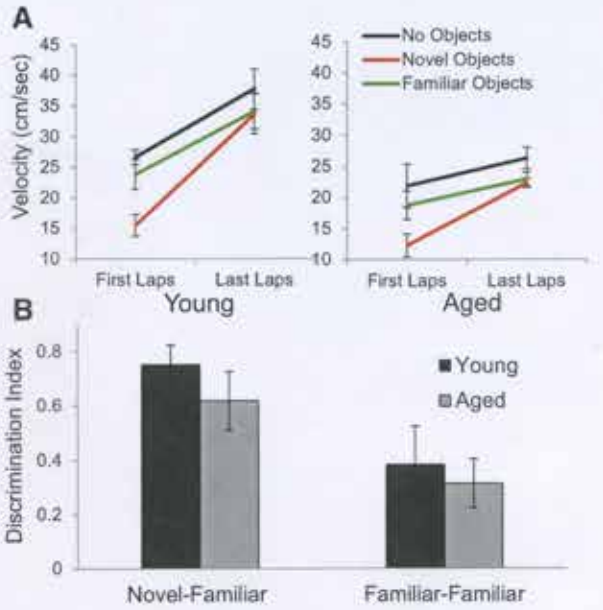

Figure 3. Running velocity of young and aged rats for the different behavioral conditions. ***A***, Comparison of running speed during the first laps (Laps 1 and 2) versus the last laps segregated by epochs without objects (black), with novel objects (red), and with familiar objects (green) for young (left) and aged (right) rats. All rats ran significantly slower during the first laps relative to the last laps ($F_{(1,20)} = 14.23, p < 0.001$; repeated measures). The difference in running speeds between the first laps and the last laps was greatest when there were novel objects on the track compared with the other conditions ($p < 0.005$ for all comparisons, Tukey HSD). ***B***, The discrimination index (difference in first and last lap velocity/mean velocity) for epochs in which the objects were novel and became familiar during later laps (Novel–Familiar) and epochs in which the objects were familiar (Familiar–Familiar) during all laps in young (black) and aged (gray) rats. There was a significant effect of Novel–Familiar versus Familiar–Familiar on the discrimination index ($F_{(1,11)} = 5.23, p < 0.001$; repeated measures). Age group did not have a significant effect on the discrimination index ($F_{(1,11)} = 1.25, p = 0.24$; repeated measures), and there was no significant interaction between age and behavioral condition ($F_{(1,11)} = 0.64, p = 0.5$; repeated measures). Error bars represent ±1 SEM.

other words, the aged rats expressed behavior that was indicative of object recognition similar to the young rats.

To further examine whether there was a difference between novel and familiar objects on running speed, a discrimination index was calculated for epochs in which the objects were novel and became familiar during later laps (novel–familiar) and for epochs in which the objects were familiar during all laps (familiar–familiar). The discrimination index was the difference in running speed between the first two laps and the last two laps divided by the mean running speed. Figure 3*B* shows the discrimination index across behavioral condition for young and aged rats. There was a significant effect of novel–familiar versus familiar–familiar on the discrimination index ($F_{(1,11)} = 5.23, p < 0.001$; repeated measures). This indicates that across all animals the running speeds between the first and last laps decreased more when objects were initially novel and became familiar compared with when familiar objects were on the track for the first laps. Age group, however, did not have a significant effect on the discrimination index ($F_{(1,11)} = 1.25, p = 0.24$; repeated measures). Moreover, there was not a significant interaction between age and behavioral condition ($F_{(1,11)} = 0.64, p = 0.5$; repeated measures). These results confirm the observation that both young and aged rats were able to recognize when objects were familiar and that this corresponded with reduced running speeds during laps in which the track contained novel objects.

Object-related activity of perirhinal cortical neurons across the life span

The activity of 1643 PRC principal neurons was monitored in this experiment. An additional 590 neurons were recorded during the control no objects–objects and objects–no objects conditions (Table 1). The numbers of PRC neurons that were recorded during these experiments were not significantly different between the young and the aged rats ($F_{(1,19)} = 0.03, p = 0.87$). Additionally, all single-unit neurons that were included in the current analyses showed stability during an entire recording session, and there was no significant difference in the mean firing rate of neurons during Rest 1 and Rest 3 ($F_{(1,10)} = 1.01, p = 0.34$; repeated-measures ANOVA). Moreover, the stability of the mean firing rates between the beginning of a recording session and the end of a recording session was not significantly different between young and aged rats ($F_{(1,10)} = 0.02, p = 0.67$; repeated-measures ANOVA). The mean firing rate during sleep episodes was 1.3 Hz for the young rats and 1.1 Hz for the aged rats, and these firing rates were not statistically different from each other ($F_{(1,10)} = 2.26, p = 0.16$). The firing rates of neurons recorded from different cortical lamina also did not systematically differ ($t_{(6)} = 1.23$, $p = 0.23$, paired-samples *t* test), and the data were collapsed between the deep and superficial layers for subsequent analyses (Table 2). Finally, age group did have a significant effect on the mean firing rate during behavior ($F_{(1,40)} = 22.52, p < 0.001$; repeated-measures ANOVA), but not on maximum firing rate ($F_{(1,40)} = 0.31, p = 0.58$; repeated-measures ANOVA). Table 3 shows the *p* values for age comparisons of the mean and maximum firing rates for the different behavioral conditions and age groups.

Table 2. Firing rates in different cortical laminae[a]

Young	No objects	20 min delay	2 h delay	Aged	No objects	20 min delay	2 h delay
8412	0.8 (V)	2.7 (V)	0.9 (V)	8413	1.0 (V)	1.2 (V)	0.9 (V)
8509	0.8 (V)	1.7 (V)	1.6 (V)	8507	1.0 (V)	1.1 (V)	
8583	1.7 (II/III)	1.2 (II/III)	1.5 (II/III)	8615	1.2 (V)	1.0 (V)	0.9 (V)
8661	2.8 and 1.3 (II/III and V)	3.0 and 3.3 (II/III and V)	2.2 and 1.2 (II/III and V)	8662	1.2 (V)	1.3 (V)	1.6 (V)
8670	2.0 and 2.4 (II/III and V)	1.6 and 1.6 (II/III and V)	1.5 and 2.1 (II/III and V)	8696	1.3 (V)	1.8 (V)	0.8 (V)
8883	1.6 (V)	1.1 (V)	0.7 (V)	8865	3.3 and 1.1 (II/III and V)	3.4 and 0.8 (II/III and V)	0.7 and 0.8 (II/III and V)

[a]Mean firing rate (Hz) of cells recorded from pairs of young and aged rats. Layers in parentheses.

Table 3. Firing rate characteristics of PRC neurons recorded in young and aged rats

	20 min delay	2 h delay	No objects	*p* value
Mean firing rate				
Young rats	1.84 ± 0.21 Hz	1.44 ± 0.20 Hz	1.59 ± 0.19 Hz	$p = 0.33$
Aged rats	1.26 ± 0.09 Hz	1.00 ± 0.11 Hz	1.21 ± 0.06 Hz	$p = 0.16$
p value	$p < 0.05$	$p < 0.05$	$p < 0.05$	
Maximum firing rate				
Young rats	5.31 ± 0.31 Hz	5.48 ± 0.60 Hz	4.25 ± 0.33 Hz	$p = 0.07$
Aged rats	4.78 ± 0.10 Hz	4.69 ± 0.18 Hz	4.97 ± 0.24 Hz	$p = 0.24$
p value	$p = 0.44$	$p = 0.83$	$p = 0.16$	

In the hippocampus, the firing rate of CA1 pyramidal neurons is modulated by velocity (McNaughton et al., 1983a; Maurer et al., 2005) in both young and old animals (Shen et al., 1997). Therefore, a possible explanation for the higher mean firing rates of young compared with aged PRC neurons could be different running velocities between age groups (Fig. 3). When firing rate was compared with velocity in the aged rats for velocities between 3 and 51 cm/s, it was observed that, similar to young animals, running speed did not significantly modulate PRC neuron firing rate during any of the behavioral conditions (Fig. 4). These data suggest that the firing-rate difference between young and old rats cannot be accounted for by the aged rats' slower running speeds. Moreover, it confirms previous observations that, in contrast to neurons in the hippocampus (McNaughton et al., 1983a; Maurer et al., 2005) and medial entorhinal cortex (Sargolini et al., 2006), PRC neuron firing rates are not modulated by velocity (Burke et al., 2012a).

An alternative explanation for the decreased firing rates in aged compared with young rats could be found in the differential effect of relative novelty and familiarity on PRC neuron firing rates (Zhu and Brown, 1995; Zhu et al., 1995). Specifically, it has been hypothesized that aged rats (Robitsek et al., 2008) and humans (Daselaar et al., 2006) may have an enhanced familiarity signal in the PRC that could possibly compensate for a decline in hippocampal-dependent recollection. Recent data from young animals, however, have not observed an effect of novel versus familiar stimuli on the firing rates of PRC principal neurons (Burke et al., 2012a; Thome et al., 2012; Woloszyn and Sheinberg, 2012). The possibility remains that aged PRC principal neurons may show decremental activity patterns as stimuli go from being novel to familiar. Thus, the firing rate was measured across laps for Epochs 1 and 2 of the different behavioral conditions, and then was normalized within a cell by calculating the *Z*-score firing rate for each lap. The normalized firing rate change between the first and last laps within an epoch for the counterclockwise and clockwise laps was then quantified. There was no systematic change in the normalized firing rate over laps during any of the behavioral conditions for either the young or the aged rats ($F_{(15,120)} = 0.41$, $p = 0.97$; repeated-measures ANOVA). Moreover, the change in normalized firing rate between Lap 1 and the last lap was not significantly different between young and aged rats ($F_{(1,10)} = 0.20$, $p = 0.66$; repeated-measures ANOVA).

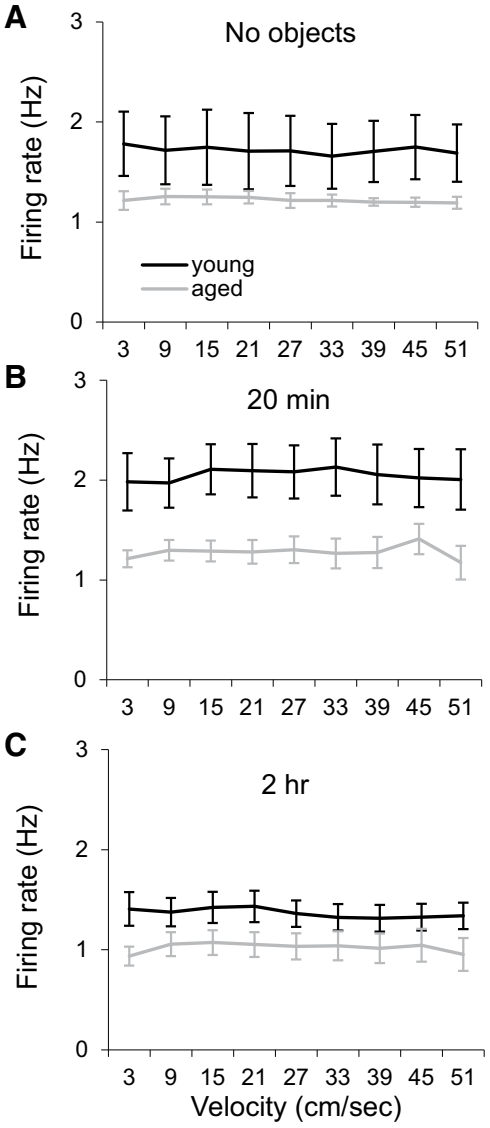

Figure 4. Firing rate by velocity. ***A–C***, Mean firing rate was not significantly modulated by velocity in either the young (black) or the aged (gray) rats for the (***A***) no objects– both epochs, (***B***) objects– both epochs with a 20 min delay, and (***C***) objects– both epochs with a 2 h delay ($r_{(53)} < 0.1, p > 0.5$ for all comparisons; Pearson's correlation coefficient). Error bars represent ±1 SEM.

Although the population of recorded PRC neurons did not show a change in firing rate between conditions with novel objects compared with the other behavioral conditions, it is still possible that a subset of PRC neurons might show a response decrement as objects go from being novel to relatively familiar

and that this decrement was not detected when the data were collapsed across all active neurons. To examine this possibility, PRC neurons that had firing rates at least 2 SDs above mean firing rate during Lap 1 were identified. The proportions of recorded PRC neurons that met this criterion were then compared between the different behavioral conditions and epochs. Approximately 5% of all the recorded PRC neurons fit this description, but this did not vary significantly between behavioral condition ($F_{(15,120)} = 1.51$, $p = 0.21$; repeated-measures ANOVA). Moreover, the proportion of cells that showed a response decrement between Lap 1 and the subsequent laps was not significantly different between the young and the aged rats ($F_{(1,10)} = 3.4$, $p = 0.11$, repeated-measures ANOVA). Figure 5 illustrates the mean proportion of the recorded PRC neurons in young and aged rats during Epochs 1 and 2 that had a firing rate ≥2 SDs above their average firing rate in (*A*) the no objects–both epochs, (*B*) the objects–both epochs with a 20 min delay, and (*C*) the objects–both epochs with a 2 h delay. Together, these data indicate no evidence of a response decrement in the activity of PRC neurons as objects went from novel to familiar in either the young or the aged rats.

Similar to previous reports in young rats (Burke et al., 2012a; Deshmukh et al., 2012), when animals traversed the track with objects on it, PRC neurons showed a selective increase in their firing rates at the locations of objects. This occurred when objects were novel (during Epoch 1 of the objects–both epochs conditions), as well as when objects were familiar (during Epoch 2 of the objects–both epochs conditions) in both age groups. Figure 6 shows representative examples of PRC neuron object field activity recorded from young (*A*) and aged (*B*) rats.

Placing objects on a track increases the information content of PRC spiking (Burke et al., 2012a), which can be used to quantify the proportion of PRC neurons that increase their firing rate at locations containing objects (see Materials and Methods). Similar to young animals, PRC neurons in both age groups had significantly higher information scores in conditions with objects relative to the no object–both epochs condition ($F_{(3,40)} = 3.03$, $p < 0.05$; repeated-measures ANOVA). The mean information content, however, was significantly reduced in the aged compared with young rats ($F_{(1,40)} = 8.23$, $p < 0.01$; repeated-measures ANOVA) for the conditions with objects ($p < 0.5$), but not for the no objects–both epochs condition ($p = 0.54$; Fig. 7). To determine whether the object-related firing properties of PRC cells were present from the very first exposure to objects on the track, the mean information content was calculated and the first behavioral experience with objects in Epoch 1 was compared with the last behavioral experience with objects in Epoch 2. In both the young and the aged rats, there was no difference in the mean information per spike between the first exposure to objects and the last ($t_{(11)} = 0.41$, $p = 0.69$, paired-samples *t* test). Because the information scores for the first and last exposure were virtually identical (0.58 bits/spike vs 0.63 bits/spike), it appears that objects on the track increased information content *de novo*.

The findings that aged PRC principal cell activity patterns show both reduced firing and lower information content during behavior compared with young rats suggests that in advanced age PRC neurons may be less responsive to stimuli. To test this directly, the proportion of neurons with object fields was compared across age groups and behavioral conditions. The young rats had a significantly higher proportion of PRC cells that expressed object fields compared with the aged rats ($F_{(1,40)} = 44.53$, $p < 0.001$; repeated-measured ANOVA), and this was the case for conditions with objects ($p < 0.05$ for all comparisons; Tukey HSD),

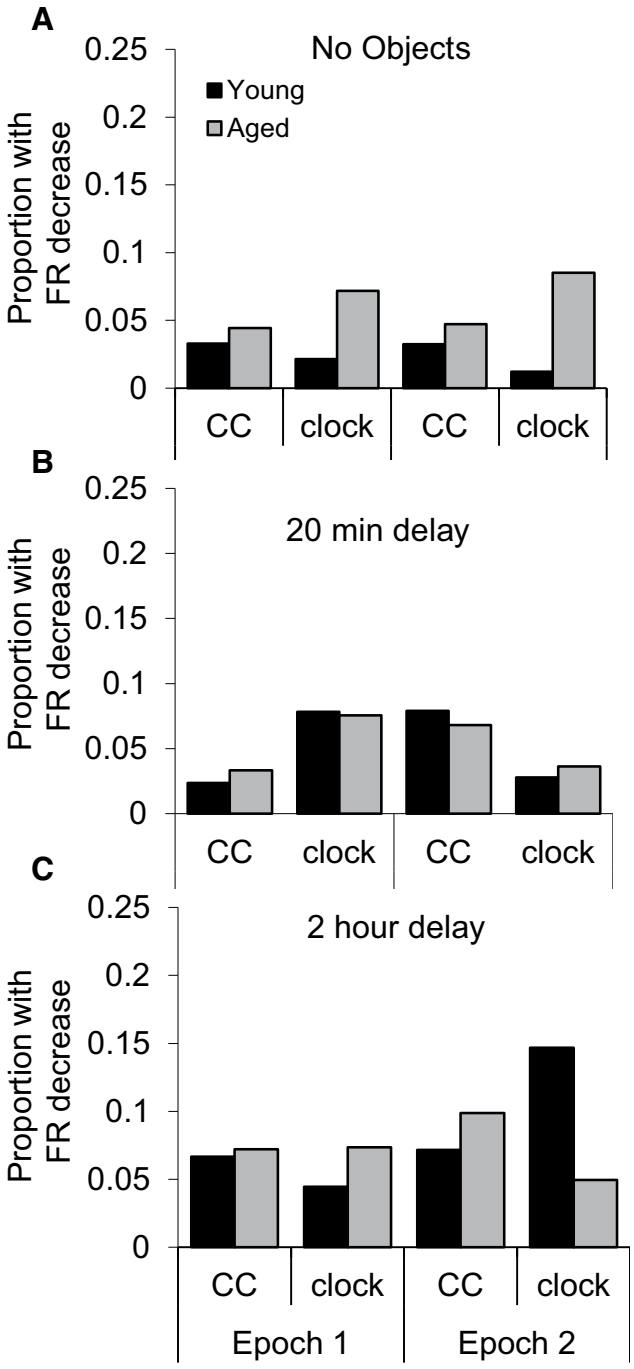

Figure 5. The proportion of recorded PRC neurons that show a response decrement. ***A–C***, In both young (black) and aged (gray) rats, no significant difference was found in the proportion of cells that had a response decrement between the (***A***) no objects– both epochs, (***B***) objects–both epochs with a 20 min delay, and (***C***) objects– both epochs with a 2 h delay ($F_{(15,120)} = 1.51$, $p = 0.21$; repeated-measures ANOVA). Additionally, the young and the aged rats did not differ in the proportion of cells that showed a response decrement between the first lap and subsequent laps ($F_{(1,10)} = 3.4$, $p = 0.11$, repeated-measures ANOVA). Error bars represent ±1 SEM. CC, Counterclockwise running direction; clock, clockwise running direction.

but not for the no objects–both epochs condition ($p = 0.12$). When the age groups were analyzed together, behavioral condition also had a significant effect on the proportion of PRC neurons with object fields ($F_{(3,40)} = 10.14$, $p < 0.001$; repeated-measures ANOVA). *Post hoc* comparisons indicated that during the no objects–both epochs condition, significantly fewer neurons met the

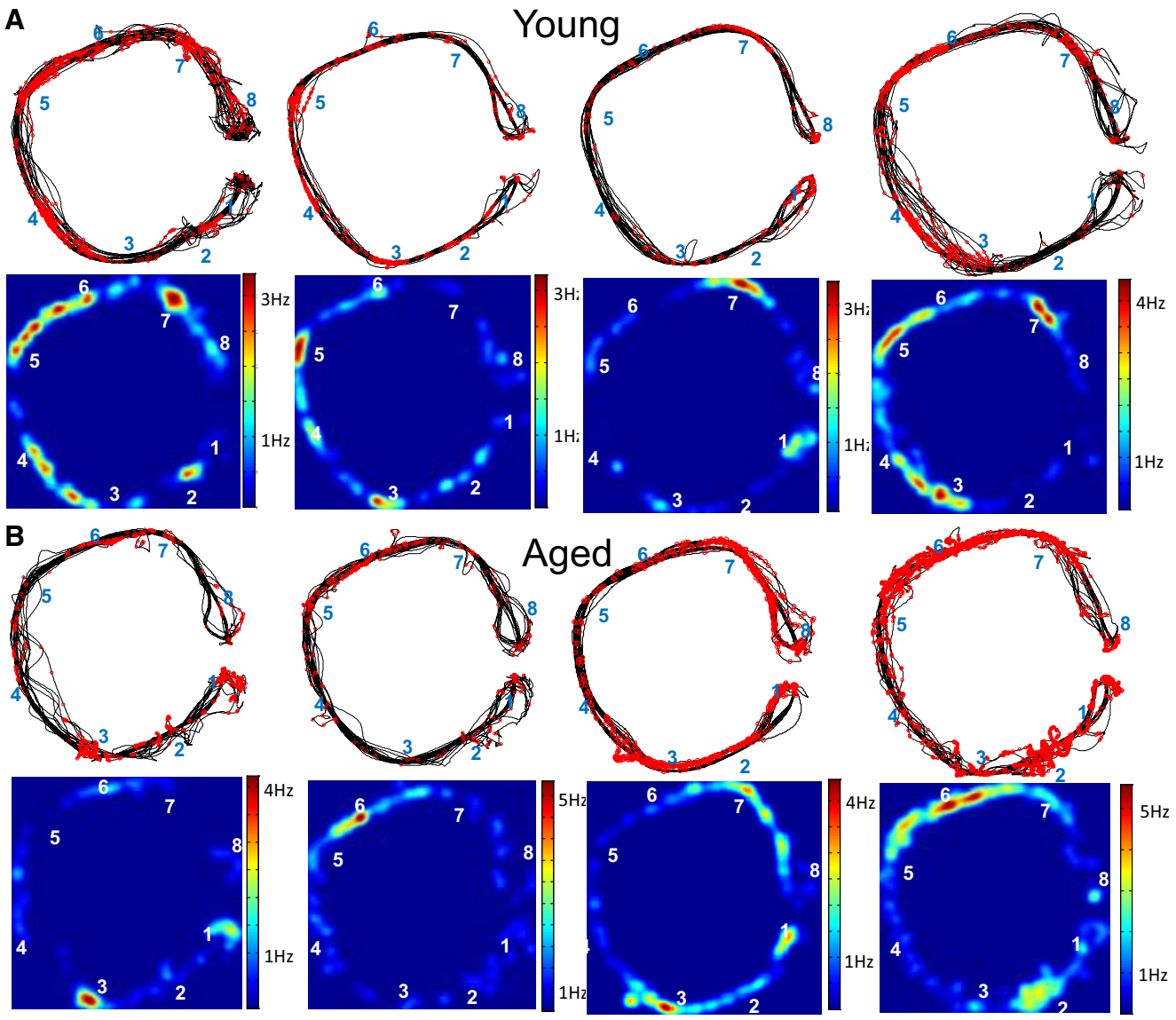

Figure 6. PRC neuron activity patterns in young and aged rats. ***A***, The activity of four representative PRC neurons recorded from young rats under conditions with objects on the track. Top, Black trace, Path of the rats. Red spots indicate the locations of spikes. The blue numbers represent the locations of objects. Bottom, Occupancy-normalized firing-rate maps of the cells shown in ***A***. ***B***, Same as in ***A*** for four representative neurons recorded in aged rats. Note the increase in spiking at several of the locations containing objects.

criteria for having object fields relative to behavioral conditions with objects. Importantly, it did not appear that differences between the distributions of neurons recorded from deep versus superficial layers in the two age groups can account for the reduced proportion of PRC cells with object fields. Specifically, for the three rats that had tetrodes in both Layer V and Layers II/III of the PRC, there was no significant difference in the proportion of cells with object fields between the different layers of cortex ($t_{(5)} = 0.24$, $p = 0.82$; paired-sample *t* test). Figure 8*A* shows the mean proportion of PRC neurons that had object fields for the different behavioral conditions. These data indicate that PRC neurons in both young and aged rats show object-related spiking, but that the young rats have a higher proportion of neurons that show object fields.

The age-associated reduction in the proportion of PRC principal cells that expressed object fields cannot account for the lower firing rates of PRC neurons during the no objects–both epochs condition in old compared with young rats, because in this condition the same proportion of neurons in young and old rats met the criteria for having an object field. An alternative explanation for the lower mean firing rates in aged compared with young rats could be an increase in the proportion of cells that fired during both Rest 1 and Rest 3 but did not fire during behavior in old animals. Consistent with this idea is the observation that the proportions of neurons that did not show any activity during an episode of track running (mean firing rate <0.2 spikes/occupancy) was significantly higher in the aged compared with the young rats ($F_{(1,40)} = 34.80$, $p < 0.001$; repeated-measures ANOVA; Fig. 8*B*). This difference was observed during all behavioral conditions ($p < 0.05$ for all comparisons, Tukey HSD). In both young and old rats, however, there was no significant effect of condition on the proportion of inactive neurons ($F_{(3,40)} = 0.82$, $p = 0.49$; repeated-measures ANOVA; Fig. 8*B*). Because the proportion of object fields significantly increases in the object condition, and there is no difference across conditions in number of inactive cells, it does not appear that the "quiet neurons" were the cells that acquired objects fields.

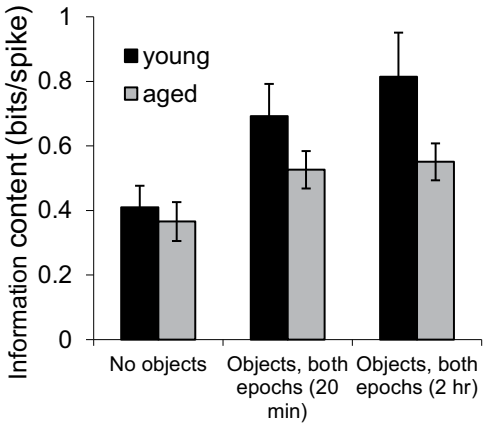

Figure 7. PRC neuron information content. The mean information content (*y*-axis) of the PRC neurons that showed activity during track running for the young (black) and aged (gray) rats in the different behavioral conditions. There was a significant effect of behavioral condition ($F_{(3,40)} = 3.03$, $p < 0.05$; repeated-measures ANOVA) and age ($F_{(1,40)} = 8.23$, $p < 0.01$; repeated-measures ANOVA) on the information content of PRC principal cell firing. Young and old rats did not differ in the no object condition, but young rats had significantly higher information content in the object conditions. Error bars represent ±1 SEM.

Figure 8*C* shows the proportions of neurons that showed nonselective activity (mean firing rate >0.2 spikes/occupancy but no object field) on the track during the four different behavioral conditions. There was a significant effect of condition on the proportion of neurons with nonselective spiking on the track ($F_{(3,40)} = 15.14$, $p < 0.001$; repeated-measures ANOVA). Specifically, in both young and aged rats, significantly more PRC neurons showed nonselective activity on the track during the no objects conditions relative to the conditions with objects ($p < 0.5$ for all comparisons). These data indicate that it is the neurons with nonselective activity on the track that will potentially develop object fields when stimuli are added to the track. Thus, it is possible that a level of baseline activity prepares a portion of the PRC neuron population to respond when a salient feature is encountered in an environment.

Age also significantly affected the proportion of neurons with nonselective spiking on the track ($F_{(1,40)} = 7.30$, $p < 0.01$; repeated-measures ANOVA). Specifically, the young rats had a significantly larger proportion of nonselective neurons, relative to the aged rats, during the no objects condition ($t_{(11)} = 4.10$, $p < 0.01$; paired-samples *t* test), but not during conditions with objects ($p > 0.4$ for all comparisons). Interestingly, there was an ~17% reduction in the proportion of nonselective neurons between the young and aged rats. This is comparable to the ~14% reduction in the proportion of neurons expressing object fields between the young and old animals. Thus, it is possible that the old rats have fewer neurons with object fields because initially, under conditions without objects, they have a smaller pool of neurons that are prepared to show selective spiking when salient features are added to an environment.

To test this idea directly, PRC neurons were recorded during two control conditions: no objects–objects and objects–no objects. This enabled the effects of objects to be measured on the same population of PRC neurons. Figure 9*A–D* shows a representative example of nonspecific activity of PRC neurons when no objects are on the track (left) that then express object fields when objects are on the track (right) in a young (top) and an aged rat (bottom). The patterns of firing in Figure 9*A*, *C* lend further

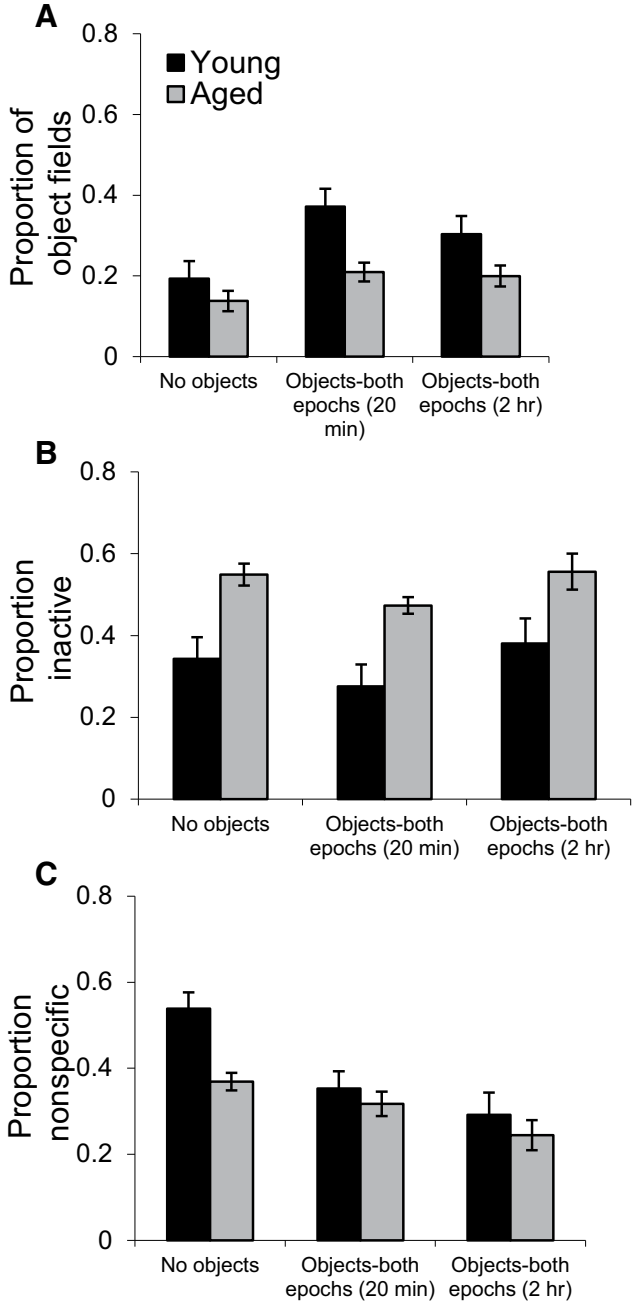

Figure 8. Proportion of PRC neurons with object fields, no firing, or nonselective firing during behavior. ***A***, The proportion of PRC neurons with object fields (*y*-axis) in young (black) and aged (gray) rats across the different behavior conditions (*x*-axis). The young rats had significantly more cells with object fields relative to the aged animals for the objects– both epochs with a 20 min delay ($t_{(11)} = 3.50$, $p < 0.01$; paired-samples *t* test), and the objects– both epochs with a 2 h delay ($t_{(9)} = 3.26$, $p < 0.05$; paired-samples *t* test). ***B***, The proportion of PRC neurons that fired during rest, but did not show activity during behavior in young (black) and aged (gray) rats. Across all behavioral conditions, significantly more PRC neurons were inactive during track running in the aged compared with the young rats ($F_{(1,40)} = 34.80$, $p < 0.001$; repeated-measures ANOVA). ***C***, The proportions of neurons that were active on the maze but did not show selective spiking at an object location were significantly greater for the no objects condition relative to the conditions with objects ($p < 0.05$ for all comparisons). Aged rats showed significantly fewer neurons with nonselective activity on the track relative to the young rats during the no objects conditions ($t_{(11)} = 4.10$, $p < 0.01$; paired-samples *t* test), but not during conditions with objects ($p > 0.1$ for all comparisons). Error bars are ±1 SEM.

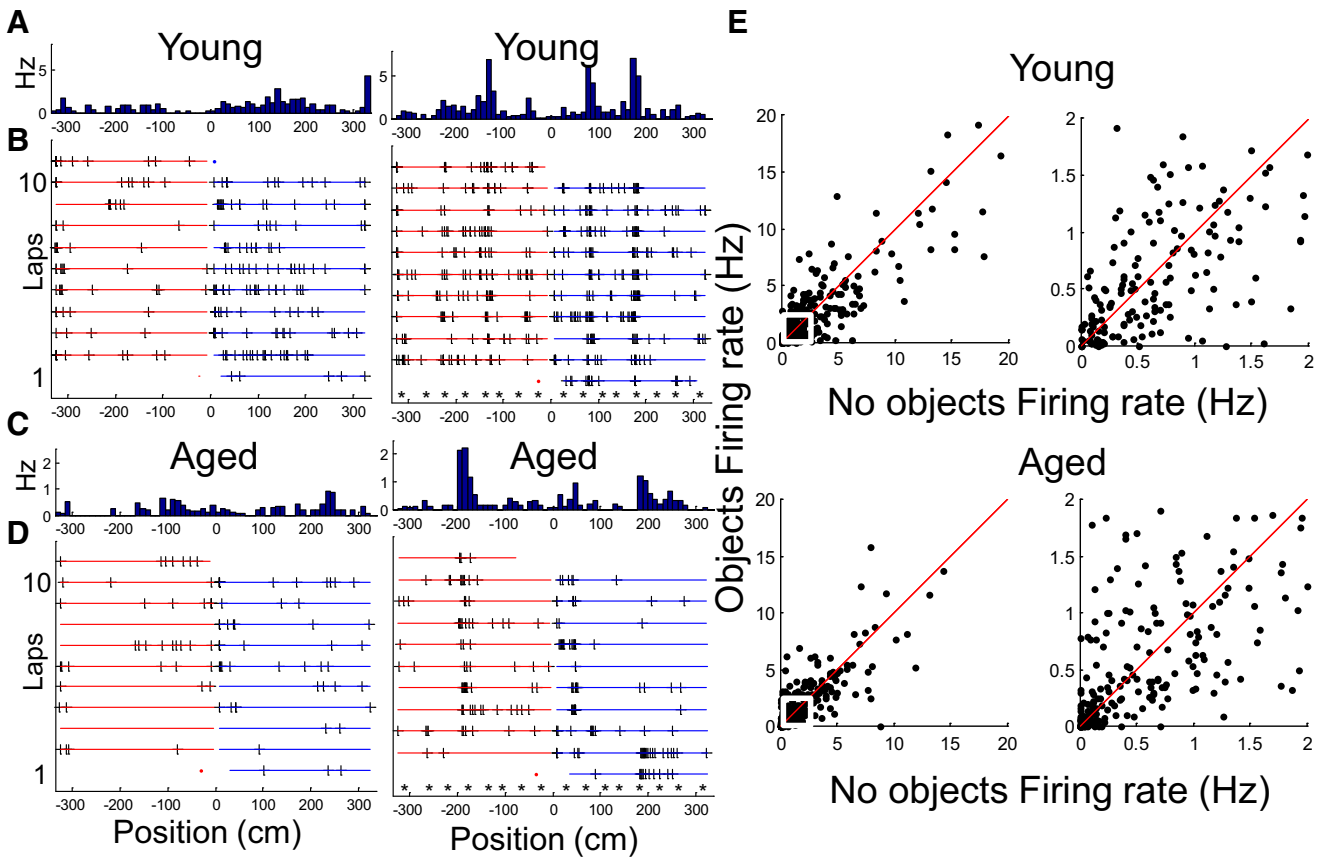

Figure 9. Perirhinal cortical neuron activity in the no object– object condition. ***A–D***, The firing patterns for a representative PRC neuron from a young (***A***, ***B***) and an aged (***C***, ***D***) rat during Epoch 1 without objects (left) and Epoch 2 (right) in which the track contained objects. The activity from the same cells are shown in the left and right panels. The firing-rate histogram by "linearized" position is shown in ***A*** for young rats and ***C*** for aged rats. The *x*-axis is positioned on the track with zero indicating the position of the barrier. Distance from the barrier is measures in centimeters. Positive numbers are for laps when the rat was running in the clockwise direction while negative numbers indicate the position when the rat was running in the counterclockwise direction. The *y*-axis is the occupancy-normalized firing rate of the neuron. Spike raster plots across laps are shown in ***B*** for young rats and in ***D*** for aged rats. Each horizontal line indicates a lap and blue lines are the laps in which the rat ran in the counterclockwise direction while red lines represent laps run in the clockwise direction. The asterisks indicate the position of the objects. In both the young and aged rat, there was nonspecific activity during the first epoch and significant object field firing during the second epoch. ***E***, The firing rates of individual neurons during the no objects epoch plotted against the firing rates during the epoch with objects for young (top) and aged (bottom) rats. The left panels show all cells and the right panels show only those cells from the left panels that have firing rates of <2 Hz (white square in left panels). Note, the higher density of low firing-rate cells in the aged rats. There was a significant correlation between firing rate across epochs with and without objects ($R^2 = 0.79$, $F_{(3,23)} = 24.32$, $p < 0.001$). Age of the animal ($t_{(23)} = 0.25$, $p = 0.81$) and whether the track contained objects during the first or second epoch ($t_{(23)} = 0.54$, $p = 0.53$) did not significantly affect this relationship.

support to the hypothesis that it is the cells with nonspecific activity that are primed to express object fields. In line with this idea, within the same population of cells, placing objects on the track did not significantly affect firing rate ($F_{(1,20)} = 0.41$, $p = 0.53$; repeated measures) or the proportion of cells that did not fire during behavior ($F_{(1,20)} = 2.56$, $p = 0.12$; repeated measures). Figure 9*E* shows the firing rates of neurons during the no objects epochs plotted against the firing rates during the epochs with objects for young (top) and aged (bottom) rats. It is evident from Figure 9*E* that there was no cluster of cells above unity. Therefore, the "quiet" neurons during the no objects epoch also do not fire when objects are on the track. Moreover, there was a significant correlation between firing rates across the no object and object epochs ($R^2 = 0.79$, $F_{(3,23)} = 24.32$, $p < 0.001$). Age of the animal did not significantly affect this relationship ($t_{(23)} = 0.25$, $p = 0.81$). These data lend further support to the idea that objects adjust the spike timing of PRC neurons rather than increasing overall excitability levels.

In both young and aged rats, within the same population of cells, the PRC neurons recorded during the epochs with objects had significantly higher information content ($F_{(1,20)} = 17.78$, $p < 0.001$; repeated measures) and a significantly higher proportion of cells that met the criteria for having an object field ($F_{(1,20)} = 21.62$, $p < 0.001$; repeated measures) compared with the epochs when the track was empty. When the aged groups were examined separately, consistent with the data collected during the no objects–both epochs and objects–both epochs conditions, the aged rats had a significantly lower proportion of PRC cells that expressed object fields when objects were on the track relative to the young animals ($F_{(1,20)} = 4.52$, $p < 0.05$; repeated measures). Moreover, similar to the other behavioral conditions, the mean firing rate of PRC neurons was significantly lower in the aged compared with the young rats ($F_{(1,22)} = 5.57$, $p < 0.05$; repeated measures). Therefore, in old rats, when three-dimensional stimuli are added to the track, there are fewer neurons primed to respond to objects, which results in a lower proportion of cells with object fields. This is consistent with the hypothesis that PRC-dependent stimulus representation is impaired in advanced age.

Perirhinal cortical activity across delays

To evaluate whether PRC neuron activity patterns were similar between epochs, the correlation of PRC neuron firing-rate vec-

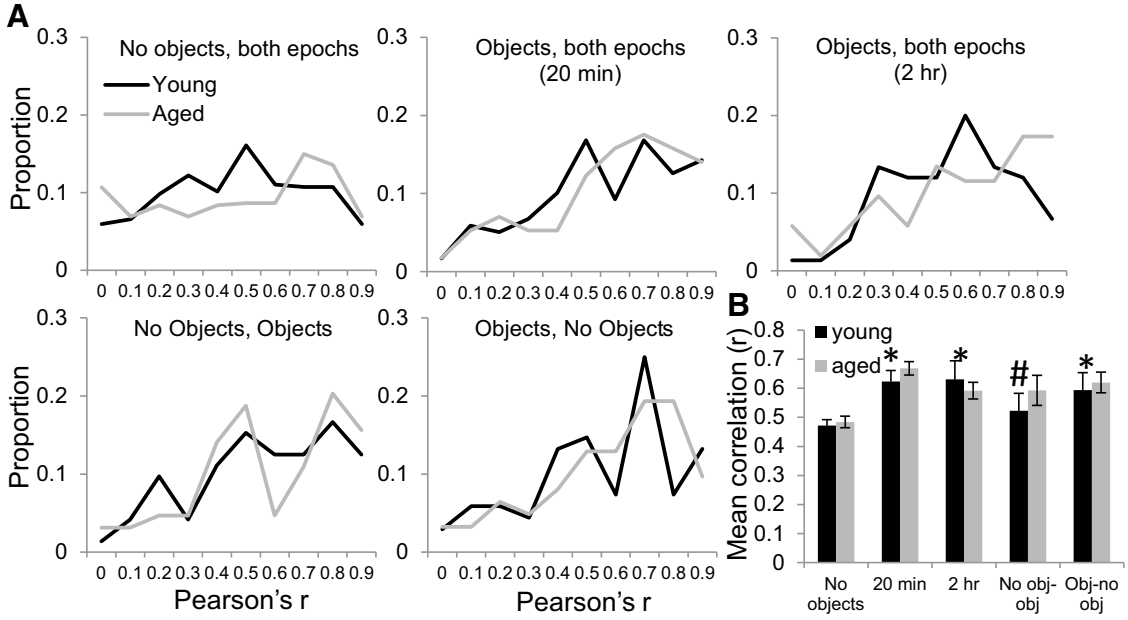

Figure 10. Activity pattern correlations across epochs. ***A***, The normalized frequency histograms of the Pearson's correlation coefficients of the activity during Epoch 1 and Epoch 2 for the different behavioral conditions. ***B***, The mean correlation values averaged across rats. Behavioral condition had a significant effect on the correlated activity ($F_{(5,45)} = 49.32$, $p < 0.001$; repeated measures). Planned orthogonal contrasts revealed that the mean correlation values of PRC neuron activity across epochs was significantly less for the no objects– both epochs condition relative to the conditions with objects during both epochs, and the objects–no objects control condition (indicated by $^{*}p < 0.01$ for all comparisons; simple contrast). The no objects– objects conditions was significantly less correlated than the 20 min delay condition (indicated by $^{\#}p < 0.05$; simple contrast). Age group did not have a significant effect on correlated activity patterns ($F_{(1,9)} = 1.02$, $p = 0.34$; repeated measures).

tors between Epoch 1 and Epoch 2 was calculated for the different behavioral conditions. Figure 10*A* shows the normalized frequency histograms of the Pearson's correlation coefficients between Epoch 1 and Epoch 2 activity patterns for the different behavioral conditions in young (black) and aged (gray) rats, and Figure 10*B* shows the mean correlation values averaged across rats. Behavioral condition had a significant effect on the correlation values ($F_{(5,45)} = 49.32$, $p < 0.001$; repeated measures) such that the PRC neuron activity correlations between epochs were significantly lower for the no objects–both epochs condition relative to the conditions with objects during both epochs (20 min and 2 h delays; $p < 0.01$ for both comparisons; simple contrast). Together these data indicate that, contrary to object-related firing, the nonspecific activity is not spatially consistent across delays. Additionally, the between-epoch correlations for the no objects–both epochs condition was not significantly different from the no objects–objects control condition ($p = 0.1$; simple contrast), but was significantly lower than the objects–no objects condition ($p < 0.01$; simple contrast). This suggests that some PRC neurons may show persistent object-related activity even after the stimulus has been removed, which has been reported for a small subset of lateral entorhinal cortical neurons (Deshmukh and Knierim, 2011; Tsao et al., 2013).

Importantly, age group did not have a significant effect on the extent of correlated activity patterns ($F_{(1,9)} = 1.02$, $p = 0.34$; repeated measures). Moreover, age group did not significantly interact with behavioral condition ($F_{(5,45)} = 0.47$, $p = 0.79$; repeated measures), which indicates that the correlated activity patterns of PRC neurons across behavioral epochs did not vary between young and old rats as a function of experience with the objects. These data are consistent with the observation that old animals are able to identify previously experienced objects as familiar within the same environment for delays up to 24 h (Burke et al., 2010). Age also did not significantly affect rate remapping (data not shown). Together these data indicate that aged rats have fewer cells that are active in the presence of objects. Once the representations of complex stimuli are established within the PRC, however, the aged rats are just as able to maintain stable activity patterns in response to familiar stimuli for delays up to 2 h.

Discussion

Object fields in young and aged rats

The current experiments provide evidence that old animals have selective impairments in stimulus representation rather than deficits in stimulus maintenance. Compared with the young rats, the aged rats had a lower proportion of neurons with object fields and a higher proportion of neurons that were inactive during track running. Interestingly, in both age groups, the proportion of inactive neurons were similar between conditions with and without objects. Thus, it appears that the neurons with nonselective activity were the subset of PRC cells that developed object fields. This is supported by the observed reduction in the proportion of neurons with nonselective activity in the object conditions and the lack of a significant firing rate change between object and no object conditions.

Together these data support two novel hypotheses regarding PRC function. First, it appears that when the track was relatively empty, a subset of PRC neurons express baseline activity with no obvious pattern. This activity could reflect circuit dynamics that predispose specific neurons to sharpen their tuning to track location when a salient feature is encountered. Second, with respect to aged rats, the decreased numbers of neurons showing nonselective activity on the empty track could arise from a loss of fidelity in the afferent input to the aged PRC. The PRC receives direct projections from the entire sensory cortex (Burwell and Amaral, 1998). With advanced age, there are disruptions in cortical inhibition in the auditory (de Villers-Sidani et al., 2010), so-

matosensory (David-Jürgens and Dinse, 2010), and visual cortices (Wang et al., 2006). This has been associated with declines in signal-to-noise ratios that could feed forward to the PRC, resulting in reduced convergence of input needed to elicit spiking. Alternatively, lower firing rates in aged PRC neurons during behavior could serve as a compensatory mechanism for disrupted inhibition at earlier stages of cortical processing. Both of these hypotheses are consistent with the observation that glutamate levels are reduced in the aged PRC (Liu et al., 2009) and with the report of reduced BOLD signal in the PRC of elderly subjects (Ryan et al., 2012).

A question remains regarding the function of PRC neurons that do not show activity under the behavior conditions of the current experiment. One possibility is that these "quiet neurons" will only become active when the animal encounters a stimulus that is emotionally salient or relevant for its survival. In line with this hypothesis is the observation that more PRC neurons respond selectively to an auditory cue after it has been paired with a foot shock (Furtak et al., 2007). Under this framework, the quiet neurons are those that require extra activation, presumably through direct basolateral amygdala (Paz et al., 2006) or prefrontal cortical input (Paz et al., 2007), to be recruited into the ensemble of active PRC neurons.

The lack of novelty and/or familiarity modulation of perirhinal cortical neuron activity in young and aged rats

A prevailing theory regarding the neurobiology of recognition memory is that the mnemonic mechanism for this behavior is a reduction in the firing rate of PRC neurons as a stimulus goes from novel to familiar (for review, see Brown and Aggleton, 2001). The results reported in the current paper along with additional recent data, however, have been unable to provide support for this idea. Specifically, monkeys performing a passive viewing task with pictures of varying levels of novelty or familiarity do not show robust firing-rate differences in principal cell activity as a function of familiarity (Thome et al., 2012; Woloszyn and Sheinberg, 2012). Moreover, another recent investigation observed no change in the proportion of PRC neurons positive for the mRNA products of the activity-associated immediate-early gene (IEG) *Arc* as objects went from novel to familiar (Burke et al., 2012b).

Several possible explanations can account for the discrepancy between different experiments regarding the effect of stimulus familiarity on PRC activity. In terms of the effect of novelty versus familiarity on IEG expression in the PRC, it is known that IEG expression can be decoupled from neuronal activity after a massed exposure to an environment (Guzowski et al., 2006). The paired viewing procedure used in c-fos imaging studies involved presenting rats with the same visual stimuli many times in a day over the course of several days (Wan et al., 1999). Therefore, it remains a possibility that the PRC shows reduced c-fos protein levels because of a post-translational decoupling from spiking activity rather than reduced neuron activity.

One explanation of the apparently contradictory reports of reduced PRC firing rates in other electrophysiological recording experiments (Miller et al., 1991; Fahy et al., 1993; Hölscher et al., 2003) could involve the fact that in these studies acute recording techniques were used. It is possible that during acute recordings there is a sampling bias for cells with higher firing rates, and these cells may be more likely to decrease their rate over time. Investigations that have not observed novelty modulation of PRC neuron firing rates have used chronically implanted recording probes (Burke et al., 2012a; Thome et al., 2012). Another, but not mutually exclusive, explanation is that most of the initial reports of reduced PRC cell firing to familiar stimuli did not isolate interneurons from principal cells. Recent data suggest that it may be the interneurons of the inferior temporal cortex, rather than excitatory cells, that show reduced activity to familiar versus novel stimuli (Woloszyn and Sheinberg, 2012).

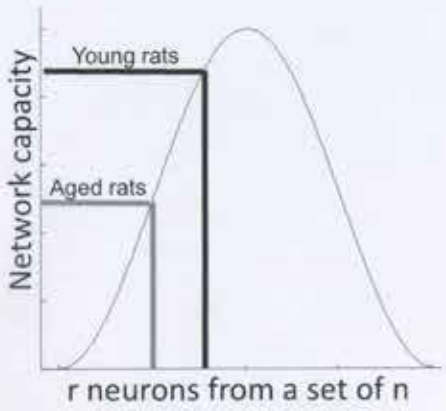

Figure 11. Population coding in the PRC. The capacity of a hypothetical network to represent distinct stimuli based on the degree to which the population code is distributed. The *x*-axis is the number of neurons (*r*) in a set of *n* neurons. Network capacity is maximal when half of the neurons are activated by a given stimulus set. In the PRC cortex, fewer neurons are activated by a stimulus set in aged (gray) compared with young (black) rats. This could have the result of decreasing the capacity of the aged PRC to represent different stimuli distinctively.

Lesion data are unequivocal concerning the fact the PRC is critical for stimulus recognition (Ennaceur and Aggleton, 1997; Málková et al., 2001; Winters and Bussey, 2005). In light of the current results, the notion that a simple rate code supports recognition may not be parsimonious. In fact, a rate code is vulnerable to noise and spike failures. Given that the probability of synaptic transmission between the PRC and its cortical efferents is low (Pelletier et al., 2004), the signal-to-noise ratio for relaying a "response decrement" might not be sufficient. Thus, it is more plausible that the PRC uses a population code, which relies on the joint activities of a number of neurons, each of which has a different distribution of responses over some set of inputs (Georgopoulos et al., 1986).

Linking physiology to age-associated recognition memory impairments

Recent data have revealed that age-associated recognition memory impairments arise from aged animals "falsely" recognizing novel stimuli (Burke et al., 2010). It has been hypothesized that this results from old animals showing an increased vulnerability to distracting stimuli encountered during long delays (Burke et al., 2010). Importantly, animals with PRC lesions show the same pattern of results, and the tendency to falsely remember a novel stimulus can be reversed by depriving lesioned animals of sensory input during the delay period (McTighe et al., 2010). These data imply that recognition memory deficits in animals with a compromised PRC are not due to the "forgetting" of previously experienced stimuli, but rather manifests from a reduced ability to discriminate novel stimuli from those that have been experienced (Burke et al., 2010; McTighe et al., 2010). This type of discrimination deficit could arise from impairments in high-level stimulus perception that arise following damage to the PRC (Murray and Bussey, 1999; Murray et al., 2007), because of a reduced ability to pattern separate between stimuli that share features. In

line with this idea is the observation that aged rats, monkeys (Burke et al., 2011), and humans (Ryan et al., 2012) have difficulty discriminating between complex stimuli that share features even when the mnemonic demands of the task are low.

In line with the behavioral observations discussed above, the physiological data reported here suggest that aged animals do not forget previously experienced stimuli. That is, the older rats' PRC neurons show the same levels of correlated activity across delays up to 2 h. Aged rats, however, appear to have a reduced pool of active PRC neurons available and prepared to represent new stimulus sets. Figure 11 shows how the capacity of a theoretical network is affected by increasing or decreasing the number of neurons that are active when a stimulus set is presented. The theoretical functional consequence of fewer neurons being activated by objects is reduced capacity to represent different objects with a unique neural code. This could explain why aged rats tend to regard novel objects as familiar (Burke et al., 2010).

An assumption regarding the cognitive consequences of normal aging is that the aspect of recognition memory supported by PRC-dependent familiarity judgments is preserved across the lifespan, while recollection is particularly vulnerable (Spencer and Raz, 1995; Daselaar et al., 2006). This hypothesis, however, may not be consistent with the observation that aged subjects show a significant increase in false recognition (Norman and Schacter, 1997; Jacoby et al., 2005; Toner et al., 2009). Moreover, other investigations have reported that aging is associated with deficits in familiarity as well as recollective processes (Davidson and Glisky, 2002; Prull et al., 2006; Toth and Parks, 2006; Duarte et al., 2010). These data, along with the current findings, call into question the notion that recollection is particularly vulnerable to advanced age in the absence of changes in familiarity. In fact it is probable that degradation of PRC-dependent stimulus representation contributes to impairments in recollection and episodic memory, both of which require the association of sensory stimuli with a spatial and temporal context.

References

Barnes CA, Rao G, McNaughton BL (1996) Functional integrity of NMDA-dependent LTP induction mechanisms across the lifespan of F-344 rats. Learn Mem 3:124–137. CrossRef Medline

Barthó P, Hirase H, Monconduit L, Zugaro M, Harris KD, Buzsáki G (2004) Characterization of neocortical principal cells and interneurons by network interactions and extracellular features. J Neurophysiol 92:600–608. CrossRef Medline

Brown MW, Aggleton JP (2001) Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat Rev Neurosci 2:51–61. CrossRef Medline

Bucci DJ, Phillips RG, Burwell RD (2000) Contributions of postrhinal and perirhinal cortex to contextual information processing. Behav Neurosci 114:882–894. CrossRef Medline

Burke SN, Wallace JL, Nematollahi S, Uprety AR, Barnes CA (2010) Pattern separation deficits may contribute to age-associated recognition impairments. Behav Neurosci 124:559–573. CrossRef Medline

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 125:836–847. CrossRef Medline

Burke SN, Maurer AP, Hartzell AL, Nematollahi S, Uprety A, Wallace JL, Barnes CA (2012a) Representation of three-dimensional objects by the rat perirhinal cortex. Hippocampus 22:2032–2044. CrossRef Medline

Burke SN, Hartzell AL, Lister JP, Hoang LT, Barnes CA (2012b) Layer V perirhinal cortical ensemble activity during object exploration: a comparison between young and aged rats. Hippocampus 22:2080–2093. CrossRef Medline

Burwell RD, Amaral DG (1998) Cortical afferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. J Comp Neurol 398:179–205. CrossRef Medline

Chowdhury S, Shepherd JD, Okuno H, Lyford G, Petralia RS, Plath N, Kuhl D, Huganir RL, Worley PF (2006) Arc/Arg3.1 interacts with the endocytic machinery to regulate AMPA receptor trafficking. Neuron 52:445–459. CrossRef Medline

Daselaar SM, Fleck MS, Dobbins IG, Madden DJ, Cabeza R (2006) Effects of healthy aging on hippocampal and rhinal memory functions: an event-related fMRI study. Cereb Cortex 16:1771–1782. Medline

David-Jürgens M, Dinse HR (2010) Effects of aging on paired-pulse behavior of rat somatosensory cortical neurons. Cereb Cortex 20:1208–1216. CrossRef Medline

Davidson PS, Glisky EL (2002) Neuropsychological correlates of recollection and familiarity in normal aging. Cogn Affect Behav Neurosci 2:174–186. CrossRef Medline

Deshmukh SS, Knierim JJ (2011) Representation of non-spatial and spatial information in the lateral entorhinal cortex. Front Behav Neurosci 5:69. CrossRef Medline

Deshmukh SS, Johnson JL, Knierim JJ (2012) Perirhinal cortex represents nonspatial, but not spatial, information in rats foraging in the presence of objects: comparison with lateral entorhinal cortex. Hippocampus 22: 2045–2058. CrossRef Medline

de Villers-Sidani E, Alzghoul L, Zhou X, Simpson KL, Lin RC, Merzenich MM (2010) Recovery of functional and structural age-related changes in the rat primary auditory cortex with operant training. Proc Natl Acad Sci U S A 107:13900–13905. CrossRef Medline

Duarte A, Graham KS, Henson RN (2010) Age-related changes in neural activity associated with familiarity, recollection and false recognition. Neurobiol Aging 31:1814–1830. CrossRef Medline

Ennaceur A, Aggleton JP (1997) The effects of neurotoxic lesions of the perirhinal cortex combined to fornix transection on object recognition memory in the rat. Behav Brain Res 88:181–193. CrossRef Medline

Ennaceur A, Delacour J (1988) A new one-trial test for neurobiological studies of memory in rats. 1: behavioral data. Behav Brain Res 31:47–59. CrossRef Medline

Fahy FL, Riches IP, Brown MW (1993) Neuronal activity related to visual recognition memory: long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. Exp Brain Res 96:457–472. Medline

Fletcher BR, Calhoun ME, Rapp PR, Shapiro ML (2006) Fornix lesions decouple the induction of hippocampal arc transcription from behavior but not plasticity. J Neurosci 26:1507–1515. CrossRef Medline

Furtak SC, Allen TA, Brown TH (2007) Single-unit firing in rat perirhinal cortex caused by fear conditioning to arbitrary and ecological stimuli. J Neurosci 27:12277–12291. CrossRef Medline

Gage GJ, Kipke DR, Shain W (2012) Whole animal perfusion fixation for rodents. J Vis Exp 65:3564. CrossRef Medline

Gallagher M, Burwell R, Burchinal M (1993) Severity of spatial learning impairment in aging: development of a learning index for performance in the Morris water maze. Behav Neurosci 107:618–626. CrossRef Medline

Georgopoulos AP, Schwartz AB, Kettner RE (1986) Neuronal population coding of movement direction. Science 233:1416–1419. CrossRef Medline

Gothard KM, Skaggs WE, Moore KM, McNaughton BL (1996) Binding of hippocampal CA1 neural activity to multiple reference frames in a landmark-based navigation task. J Neurosci 16:823–835. Medline

Guzowski JF, Lyford GL, Stevenson GD, Houston FP, McGaugh JL, Worley PF, Barnes CA (2000) Inhibition of activity-dependent arc protein expression in the rat hippocampus impairs the maintenance of long-term potentiation and the consolidation of long-term memory. J Neurosci 20:3993–4001. Medline

Guzowski JF, Miyashita T, Chawla MK, Sanderson J, Maes LI, Houston FP, Lipa P, McNaughton BL, Worley PF, Barnes CA (2006) Recent behavioral history modifies coupling between cell activity and Arc gene transcription in hippocampal CA1 neurons. Proc Natl Acad Sci U S A 103: 1077–1082. CrossRef Medline

Harris KD, Hirase H, Leinekugel X, Henze DA, Buzsáki G (2001) Temporal interaction between single spikes and complex spike bursts in hippocampal pyramidal cells. Neuron 32:141–149. CrossRef Medline

Higuchi S, Miyashita Y (1996) Formation of mnemonic neuronal responses to visual paired associates in inferotemporal cortex is impaired by perirhinal and entorhinal lesions. Proc Natl Acad Sci U S A 93:739–743. CrossRef Medline

Hölscher C, Rolls ET, Xiang J (2003) Perirhinal cortex neuronal activity

related to long-term familiarity memory in the macaque. Eur J Neurosci 18:2037–2046. CrossRef Medline

Insel N, Patron LA, Hoang LT, Nematollahi S, Schimanski LA, Lipa P, Barnes CA (2012) Reduced gamma frequency in the medial frontal cortex of aged rats during behavior and rest: implications for age-related behavioral slowing. J Neurosci 32:16331–16344. CrossRef Medline

Jacoby LL, Bishara AJ, Hessels S, Toth JP (2005) Aging, subjective experience, and cognitive control: dramatic false remembering by older adults. J Exp Psychol Gen 134:131–148. CrossRef Medline

Kholodar-Smith DB, Allen TA, Brown TH (2008) Fear conditioning to discontinuous auditory cues requires perirhinal cortical function. Behav Neurosci 122:1178–1185. CrossRef Medline

Liu P, Smith PF, Darlington CL (2008) Glutamate receptor subunits expression in memory-associated brain structures: regional variations and effects of aging. Synapse 62:834–841. CrossRef Medline

Liu P, Jing Y, Zhang H (2009) Age-related changes in arginine and its metabolites in memory-associated brain structures. Neuroscience 164:611–628. CrossRef Medline

Málková L, Bachevalier J, Mishkin M, Saunders RC (2001) Neurotoxic lesions of perirhinal cortex impair visual recognition memory in rhesus monkeys. Neuroreport 12:1913–1917. CrossRef Medline

Maurer AP, Vanrhoads SR, Sutherland GR, Lipa P, McNaughton BL (2005) Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus. Hippocampus 15:841–852. CrossRef Medline

McNaughton BL, Barnes CA, O'Keefe J (1983a) The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. Exp Brain Res 52:41–49. Medline

McNaughton BL, O'Keefe J, Barnes CA (1983b) The stereotrode: a new technique for simultaneous isolation of several single units in the central nervous system from multiple unit records. J Neurosci Methods 8:391–397. CrossRef Medline

McTighe SM, Cowell RA, Winters BD, Bussey TJ, Saksida LM (2010) Paradoxical false memory for objects after brain damage. Science 330:1408–1410. CrossRef Medline

Miller EK, Li L, Desimone R (1991) A neural mechanism for working and recognition memory in inferior temporal cortex. Science 254:1377–1379. CrossRef Medline

Morris R (1984) Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods 11:47–60. CrossRef Medline

Moyer JR Jr, Furtak SC, McGann JP, Brown TH (2011) Aging-related changes in calcium-binding proteins in rat perirhinal cortex. Neurobiol Aging 32:1693–1706. CrossRef Medline

Murray EA, Bussey TJ (1999) Perceptual-mnemonic functions of the perirhinal cortex. Trends Cogn Sci 3:142–151. CrossRef Medline

Murray EA, Wise SP (2012) Why is there a special issue on perirhinal cortex in a journal called Hippocampus? The perirhinal cortex in historical perspective. Hippocampus 22:1941–1951. CrossRef Medline

Murray EA, Bussey TJ, Saksida LM (2007) Visual perception and memory: a new view of medial temporal lobe function in primates and rodents. Annu Rev Neurosci 30:99–122. CrossRef Medline

Norman KA, Schacter DL (1997) False recognition in younger and older adults: exploring the characteristics of illusory memories. Mem Cognit 25:838–848. CrossRef Medline

Oler JA, Markus EJ (1998) Age-related deficits on the radial maze and in fear conditioning: hippocampal processing and consolidation. Hippocampus 8:402–415. CrossRef Medline

O'Neill J, Senior T, Csicsvari J (2006) Place-selective firing of CA1 pyramidal cells during sharp wave/ripple network patterns in exploratory behavior. Neuron 49:143–155. CrossRef Medline

Paz R, Pelletier JG, Bauer EP, Paré D (2006) Emotional enhancement of memory via amygdala-driven facilitation of rhinal interactions. Nat Neurosci 9:1321–1329. CrossRef Medline

Paz R, Bauer EP, Paré D (2007) Learning-related facilitation of rhinal interactions by medial prefrontal inputs. J Neurosci 27:6542–6551. CrossRef Medline

Pelletier JG, Apergis J, Paré D (2004) Low-probability transmission of neocortical and entorhinal impulses through the perirhinal cortex. J Neurophysiol 91:2079–2089. CrossRef Medline

Prull MW, Dawes LL, Martin AM 3rd, Rosenberg HF, Light LL (2006) Recollection and familiarity in recognition memory: adult age differences and neuropsychological test correlates. Psychol Aging 21:107–118. CrossRef Medline

Rapp PR, Deroche PS, Mao Y, Burwell RD (2002) Neuron number in the parahippocampal region is preserved in aged rats with spatial learning deficits. Cereb Cortex 12:1171–1179. CrossRef Medline

Recce ML, O'Keefe J (1989) The tetrode: an improved technique for multi-unit extracellular recording. Soc Neurosci Abstr 15:1250.

Robitsek RJ, Fortin NJ, Koh MT, Gallagher M, Eichenbaum H (2008) Cognitive aging: a common decline of episodic recollection and spatial memory in rats. J Neurosci 28:8945–8954. CrossRef Medline

Ryan L, Cardoza JA, Barense MD, Kawa KH, Wallentin-Flores J, Arnold WT, Alexander GE (2012) Age-related impairment in a complex object discrimination task that engages perirhinal cortex. Hippocampus 22:1978–1989. CrossRef Medline

Sargolini F, Fyhn M, Hafting T, McNaughton BL, Witter MP, Moser MB, Moser EI (2006) Conjunctive representation of position, direction, and velocity in entorhinal cortex. Science 312:758–762. CrossRef Medline

Schimanski LA, Lipa P, Barnes CA (2013) Tracking the course of hippocampal representations during learning: when is the map required? J Neurosci 33:3094–3106. CrossRef Medline

Schmitzer-Torbert N, Jackson J, Henze D, Harris K, Redish AD (2005) Quantitative measures of cluster quality for use in extracellular recordings. Neuroscience 131:1–11. CrossRef Medline

Shen J, Barnes CA, McNaughton BL, Skaggs WE, Weaver KL (1997) The effect of aging on experience-dependent plasticity of hippocampal place cells. J Neurosci 17:6769–6782. Medline

Skaggs WE, McNaughton BL, Gothard KM, Markus EJ (1993) An information-theoretic to deciphering the hippocampal code. In: Advances in neural information processing (Hanson SJ, Cowan JD, Giles CL, eds), pp 1030–1037. San Mateo, CA: Morgan Kaufmann.

Spatz C (2011) Basic statistics: tales of distributions, 10th edition. Belmont, CA: Wadsworth Cengage Learning.

Spencer WD, Raz N (1995) Differential effects of aging on memory for content and context: a meta-analysis. Psychol Aging 10:527–539. CrossRef Medline

Thome A, Erickson CA, Lipa P, Barnes CA (2012) Differential effects of experience on tuning properties of macaque MTL neurons in a passive viewing task. Hippocampus 22:2000–2011. CrossRef Medline

Toner CK, Pirogovsky E, Kirwan CB, Gilbert PE (2009) Visual object pattern separation deficits in nondemented older adults. Learn Mem 16:338–342. CrossRef Medline

Toth JP, Parks CM (2006) Effects of age on estimated familiarity in the process dissociation procedure: the role of noncriterial recollection. Mem Cognit 34:527–537. CrossRef Medline

Tsao A, Moser MB, Moser EI (2013) Traces of experience in the lateral entorhinal cortex. Curr Biol 23:399–405. CrossRef Medline

Wan H, Aggleton JP, Brown MW (1999) Different contributions of the hippocampus and perirhinal cortex to recognition memory. J Neurosci 19:1142–1148. Medline

Wang H, Xie X, Li X, Chen B, Zhou Y (2006) Functional degradation of visual cortical cells in aged rats. Brain Res 1122:93–98. CrossRef Medline

Winters BD, Bussey TJ (2005) Glutamate receptors in perirhinal cortex mediate encoding, retrieval, and consolidation of object recognition memory. J Neurosci 25:4243–4251. CrossRef Medline

Woloszyn L, Sheinberg DL (2012) Effects of long-term visual experience on responses of distinct classes of single units in inferior temporal cortex. Neuron 74:193–205. CrossRef Medline

Zhu XO, Brown MW (1995) Changes in neuronal activity related to the repetition and relative familiarity of visual stimuli in rhinal and adjacent cortex of the anaesthetised rat. Brain Res 689:101–110. CrossRef Medline

Zhu XO, Brown MW, Aggleton JP (1995) Neuronal signalling of information important to visual recognition memory in rat rhinal and neighbouring cortices. Eur J Neurosci 7:753–765. CrossRef Medline

Brief Communications

Linking Redox Regulation of NMDAR Synaptic Function to Cognitive Decline during Aging

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NMDA receptors (NMDARs) play a critical role in learning and memory; however, there is a lack of evidence for a direct relationship between a well characterized decline in NMDAR function and impaired cognition during aging. The present study was designed to test the idea that a redox-mediated decrease in the NMDAR component of synaptic transmission during aging is related to a specific cognitive phenotype: impaired memory for rapidly acquired novel spatial information. Young and middle-aged male F344 rats were provided 1 d of training on the spatial version of the water maze, and retention was examined 24 h later. The performance of young rats was used as a criterion for classifying middle-aged rats as impaired and unimpaired on the task. Subsequent construction of CA3–CA1 synaptic input–output curves in hippocampal slices confirmed an age-related decrease in synaptic responses, including the NMDAR component of synaptic transmission. Examination of synaptic transmission according to behavioral classification revealed that animals classified as impaired exhibited a decrease in the total and the NMDAR component of the synaptic response relative to unimpaired animals. Furthermore, bath application of the reducing agent dithiothreitol increased the NMDAR component of the synaptic response to a greater extent in impaired animals relative to unimpaired and young rats. These results provide evidence for a link between the redox-mediated decline in NMDAR function and emergence of an age-related cognitive phenotype, impairment in the rapid acquisition and retention of novel spatial information.

Introduction

The NMDA receptor (NMDAR) component of synaptic transmission declines during aging (Barnes et al., 1997; Billard and Rouaud, 2007; Bodhinathan et al., 2010a). NMDARs are intimately involved in memory; however, there is a lack of evidence for a direct link between decreased NMDAR function and age-related memory impairment (Foster, 2012). Research indicates that NMDARs are involved in memory for rapidly acquired and flexible spatial information (e.g., working memory), rather than the incremental acquisition of a reference memory (Nakazawa et al., 2003; Bannerman et al., 2008; von Engelhardt et al., 2008), and NMDAR antagonists disrupt retention of novel spatial information as retention intervals increase (Steele and Morris, 1999; McDonald et al., 2005). Interestingly, the acquisition and retention of novel or flexible spatial information is highly sensitive to aging, developing in middle age, before spatial reference memory deficits (Jucker et al., 1988; Ando and Ohashi, 1991; Foster, 2012). The results suggest that a deficit in the rapid acquisition and consolidation of spatial information is an early phenotype of cognitive aging, possibly due to a decline NMDAR function.

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Recent work demonstrates that an age-related decrease in NMDAR function is related to oxidative stress and a postsynaptic shift in the intracellular oxidation–reduction (redox) environment (Bodhinathan et al., 2010a; Robillard et al., 2011; Haxaire et al., 2012). Increased oxidative stress and diminished NMDAR-dependent synaptic plasticity develop in middle age (Zhang et al., 1993; Rex et al., 2005; Ghosh et al., 2012), suggesting that NMDAR function may decline in middle age. The current study focuses on middle age to examine the idea that cognitive deficits that arise at this time are related to a redox-mediated decline in NMDAR synaptic responses.

Materials and Methods

Animals. Procedures involving animals have been reviewed and approved by the Institutional Animal Care and Use Committee of the University of Florida, and are in accordance with guidelines established by the US Public Health Service Policy on Humane Care and Use of Laboratory Animals. Young (5–8 months, $n = 11$) and middle-aged (12–16 months, $n = 34$) male Fischer 344 rats were obtained from National Institute on Aging colony at Harlan.

Behavioral characterization. Methods for behavioral assessment of cognition using the water maze have been published previously (Kumar et al., 2012; Foster et al., 2012; Speisman et al., 2013). Rats were first trained on the cue discrimination version of the water escape task using five blocks of three trials with all training massed into 1 d. Three days later, animals were trained on the spatial discrimination version of the task. Procedures for spatial learning were similar to the cue training, consisting of six blocks of three trials with all training massed into a single day. Probe trials delivered between blocks five and six and 24 h later were used to evaluate the use of a spatial search strategy.

Hippocampal slice preparation and electrophysiological recordings. Methods for hippocampal slice preparation and electrophysiological re-

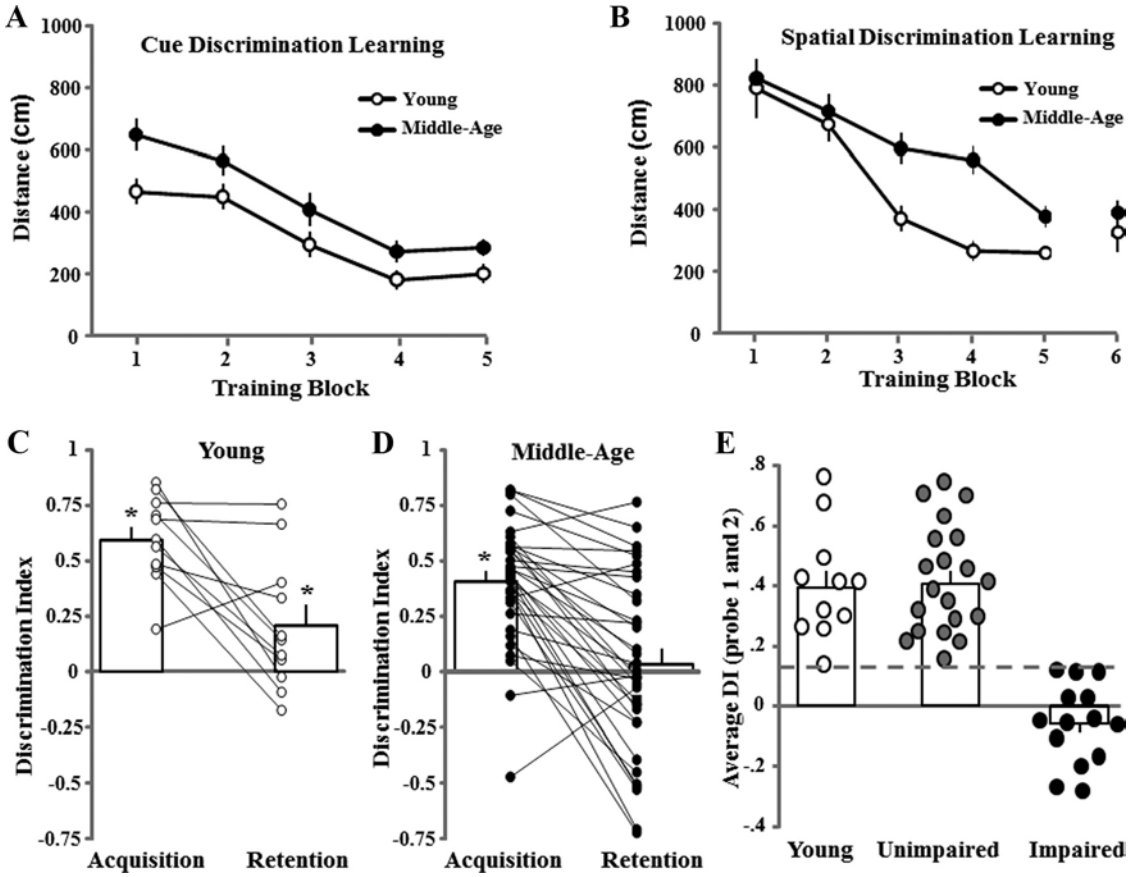

Figure 1. Characterization of learning and memory on the water maze. ***A***, ***B***, Mean distance traveled (±SEM) per training block during performance of the cue (***A***) and spatial discrimination tasks (***B***) for young (open circles, $n = 11$) and middle-aged (filled circles, $n = 34$) rats. ***C***, ***D***, Bars represent the mean ± SEM discrimination index (DI) scores for the acquisition and retention probe trials for young (***C***) and middle-aged (***D***) rats. The line graphs show individual DI scores. The DI scores were computed for the 60 s probe trials according to the formula $(G - O)/(G + O)$, where G and O represent the percentages of time spent in the goal and in opposite quadrants, respectively. The asterisk indicates that the mean discrimination index is >0 (i.e., chance performance). ***E***, The DI scores were averaged across the two probe trials for each animal. A cutoff criterion (dashed line) was set at the lowest value for young animals (open circles). Animals with scores below this criterion were classified as impaired (filled circles, $n = 14$), and those above this value were classified as unimpaired (gray circles, $n = 20$). The open bars represent the mean of the averaged DI scores for each group.

cording of total and NMDAR-mediated synaptic responses have been published previously (Bodhinathan et al., 2010a). Briefly, 1–2 weeks following behavioral characterization, hippocampi were harvested and slices (~400 μm) were cut parallel to the alvear fibers. Slices were placed in a recording chamber and were bathed in 30 ± 0.5°C oxygenated artificial CSF (ACSF) as follows (in mM): NaCl 124, KCl 2, KH_2PO_4 1.25, $MgSO_4$ 2, $CaCl_2$ 2, $NaHCO_3$ 26, and glucose 10.

Extracellular field EPSPs (fEPSPs) from stratum radiatum of CA1 were recorded with glass micropipettes (4–6 MΩ) filled with ACSF. A stimulating electrode was positioned ~1 mm away in the middle of the stratum radiatum. Field potentials (0.033 Hz) were evoked by diphasic stimulus pulses (100 μs). Signals were amplified, filtered (1 Hz and 1 kHz), and stored on computer for off-line analysis.

To obtain the NMDAR-mediated component of synaptic transmission (NMDAR–fEPSP), slices were incubated in ACSF containing low Mg^{2+} (0.5 mM), 6,7-dinitroquinoxaline-2,3-dione (DNQX; 30 μM) and picrotoxin (PTX; 10 μM). Input–output curves for the total and NMDAR–fEPSP slope (in millivolts per milliseconds) were constructed for increasing stimulation intensities. To examine dithiothreitol (DTT) effects, the baseline response was set at ~50% of maximum, and responses were collected for at least 10 min before and 60 min after drug application. The DTT dose (0.5 mM) was selected due to previous studies that show this dose is within a range that can increase NMDAR responses specifically in aged animals, and in young animals under oxidizing conditions, and yet is below a dose that impairs enzyme activity (Tang and Aizenman, 1993; Bodhinathan et al., 2010a).

DNQX (Sigma) was initially dissolved in dimethylsulfoxide (DMSO; Sigma) and diluted in ACSF to a final DMSO concentration of <0.01% and to a final DNQX concentration of 30 μM. PTX (Tocris Bioscience) was initially dissolved in ethanol and diluted in ACSF to a final ethanol concentration of 0.0001% and to a final PTX concentration of 10 μM. DTT was directly dissolved in ACSF.

Statistical analysis. ANOVAs were used to establish main effects. Follow-up ANOVAs or Fisher's PLSD *post hoc* tests ($p < 0.05$) were used to localize differences. In some cases, *t* tests were used to determine whether search behavior was different from chance and whether DTT induced a change in the synaptic response. Where stated, *n* represents the number of animals used in each experiment.

Results

Characterization of spatial learning and memory

An ANOVA on escape path length across the five blocks of cue discrimination training indicated a significant age effect ($F_{(1,172)} = 8.8$, $p < 0.005$) due to a greater path length for middle-aged ($n = 34$) compared with young ($n = 11$) animals (Fig. 1*A*). *Post hoc* ANOVAs indicated a significant effect of training ($p < 0.0001$) in each age group, and no age difference was observed for the final block, indicating that groups acquired the cue task to about the same extent.

An ANOVA examining age and training effects for escape path length across blocks during spatial training indicated a significant age effect ($F_{(1,215)} = 8.9$, $p < 0.005$) due to shorter escape path

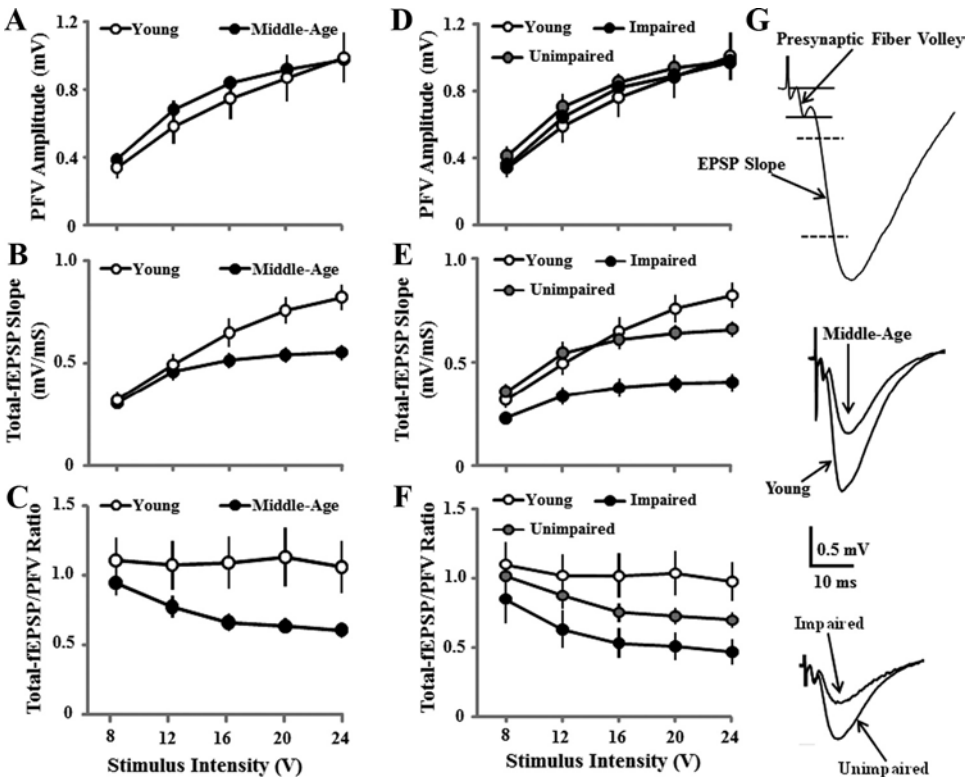

Figure 2. Decreased hippocampal synaptic strength during aging is related to cognitive function. ***A–C***, Input–output curves for the mean ± SEM amplitude of the PFV (***A***), slope of total–fEPSP (***B***), and ratio of total–fEPSP/PFV (***C***) evoked by increasing stimulation voltage (V). Despite a similar PFV, a decrease in the synaptic response was observed in middle-aged (filled circles, $n = 34$) relative to young (open circles, $n = 11$) animals. ***D–F***, Examination of synaptic transmission according to behavioral classification revealed that the decrease in the synaptic response was specific to animals classified as impaired (filled circles, $n = 14$), and the slope of the total–fEPSP (***E***) and ratio of total-fEPSP/PFV (***F***) were not different between unimpaired (gray circles, $n = 20$) and young (open circles, $n = 11$) animals. ***G***, Representative field potential recordings in CA1 stratum radiatum showing (top) the regions for PFV and EPSP measures. The calibration bars are for the middle and bottom panels. The EPSP traces for the middle and bottom panels provide examples of responses for young and middle-aged animals (middle) and impaired and unimpaired animals (bottom), which exhibited similar PFVs and differences in the EPSP slope.

length of young relative to middle-aged animals (Fig. 1*B*). ANOVAs within each age group indicated a significant effect of training ($p < 0.0001$), and no age difference was observed for the final training block. An ANOVA on the discrimination index scores across the acquisition and retention probe trials indicated a tendency ($p = 0.057$) for an age difference and a significant difference across the 24 h period ($F_{(1,43)} = 38.7$, $p < 0.0001$) due to a decrease in performance from acquisition to retention testing. One-group *t* tests indicated that performance was above chance for both probe trials in young animals, and for the acquisition probe trial in middle-aged animals (Fig. 1*C*,*D*). The performance on the retention probe trial for middle-aged rats was not different from chance, which is consistent with increased forgetting of the novel spatial information (Foster, 2012). To classify middle-aged animals as impaired or unimpaired on the spatial task, the discrimination index scores were averaged across the two probe trials and a cutoff criterion was set at the lowest value for young animals (score = 0.134; Fig. 1*E*). Middle-aged animals below this criterion were classified as impaired ($n = 14$, 41%), and those above this value were classified as unimpaired ($n = 20$, 59%). Reanalysis of performance during training on the cue and spatial discrimination tasks indicated no difference between impaired and unimpaired middle-aged animals (data not shown).

Basal synaptic transmission is reduced in impaired animals

Input–output curves for presynaptic fiber volley (PFV) and total–fEPSP slope confirmed decreased synaptic transmission with advancing age. ANOVAs indicated the effects of stimulation intensity ($F_{(4,172)} = 123.0$, $p < 0.0001$) in the absence of an age difference or an interaction for the PFV amplitude (Fig. 2*A*) and an age × stimulation intensity interaction for the total–fEPSP slope ($F_{(4,172)} = 15.5$, $p < 0.0001$) due to increased synaptic responses in young animals for higher stimulation intensities (Fig. 2*B*). The total-fEPSP/PFV ratio was calculated as an index of synaptic efficacy, and an ANOVA confirmed an age effect ($F_{(1,172)} = 5.1$, $p < 0.05$) due to reduced efficacy in middle-aged animals (Fig. 2*C*).

To determine whether decreased synaptic efficacy was associated with impaired cognitive function, the older animals were separated according to behavioral classification and analysis was conducted on all three groups (impaired, unimpaired, and young). The PFV increased with stimulation intensity ($F_{(4,168)} = 160.8$, $p < 0.0001$), but was not related to behavioral classification (Fig. 2*D*). An interaction of behavioral classification and stimulation intensity was observed for the total–fEPSP slope ($F_{(8,168)} = 10.0$, $p < 0.0001$), and *post hoc* tests indicated that the response was depressed for impaired animals relative to unimpaired and young animals (Fig. 2*E*). An ANOVA on the total–fEPSP/PFV ratio confirmed a group effect ($F_{(2,168)} = 3.9$, $p < 0.05$) due to reduced synaptic efficacy for impaired animals relative to young animals (Fig. 2*F*).

The PFV for the NMDAR–fEPSP increased with increasing stimulation ($F_{(6,258)} = 189.2$, $p < 0.0001$) and was not affected by age (Fig. 3*A*). In contrast, an age effect was observed for the NMDAR–fEPSP slope ($F_{(1,258)} = 6.7$ $p < 0.05$; Fig. 3*B*) and the NMDAR–fEPSP/PFV ratio ($F_{(1,258)} = 8.1$, $p < 0.01$; Fig. 3*C*) due

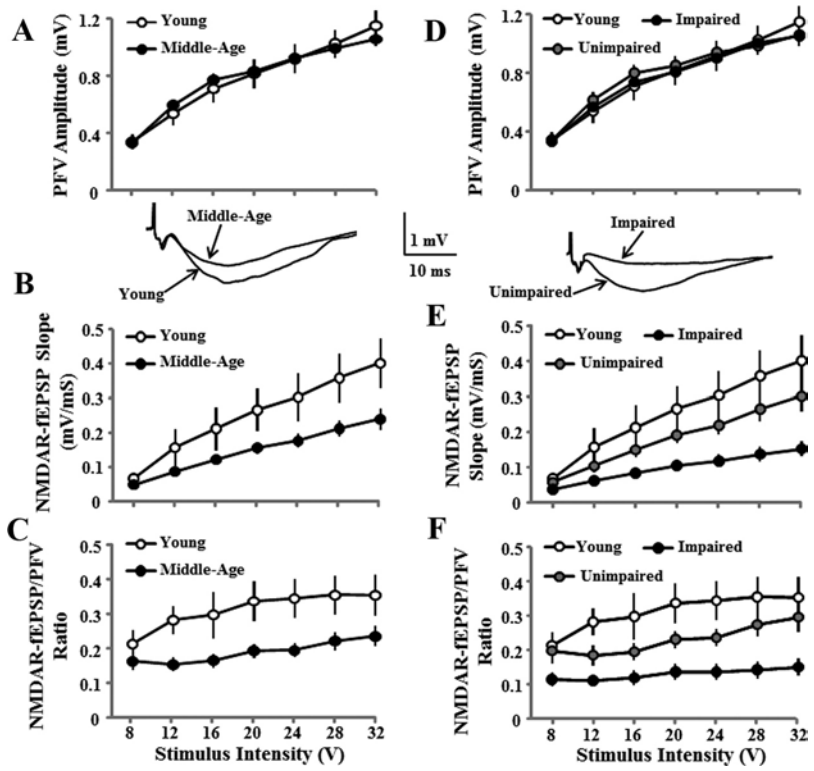

Figure 3. Reduced hippocampal NMDAR–fEPSP slope is related to cognitive function. ***A–C***, Input–output curves for the mean SEM PFV amplitude (***A***), NMDAR–fEPSP slope (***B***), and ratio of NMDAR–fEPSP/PFV (***C***) evoked by increasing the stimulation voltage (V). An age-related decrease in the synaptic response was observed in middle-aged (filled circles, $n = 34$) relative to young (open circles, $n = 11$) animals. ***D–F***, The decrease in the slope of the NMDAR–fEPSP (***E***) and ratio of the NMDAR–fEPSP/PFV (***F***) was specific for cognitively impaired (filled circles, $n = 14$) animals relative to unimpaired (gray circles, $n = 20$) and young (open circles, $n = 11$) animals. The inserts are representative NMDAR–fEPSP traces for young and middle-aged (left) and impaired and unimpaired (right) animals.

to greater responses in younger animals. When middle-aged animals were separated according to behavioral classification, the PFV for the NMDAR–fEPSP slope was not related to behavioral classification (Fig. 3*D*). An effect of group classification was observed for the NMDAR–fEPSP slope ($F_{(2,252)} = 6.1$, $p < 0.005$) and the NMDAR—fEPSP slope for impaired animals was decreased relative to the unimpaired and young animals (Fig. 3*E*). A main effect of group classification ($F_{(2,252)} = 7.6$, $p < 0.005$) was observed for the NMDAR–fEPSP/PFV ratio and *post hoc* tests confirmed that synaptic efficacy for impaired animals was decreased relative to the unimpaired and young animals (Fig. 3*F*).

Redox environment contributes to the decline in NMDAR function

In a subset of young ($n = 3/5$ animals/slices), middle-aged unimpaired ($n = 12/16$), and middle-aged impaired ($n = 7/8$) animals, the NMDAR–fEPSP slope was set a ~50% of maximum and recorded for 10 min. Subsequent application of DTT resulted in a marked increase in the synaptic response for impaired animals (Fig. 4*A*). The percentage change in the PFV and NMDAR–fEPSP slope was averaged during the last 5 min of the 1 h recording, and averages were subjected to ANOVAs. An effect of behavioral classification was observed on the percentage change in the NMDAR–fEPSP slope ($F_{(2,19)} = 7.3$, $p < 0.005$) due to a large increase in impaired animals relative to the other two groups (Fig. 4*A*). For impaired animals, an increase was observed in 100% of the slices (8 of 8 slices), and the raw NMDAR–fEPSP slope values were increased above baseline (paired *t* test, $p > 0.05$; Fig. 4*E*). The slope values were not increased for the other two groups, and an increase was observed in only ~50% of the slices (young animals, 2 of 5 slices; unimpaired animals, 8 of 16 slices; Fig. 4*C*,*D*). Consistent with previous studies, no effect of DTT was observed on the PFV amplitude (Fig. 4*F*), paired-pulse facilitation (50 ms interpulse interval), or the total–fEPSP slope.

Discussion

Disruption of memory for rapidly acquired novel spatial information develops in middle age, before impaired acquisition of spatial reference memories, which is generally limited to the oldest animals (Jucker et al., 1988; Ando and Ohashi, 1991; Foster, 2012). In the current study, we demonstrate that the emergence of impaired retention of novel spatial information is associated with a redox-sensitive decrease in NMDAR synaptic transmission.

An age-related decrease in CA1 synaptic transmission is well characterized and is not associated with a change in measures of presynaptic function, PFV, or paired-pulse facilitation (Landfield et al., 1986; Barnes et al., 1992; Deupree et al., 1993; Norris et al., 1998; Hsu et al., 2002). Similarly, redox agents do not alter the PFV or paired-pulse facilitation. Rather, the effects of DTT are specific for the NMDAR component of synaptic transmission and are not observed for the AMPA receptor component (Aizenman et al., 1990; Gozlan et al., 1995; Bernard et al., 1997; Bodhinathan et al., 2010a). NMDAR function is increased by postsynaptic injection of the relatively membrane-impermeable redox buffer glutathione, suggesting a postsynaptic mechanism (Bodhinathan et al., 2010a). The current study demonstrates that the redox-related depression of NMDARs emerges in middle age, particularly in animals that exhibit impaired cognition. Redox regulation of NMDARs contributes to age-related impairment of long-term potentiation (LTP; Bodhinathan et al., 2010a; Robillard et al., 2011), which also emerges during middle age in association with impaired cognition (Rex et al., 2005; Fouquet et al., 2011). Finally, treatments to enhance NMDAR function improve the rapid acquisition of spatial information (Burgdorf et al., 2011; Brim et al., 2013), suggesting that decreased NMDAR function underlies impaired memory for rapidly acquired novel spatial information.

Impairment in spatial reference memory does not correlate with the decrease in NMDAR-mediated synaptic transmission (Tombaugh et al., 2002; Boric et al., 2008). This may not be surprising since the incremental acquisition of reference memory is observed for many pharmacological or genetic conditions that decrease hippocampal NMDAR function (Foster, 2012). Rather, disruption of hippocampal NMDARs impairs the consolidation of novel, rapidly acquired spatial information (Steele and Morris, 1999; McDonald et al., 2005; Bannerman et al., 2008; von Engelhardt et al., 2008). The results

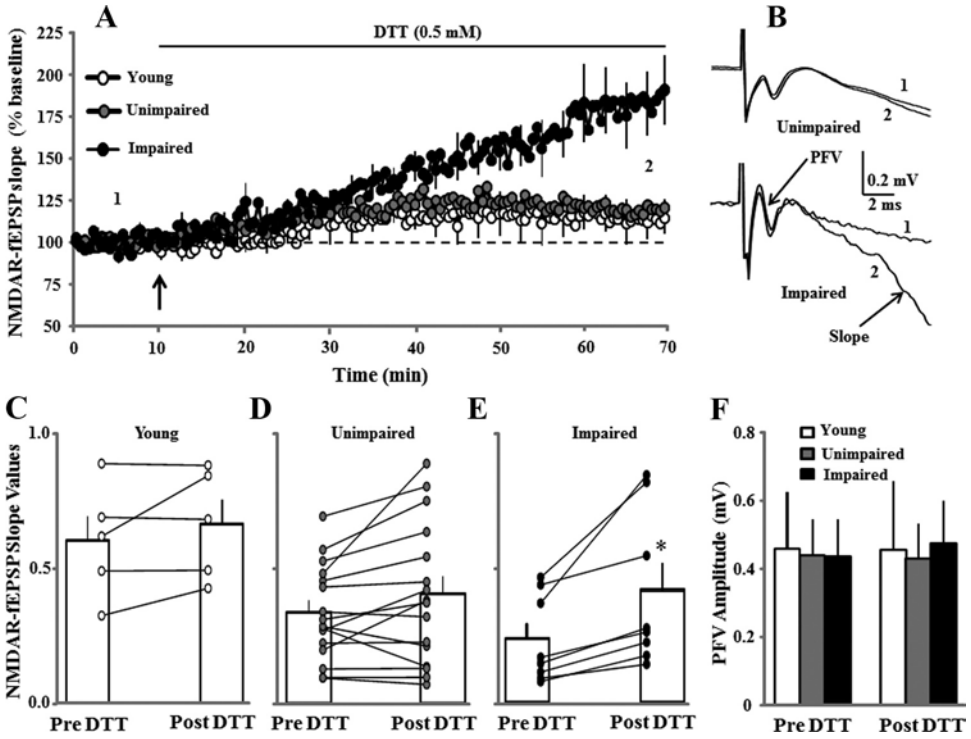

Figure 4. Redox environment contributes to the decline in NMDAR function associated with cognitive impairment. ***A***, Time course of changes in the slope of NMDAR–fEPSP obtained from hippocampal slices 10 min before and 60 min after bath application of the reducing agent DTT (0.5 mM, solid line) for young (open circles, $n = 3/5$ animals/slices), unimpaired (gray circles, $n = 12/16$ animals/slices), and impaired (filled circles, $n = 7/8$ animals/slices) animals. ***B***, Representative traces illustrating the change in the NMDAR–fEPSP slope in the middle-aged unimpaired (top) and middle-aged impaired (bottom) animals under control conditions (1) and at the end of a 60 min (2) application of DTT. Note that DTT did not affect the PFV. ***C–E***, Bars represent the mean ± SEM NMDAR–fEPSP slope recorded for the pre- and post-DTT time points for young (***C***), unimpaired (***D***), and impaired (***E***) animals. The line graphs show the change in the response for individual slices. ***F***, Bars represent the mean ± SEM PFV amplitude before and after the application of DTT across the various groups. The asterisk indicates a significant increase in NMDAR–fEPSP slope from the pre-DTT condition.

indicate that the decrease in NMDAR function contributes to an early phenotype of cognitive decline: impaired spatial working memory.

Differences in the onset or progression of working and reference memory deficits may depend on independent mechanisms that age differentially (Foster, 2012). Alternatively, a decline in NMDAR function may precipitate more severe learning deficits with advancing age. *In vitro* studies indicate that synaptic NMDAR activity is important for transcription related to neuroprotection and antioxidant defenses (Hardingham et al., 2002; Papadia et al., 2008; Zhang et al., 2011). Thus, a decline in synaptic NMDAR signaling could render cells more vulnerable to aging stressors, including oxidative stress. Similarly, a redox shift may contribute to several aspects of hippocampal senescence, including increases in the Ca^{2+}-dependent afterhyperpolarization (AHP), oxidative damage, neuronal vulnerability, and impaired cognition (Bodhinathan et al., 2010a; Ghosh et al., 2012; Lee et al., 2012). For example, growth of the AHP is associated with impaired learning (Tombaugh et al., 2005; Matthews et al., 2009), decreased NMDAR synaptic responses (Kumar and Foster, 2004), and impaired LTP (Foster and Norris, 1997; Foster, 2012). In turn, the redox state of ryanodine receptors mediates the age-related growth in the AHP through the release of Ca^{2+} from intracellular stores (Kumar and Foster, 2004; Bodhinathan et al., 2010b). The results suggest that the disruption of feedback loops involving redox state, excitatory/inhibitory neural activity, and activity-induced transcription may contribute to the development of brain aging.

References

Aizenman E, Hartnett KA, Reynolds IJ (1990) Oxygen free radicals regulate NMDA receptor function via a redox modulatory site. Neuron 5:841–846. CrossRef Medline

Ando S, Ohashi Y (1991) Longitudinal study on age-related changes of working and reference memory in the rat. Neurosci Lett 128:17–20. CrossRef Medline

Bannerman DM, Niewoehner B, Lyon L, Romberg C, Schmitt WB, Taylor A, Sanderson DJ, Cottam J, Sprengel R, Seeburg PH, Köhr G, Rawlins JN (2008) NMDA receptor subunit NR2A is required for rapidly acquired spatial working memory but not incremental spatial reference memory. J Neurosci 28:3623–3630. CrossRef Medline

Barnes CA, Rao G, Foster TC, McNaughton BL (1992) Region-specific age effects on AMPA sensitivity: electrophysiological evidence for loss of synaptic contacts in hippocampal field CA1. Hippocampus 2:457–468. CrossRef Medline

Barnes CA, Rao G, Shen J (1997) Age-related decrease in the N-methyl-D-aspartateR-mediated excitatory postsynaptic potential in hippocampal region CA1. Neurobiol Aging 18:445–452. CrossRef Medline

Bernard CL, Hirsch JC, Khazipov R, Ben-Ari Y, Gozlan H (1997) Redox modulation of synaptic responses and plasticity in rat CA1 hippocampal neurons. Exp Brain Res 113:343–352. CrossRef Medline

Billard JM, Rouaud E (2007) Deficit of NMDA receptor activation in CA1 hippocampal area of aged rats is rescued by D-cycloserine. Eur J Neurosci 25:2260–2268. CrossRef Medline

Bodhinathan K, Kumar A, Foster TC (2010a) Intracellular redox state alters NMDA receptor response during aging through Ca^{2+}/calmodulin-dependent protein kinase II. J Neurosci 30:1914–1924. CrossRef Medline

Bodhinathan K, Kumar A, Foster TC (2010b) Redox sensitive calcium stores underlie enhanced after hyperpolarization of aged neurons: role for ryanodine receptor mediated calcium signaling. J Neurophysiol 104: 2586–2593. CrossRef Medline

Boric K, Muñoz P, Gallagher M, Kirkwood A (2008) Potential adaptive function for altered long-term potentiation mechanisms in aging hippocampus. J Neurosci 28:8034–8039. CrossRef Medline

Brim BL, Haskell R, Awedikian R, Ellinwood NM, Jin L, Kumar A, Foster TC, Magnusson KR (2013) Memory in aged mice is rescued by enhanced expression of the GluN2B subunit of the NMDA receptor. Behav Brain Res 238:211–226. CrossRef Medline

Burgdorf J, Zhang XL, Weiss C, Matthews E, Disterhoft JF, Stanton PK, Moskal JR (2011) The N-methyl-d-aspartate receptor modulator GLYX-13 enhances learning and memory, in young adult and learning impaired aging rats. Neurobiol Aging 32:698–706. CrossRef Medline

Deupree DL, Bradley J, Turner DA (1993) Age-related alterations in potentiation in the CA1 region in F344 rats. Neurobiol Aging 14:249–258. CrossRef Medline

Foster TC (2012) Dissecting age-related cognitive decline in rodent models: N-methyl-D-aspartate receptors and voltage-dependent Ca2+ channels in senescent synaptic plasticity. Prog Neurobiol 96:283–303. CrossRef Medline

Foster TC, Norris CM (1997) Age-associated changes in Ca(2+)-dependent processes: relation to hippocampal synaptic plasticity. Hippocampus 7:602–612. CrossRef Medline

Foster TC, Defazio RA, Bizon JL (2012) Characterizing cognitive aging of spatial and contextual memory in animal models. Front Aging Neurosci 4:12. CrossRef Medline

Fouquet C, Petit GH, Auffret A, Gaillard E, Rovira C, Mariani J, Rondi-Reig L (2011) Early detection of age-related memory deficits in individual mice. Neurobiol Aging 32:1881–1895. CrossRef Medline

Ghosh D, LeVault KR, Barnett AJ, Brewer GJ (2012) A reversible early oxidized redox state that precedes macromolecular ROS damage in aging nontransgenic and 3xTg-AD mouse neurons. J Neurosci 32:5821–5832. CrossRef Medline

Gozlan H, Khazipov R, Diabira D, Ben-Ari Y (1995) In CA1 hippocampal neurons, the redox state of NMDA receptors determines LTP expressed by NMDA but not by AMPA receptors. J Neurophysiol 73:2612–2617. Medline

Hardingham GE, Fukunaga Y, Bading H (2002) Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. Nat Neurosci 5:405–414. CrossRef Medline

Haxaire C, Turpin FR, Potier B, Kervern M, Sinet PM, Barbanel G, Mothet JP, Dutar P, Billard JM (2012) Reversal of age-related oxidative stress prevents hippocampal synaptic plasticity deficits by protecting D-serine-dependent NMDA receptor activation. Aging Cell 11:336–344. CrossRef Medline

Hsu KS, Huang CC, Liang YC, Wu HM, Chen YL, Lo SW, Ho WC (2002) Alterations in the balance of protein kinase and phosphatase activities and age-related impairments of synaptic transmission and long-term potentiation. Hippocampus 12:787–802. CrossRef Medline

Jucker M, Oettinger R, Bättig K (1988) Age-related changes in working and reference memory performance and locomotor activity in the Wistar rat. Behav Neural Biol 50:24–36. CrossRef Medline

Kumar A, Foster TC (2004) Enhanced long-term potentiation during aging is masked by processes involving intracellular calcium stores. J Neurophysiol 91:2437–2444. CrossRef Medline

Kumar A, Rani A, Tchigranova O, Lee WH, Foster TC (2012) Influence of late-life exposure to environmental enrichment or exercise on hippocampal function and CA1 senescent physiology. Neurobiol Aging 33:828.e821–e817. CrossRef Medline

Landfield PW, Pitler TA, Applegate MD (1986) The effects of high Mg2+-to-Ca2+ ratios on frequency potentiation in hippocampal slices of young and aged rats. J Neurophysiol 56:797–811. Medline

Lee WH, Kumar A, Rani A, Herrera J, Xu J, Someya S, Foster TC (2012) Influence of viral vector-mediated delivery of superoxide dismutase and catalase to the hippocampus on spatial learning and memory during aging. Antioxid Redox Signal 16:339–350. CrossRef Medline

Matthews EA, Linardakis JM, Disterhoft JF (2009) The fast and slow afterhyperpolarizations are differentially modulated in hippocampal neurons by aging and learning. J Neurosci 29:4750–4755. CrossRef Medline

McDonald RJ, Hong NS, Craig LA, Holahan MR, Louis M, Muller RU (2005) NMDA-receptor blockade by CPP impairs post-training consolidation of a rapidly acquired spatial representation in rat hippocampus. Eur J Neurosci 22:1201–1213. CrossRef Medline

Nakazawa K, Sun LD, Quirk MC, Rondi-Reig L, Wilson MA, Tonegawa S (2003) Hippocampal CA3 NMDA receptors are crucial for memory acquisition of one-time experience. Neuron 38:305–315. CrossRef Medline

Norris CM, Halpain S, Foster TC (1998) Alterations in the balance of protein kinase/phosphatase activities parallel reduced synaptic strength during aging. J Neurophysiol 80:1567–1570. Medline

Papadia S, Soriano FX, Léveillé F, Martel MA, Dakin KA, Hansen HH, Kaindl A, Sifringer M, Fowler J, Stefovska V, McKenzie G, Craigon M, Corriveau R, Ghazal P, Horsburgh K, Yankner BA, Wyllie DJ, Ikonomidou C, Hardingham GE (2008) Synaptic NMDA receptor activity boosts intrinsic antioxidant defenses. Nat Neurosci 11:476–487. CrossRef Medline

Rex CS, Kramár EA, Colgin LL, Lin B, Gall CM, Lynch G (2005) Long-term potentiation is impaired in middle-aged rats: regional specificity and reversal by adenosine receptor antagonists. J Neurosci 25:5956–5966. CrossRef Medline

Robillard JM, Gordon GR, Choi HB, Christie BR, MacVicar BA (2011) Glutathione restores the mechanism of synaptic plasticity in aged mice to that of the adult. PLoS One 6:e20676. CrossRef Medline

Speisman RB, Kumar A, Rani A, Pastoriza JM, Severance JE, Foster TC, Ormerod BK (2013) Environmental enrichment restores neurogenesis and rapid acquisition in aged rats. Neurobiol Aging 34:263–274. CrossRef Medline

Steele RJ, Morris RG (1999) Delay-dependent impairment of a matching-to-place task with chronic and intrahippocampal infusion of the NMDA-antagonist D-AP5. Hippocampus 9:118–136. CrossRef Medline

Tang LH, Aizenman E (1993) The modulation of N-methyl-D-aspartate receptors by redox and alkylating reagents in rat cortical neurones in vitro. J Physiol 465:303–323. Medline

Tombaugh GC, Rowe WB, Chow AR, Michael TH, Rose GM (2002) Theta-frequency synaptic potentiation in CA1 *in vitro* distinguishes cognitively impaired from unimpaired aged Fischer 344 rats. J Neurosci 22:9932–9940. Medline

Tombaugh GC, Rowe WB, Rose GM (2005) The slow afterhyperpolarization in hippocampal CA1 neurons covaries with spatial learning ability in aged Fisher 344 rats. J Neurosci 25:2609–2616. CrossRef Medline

von Engelhardt J, Doganci B, Jensen V, Hvalby Ø, Göngrich C, Taylor A, Barkus C, Sanderson DJ, Rawlins JN, Seeburg PH, Bannerman DM, Monyer H (2008) Contribution of hippocampal and extra-hippocampal NR2B-containing NMDA receptors to performance on spatial learning tasks. Neuron 60:846–860. CrossRef Medline

Zhang JR, Andrus PK, Hall ED (1993) Age-related regional changes in hydroxyl radical stress and antioxidants in gerbil brain. J Neurochem 61:1640–1647. CrossRef Medline

Zhang SJ, Buchthal B, Lau D, Hayer S, Dick O, Schwaninger M, Veltkamp R, Zou M, Weiss U, Bading H (2011) A signaling cascade of nuclear calcium-CREB-ATF3 activated by synaptic NMDA receptors defines a gene repression module that protects against extrasynaptic NMDA receptor-induced neuronal cell death and ischemic brain damage. J Neurosci 31:4978–4990. CrossRef Medline

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COMMENTARY

COGNITIVE FRAILTY: FRONTIERS AND CHALLENGES

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An international consensus group comprised of investigators from the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) recently convened in Toulouse, France to establish a definition for cognitive frailty in older adults. This effort was motivated by growing awareness that many people with physical frailty are also prone to cognitive problems. In "Cognitive Frailty: Rationale and Definition" (1), an initial working definition was developed, and a framework proposed for future studies of cognitive frailty.

This group should be commended for addressing the construct of cognitive frailty and an obvious gap in the clinical gerontology literature. Physical frailty is a widely recognized problem in the elderly. While age-associated cognitive dysfunction has been studied for many years, for the most part it was not conceptualized in a manner that is consistent with current definitions of physical frailty. In fact, cognition has typically not been conceptualized in this manner, and only recently has the term cognitive frailty been employed. Rockwood et al published one of the first studies to examine factors associated with frailty in the elderly (2). Frailty was conceptualized as a multidimensional construct with both physical and cognitive origins. Panza et al. used the term cognitive frailty in the title of their review of pre-dementia syndrome vascular risk factors (3). In a subsequent paper, Panza et al, attempted to specify different models of frailty in pre-dementia and dementia syndrome (4). The prognostic accuracy of frailty assessment inventories for mortality among hospitalized elderly people was examined subsequently, with results suggesting that both cognitive and physical factors were important in predicting outcome (5). We reviewed 199 manuscripts cited in PubMed in which cognitive frailty was mentioned in either the title or as a keyword. In the vast majority of these manuscripts, frailty was examined as a manifestation of cognitive dysfunction. Only recently has cognitive frailty itself become the focus of inquiry.

The term cognitive frailty is attractive as it suggests a parallel with physical frailty. The concept of physical frailty is relatively well understood in the context of aging, and has been operationalized in studies conducted over the past two decades (6-8). However, as Kelaiditi et al. point out, the operational definition of physical frailty remains unresolved (1). The situation is even more problematic for cognitive frailty, as past investigators have focused on a variety of different phenomena. The term has often been used as a general descriptor for cognitive impairment occurring as people reach advanced age. Sometimes cognitive frailty refers to cognitive disturbances or pre-dementia occurring in association with other medical conditions (9). However, Kelaiditi et al. state that cognitive frailty must be considered as being independent of dementia or pre-existing brain disorders (1). Accordingly, there seems to be several different perspectives on the nature of cognitive frailty. The fact that the construct is ambiguous and lacking a precise operational definition clearly reinforces the authors' effort to establish a common language for future studies of cognitive frailty.

An obvious question emerges: How is cognitive frailty different from cognitive reserve? Cognitive reserve refers to the capacity of a given individual to resist cognitive impairment or decline. Educational level and prior cognitive abilities have been shown to be important determinants of cognitive reserve (10-12). Cognitive reserve has been linked with resilience of brain function and structure in the presence of disease, injury, or other factors that alter physiological functioning (13). While cognitive and brain reserve undoubtedly have some common underpinnings, the relationship between these types of reserve is still not fully understood.

Kelaiditi et al maintain that "cognitive frailty is characterized by reduced cognitive reserve". Accordingly, cognitive frailty could be viewed as simply the inverse of cognitive reserve. The authors indicate that while cognitive reserve is an important element of cognitive frailty, it is also dependent on the existence of physical frailty; i.e., "the simultaneous presence of both physical frailty and cognitive impairment". They distinguish this category of older non-demented adults from cognitive impairment in the absence of physical frailty. The importance of this categorization is that it emphasizes an important and often under-recognized relationship between systemic physical illness, brain dysfunction, and cognitive impairment. It is now well established that cognitive disturbances occur secondary to various medical conditions, such as cardiovascular disease, diabetes and HIV (14-19).

The value of excluding brain disorders from cognitive frailty may be less well justified. By limiting cognitive frailty to people with physical frailty, Kelaiditi et al create four discrete categories of older non-demented adults, which may have some clinical value. However, with respect to the concept of

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cognitive frailty, there are many examples of people who are vulnerable to subsequent functional decline based on the existence of subtle cognitive and/or brain abnormalities below the threshold for clinical detection. In fact, a major thrust of current research on neurodegenerative disease focuses on the discovery of vulnerability and early markers of future functional decline. While physical disorders such as diabetes and cardiovascular risk factors contribute to this vulnerability, a variety of neurobiological and behavioral risk factors also exist that create functional vulnerability (20-22), and ultimately cognitive frailty. In fact, excluding people with brain disturbances from the definition of cognitive frailty fails to account for the fact that the effects of physical illnesses are exacerbated by the existence of a neural predisposition to cognitive decline or prior brain disturbances that reduce cognitive reserve. Furthermore, people with physical frailty who develop cognitive frailty presumably do so as their brain begins to develop neuropathological changes. Accordingly, there is value in dichotomizing cognitive frailty between people with or without pre-existing brain dysfunction, or alternatively treating brain vulnerability as a mediator of the effects of physical illness on cognitive frailty.

Defining cognitive frailty depends on determining its diagnostic criteria. Other than physical frailty, the primary criteria proposed by Kelaiditi et al. is the presence of mild cognitive impairment as defined by a clinical dementia rating (CDR) score of 0.5, without Alzheimer's disease or another progressive brain disturbance that would lead to dementia. Using these criteria, it is not clear whether people with cerebrovascular disturbances would meet these criteria or not. The authors make a point of also noting that "under different circumstances cognitive frailty may also represent a precursor of neurodegenerative processes". This is a critical point that reinforces the need to go beyond the definition of cognitive frailty as occurring in the absence of brain dysfunction. It is also likely that a CDR = 0.5 is too narrow to fully capture the heterogeneity of cognitive frailty. For example, people without cognitive impairment that rises to the level of a CDR= 0.5 may still be vulnerable to functional decline under certain conditions. This occurs commonly during hospitalization, in response to extreme stress, or to changes in the physical environment in the elderly.

In fact, it is the vulnerability to alterations in cognitive function under such conditions that may be the essential determinant of cognitive frailty. There are many people in society with cognitive limitations who would not be considered to be frail, unless they exhibit a tendency to functionally decompensate when their resources are challenged. The key to operationalizing cognitive frailty may ultimately depend of developing diagnostic challenges that would enable clinicians to determine this tendency. This will depend on determining which neurocognitive measures are most useful for detecting this vulnerability and for assessing the severity of cognitive frailty.

In sum, "Cognitive Frailty: Rationale and Definition" (1) provides a valuable starting point for the development of a coherent operational definition and for future studies of cognitive frailty. While closely linked to cognitive reserve, the construct of cognitive frailty goes beyond cognitive reserve, particularly because of its association with physical frailty and the fact that it often becomes evident in the context of acute physical illness. There seems to be considerable value in distinguishing vulnerability to cognitive functional decline among people with or without physical frailty, though there is evidence that both cognitive and physical frailty share several common pathophysiologic mechanisms and risk factors. Growing and consistent epidemiologic evidence shows that impaired physical performance, which is a component of physical frailty, measured with walking speed or the Short Physical Performance Battery (SPPB) (23), is independently associated with cognitive decline (24-36). The SPPB tests, including walking, balance and chair stands, require the complex interplay of sensory, cognitive, and motor functions. These systems may be altered early in the path to cognitive decline (36, 37), and possibly to cognitive frailty. Low walking speed and low SPPB score are also associated with elevated inflammatory cytokines and low Brain-Derived Natirurectic Factor (BDNF) (38-40), all of which are predictors of cognitive decline (41, 42).

Future research is needed to determine how phenotypic differences among people and the existence of a wide variety of preexisting manifestations of brain structure and function affect this vulnerability. Following the expert consensus, prospective studies will be needed to assess the reliability and predictive validity of the operational measure of cognitive frailty. We laud the efforts of the IANA/IAGG consensus group in laying the foundation for the emerging concept of cognitive frailty and strongly encourage future studies aimed at advancing this clinical domain.

References

1. Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ouset P, Gillette-Guyonnet S, Ritz P, Duveau F, Soto ME, Provencher V, Nourhashemi F, Salva A, Robert P, Andrieu S, Rolland Y, Touchon J, Fitten, Vellas B (2013) Cognitive Frailty: Rational and definition from an (I.A.N.A./I.A.G.G.) International Consensus Group. J Nutr Health Aging 2013;9:726-734.
2. Rockwood K, Stolee P, McDowell I (1996) Factors associated with institutionalization of older people in Canada: testing a multifactorial definition of frailty. J Am Geriatr Soc 44(5):578-582.
3. Panza F, D'Introno A, Colacicco AM, et al (2006) Cognitive frailty: Predementia syndrome and vascular risk factors. Neurobiol Aging 27(7):933-940.
4. Panza F, Solfrizzi V, Frisardi V, et al (2011) Different models of frailty in predementia and dementia syndromes. J Nutr Health Aging 15(8):711-719.
5. Pilotto A, Rengo F, Marchionni N, et al (2012) Comparing the prognostic accuracy for all-cause mortality of frailty instruments: a multicentre 1-year follow-up in hospitalized older patients. PLoS One. 7(1):e29090.
6. Abellan van Kan G, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B (2010) The assessment of frailty in older adults. Clin Geriatr Med 26(2):275-286.
7. Abellan van Kan G, Rolland Y, Andrieu S, et al (2009) Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging 13(10):881-889.
8. Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B (2008) The I.A.N.A Task Force on frailty assessment of older people in clinical

practice. J Nutr Health Aging 12(1):29-37.
9. Chouliara Z, Kearney N, Stott D, Molassiotis A, Miller M (2004) Perceptions of older people with cancer of information, decision making and treatment: a systematic review of selected literature. Ann Oncol 15(11):1596-1602.
10. Satz P, Morgenstern H, Miller EN, et al (1993) Low education as a possible risk factor for cognitive abnormalities in HIV-1: findings from the multicenter AIDS Cohort Study (MACS). J Acquir Immune Defic Syndr 6(5):503-511.
11. Stern Y (2002) What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc 8(3):448-460.
12. Stern Y, Albert S, Tang MX, Tsai WY (1999) Rate of memory decline in AD is related to education and occupation: cognitive reserve? Neurology 53(9):1942-1947.
13. Satz P, Cole MA, Hardy DJ, Rassovsky Y (2011) Brain and cognitive reserve: mediator(s) and construct validity, a critique. J Clin Exp Neuropsychol 33(1):121-130.
14. Okonkwo OC, Cohen RA, Gunstad J, Tremont G, Alosco ML, Poppas A (2010) Longitudinal trajectories of cognitive decline among older adults with cardiovascular disease. Cerebrovasc Dis 30(4):362-373.
15. Cohen RA, Poppas A, Forman DE, et al (2009) Vascular and cognitive functions associated with cardiovascular disease in the elderly. J Clin Exp Neuropsychol 31(1):96-110.
16. Gunstad J, Cohen RA, Paul RH, Tate DF, Hoth KF, Poppas A (2006) Understanding reported cognitive dysfunction in older adults with cardiovascular disease. Neuropsychiatr Dis Treat 2(2):213-218.
17. Devlin KN, Gongvatana A, Clark US, et al (2012) Neurocognitive effects of HIV, hepatitis C, and substance use history. J Int Neuropsychol Soc 18(1):68-78.
18. Cohen RA, de la Monte S, Gongvatana A, et al (2011) Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning. J Neuroimmunol 233(1-2):204-210.
19. Cohen RA, Harezlak J, Schifitto G, et al (2010) Effects of nadir CD4 count and duration of human immunodeficiency virus infection on brain volumes in the highly active antiretroviral therapy era. J Neurovirol 16(1):25-32.
20. Elie M, Cole MG, Primeau FJ, Bellavance F (1998) Delirium risk factors in elderly hospitalized patients. J Gen Intern Med 13(3):204-212.
21. Robertsson B, Blennow K, Gottfries CG, Wallin A (1998) Delirium in dementia. Int J Geriatr Psychiatry 13(1):49-56.
22. Woods AJ, Mark VW, Pitts AC, Mennemeier M (2011) Pervasive cognitive impairment in acute rehabilitation inpatients without brain injury. PM R 3(5):426-432.
23. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB (1995) Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 332(9):556-561.
24. Camargo EC, Beiser A, Tan ZS et al (2012) Walking Speed, Handgrip Strength and Risk of Dementia and Stroke: The Framingham Offspring Study. American Academy of Neurology, 64th Annual Meeting, New Orleans, April 21-28, 2012.
25. Dodge HH, Mattek NC, Austin D, Hayes TL, Kaye JA (2012) In-home walking speeds and variability trajectories associated with mild cognitive impairment. Neurology 78(24):1946-1952.
26. McGough EL, Kelly VE, Logsdon RG, McCurry SM, Cochrane BB, Engel JM, Teri L (2011) Associations between physical performance and executive function in older adults with mild cognitive impairment: gait speed and the timed "up & go" test. Phys Ther 91(8):1198-1207.
27. Fitzpatrick AL, Buchanan CK, Nahin RL, DeKosky ST, Atkinson HH, Carlson MC, Williamson JD (2007) Associations of gait speed and other measures of physical function with cognition in a healthy cohort of elderly persons. J Gerontol A Biol Sci Med Sci 62(11):1244-1251.
28. Deshpande N, Metter EJ, Bandinelli S, Guralnik J, Ferrucci L. Gait speed under varied challenges and cognitive decline in older persons: a prospective study. Age Ageing 2009; 38(5):509-514.
29. Rosano C, Simonsick EM, Harris TB, Kritchevsky SB, Brach J, Visser M, Yaffe K, Newman AB (2005) Association between physical and cognitive function in healthy elderly: the health, aging and body composition study. Neuroepidemiology 24(1-2):8-14.
30. Soumare A, Tavernier B, Alperovitch A, Tzourio C, Elbaz A (2009) A cross-sectional and longitudinal study of the relationship between walking speed and cognitive function in community-dwelling elderly people. J Gerontol A Biol Sci Med Sci 64(10):1058-1065.
31. Abellan Van KG, Rolland Y, Andrieu S, Bauer J, Beauchet O, et al (2009) Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging 13(10):881-889.
32. Wang L, Larson EB, Bowen JD, van BG (2006) Performance-based physical function and future dementia in older people. Arch Intern Med 166(10):1115-1120.
33. Hajjar I, Yang F, Sorond F, Jones RN, Milberg W, Cupples LA, Lipsitz LA (2009) A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: relationship to blood pressure and other cardiovascular risks. J Gerontol A Biol Sci Med Sci 64(9):994-1001.
34. Zimmermann LJ, Ferrucci L, Kiang L, Lu T, Guralnik JM, Criqui MH, Yihua L, McDermott MM (2011) Poorer clock draw test scores are associated with greater functional impairment in peripheral artery disease: the Walking and Leg Circulation Study II. Vasc Med 16(3):173-181.
35. Verghese J, Robbins M, Holtzer R, Zimmerman M, Wang C, Xue X, Lipton RB (2008) Gait dysfunction in mild cognitive impairment syndromes. J Am Geriatr Soc 56(7):1244-1251.
36. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X (2007) Quantitative gait dysfunction and risk of cognitive decline and dementia. J Neurol Neurosurg Psychiatry 78(9):929-935.
37. Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA (2007) Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med 69(5):483-489.
38. Brinkley TE, Leng X, Miller ME, Kitzman DW, Pahor M, Berry MJ, Marsh AP, Kritchevsky SB, Nicklas BJ (2009) Chronic inflammation is associated with low physical function in older adults across multiple comorbidities. J Gerontol A Biol Sci Med Sci 64(4):455-461.
39. Hsu FC, Kritchevsky SB, Liu Y, Kanaya A, Newman AB, Perry SE, Visser M, Pahor M, Harris TB, Nicklas BJ (2009) Association Between Inflammatory Components and Physical Function in the Health, Aging, and Body Composition Study: A Principal Component Analysis Approach. J Gerontol A Biol Sci Med Sci 64(5):581-589.
40. Scalzo P, Kummer A, Bretas TL, Cardoso F, Teixeira AL (2010) Serum levels of brain-derived neurotrophic factor correlate with motor impairment in Parkinson's disease. J Neurol 257(4):540-545.
41. Erickson KI, Prakash RS, Voss MW, Chaddock L, Heo S, McLaren M, Pence BD, Martin SA, Vieira VJ, Woods JA, McAuley E, Kramer AF (2010) Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J Neurosci 30(15):5368-5375.
42. Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, Launer L, Kuller L, Rubin S, Harris T (2003) Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology 61(1):76-80.

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